

Central Lancashire Online Knowledge (CLOK)

Title	Transcription Factors in Neurodevelopmental and Associated Psychiatric Disorders: A Potential Convergence for Genetic and Environmental Risk Factors
Type	Article
URL	https://clock.uclan.ac.uk/id/eprint/38594/
DOI	https://doi.org/10.1002/jdn.10141
Date	2021
Citation	Santos-Terra, Júlio, Deckmann, Iohanna, Fontes-Dutra, Mellanie, Schwingel, Gustavo Brum, Bambini-Junior, Victorio and Gottfried, Carmem (2021) Transcription Factors in Neurodevelopmental and Associated Psychiatric Disorders: A Potential Convergence for Genetic and Environmental Risk Factors. International Journal of Developmental Neuroscience, 81 (7). pp. 545-578. ISSN 0736-5748
Creators	Santos-Terra, Júlio, Deckmann, Iohanna, Fontes-Dutra, Mellanie, Schwingel, Gustavo Brum, Bambini-Junior, Victorio and Gottfried, Carmem

It is advisable to refer to the publisher's version if you intend to cite from the work.
<https://doi.org/10.1002/jdn.10141>

For information about Research at UCLan please go to <http://www.uclan.ac.uk/research/>

All outputs in CLOK are protected by Intellectual Property Rights law, including Copyright law. Copyright, IPR and Moral Rights for the works on this site are retained by the individual authors and/or other copyright owners. Terms and conditions for use of this material are defined in the <http://clock.uclan.ac.uk/policies/>

Santos-Terra Júlio (Orcid ID: 0000-0002-8079-452X)
Deckmann Iohanna (Orcid ID: 0000-0002-6423-1938)
Fontes-Dutra Mellanie (Orcid ID: 0000-0003-0334-0740)
SCHWINGEL GUSTAVO (Orcid ID: 0000-0002-8949-6254)

Transcription Factors in Neurodevelopmental and Associated Psychiatric Disorders: A Potential Convergence for Genetic and Environmental Risk Factors

Júlio Santos-Terra^{*1,2,3,4}, Iohanna Deckmann^{1,2,3,4}, Mellanie Fontes-Dutra^{1,2,3,4},
Gustavo Brum Schwingel^{1,2,3,4}, Victorio Bambini-Junior^{*1,3,4,5}, Carmem Gottfried^{*1,2,3,4}

¹ Translational Research Group in Autism Spectrum Disorders (GETTEA), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.

² Department of Biochemistry, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.

³ National Institute of Science and Technology on Neuroimmunomodulation (INCT-NIM), Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.

⁴ Autism Wellbeing And Research Development (AWARD) Institute, BR-UK-CA

⁵ School of Pharmacology and Biomedical Sciences, University of Central Lancashire, Preston, United Kingdom.

***CORRESPONDING AUTHORS:**

JS-T (juliosterra@gmail.com), CG (cgottfried@ufrgs.br)

Departamento de Bioquímica, ICBS, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos 2600 – 21111. CEP: 90035-003 Porto Alegre-RS, Brazil.

VB-J (VBambini-Junior@uclan.ac.uk)

School of Pharmacology and Biomedical Sciences, University of Central Lancashire, Preston, United Kingdom

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jdn.10141

Abstract

Neurodevelopmental disorders (NDDs) are a heterogeneous and highly prevalent group of psychiatric conditions marked by impairments in the nervous system. Their onset occurs during gestation, and the alterations are observed throughout the postnatal life. Although many genetic and environmental risk factors have been described in this context, the interactions between them challenge the understanding of the pathways associated with NDDs. Transcription factors (TFs) – a group of over 1,600 proteins that can interact with DNA, regulating gene expression through modulation of RNA synthesis, represent a point of convergence for different risk factors. In addition, TFs organize critical processes like angiogenesis, blood-brain barrier formation, myelination, neuronal migration, immune activation, and many others in a time and location-dependent way. In this review, we summarize important TF alterations in NDD and associated disorders, along with specific impairments observed in animal models, and, finally, establish hypotheses to explain how these proteins may be critical mediators in the context of genome-environment interactions.

Key Words: Transcription Factors; Neurodevelopmental Disorders; Psychiatric Disorders; Environment-Genome Interaction; Transcription; Animal Model.

1. Introduction

Throughout development, both genetic and environmental risk factors contribute to the onset of neural disorders. The genetic risk factor is widely acknowledged, and many genes triggering these conditions are well-described. However, the contribution of environmental risk factors to the onset of neurodevelopmental disorders (NDDs) still poses a great challenge for science since a wide range of alterations in biological pathways can lead to similar outcomes. Recently, many studies have indicated that transcription factors (TFs) could be a point of convergence to understand these interactions.

NDDs are a diverse group of early-onset conditions characterized by impairments in language, cognition, motricity, and many other aspects. This group includes specific learning disorders, motor disorders, and communication disorders, attention deficit hyperactivity disorder (ADHD), intellectual disabilities (ID) and autism spectrum disorder (ASD) (American Psychiatric Association, 2013) (Figure 1). In this context, we reviewed the NDDs with a solid and well-established association with imbalance in the levels/ function of TFs. Specific learning disorders, motor disorders, communication disorders, and ADHD have few descriptions in the literature regarding changes in TFs throughout neurodevelopment; therefore, they were not considered in the study.

ASD is one of the most increasingly prevalent NDD, with a rate of 1:54 among children up to 8 years of age in the USA (Maenner et al., 2020) being characterized by a dyad of behavioral characteristics: 1. deficits in communication and social interaction, and 2. presence of repetitive and stereotyped behaviors, in addition to restricted interest in activities. Recent genetic studies indicate an overlap of symptoms and pathogenic mechanisms among NDDs (like ASD and ID) and other psychiatric disorders, such as schizophrenia (Morris-Rosendahl and Crocq, 2020).

Schizophrenia is characterized by positive symptoms (hallucinations or delusions) and negative symptoms (such as poverty of speech and impairments in cognition). It is estimated to affect about 1.5 per 10,000 people (McGrath et al., 2008), with symptoms typically starting in early adulthood, around 20 years of age (Association, 2013). Therefore, considering the emerging evidence of overlap with ASD symptoms, schizophrenia was included in the study (Figure 1).

In the present review, we described: 1. General features of TFs in NDDs, providing an overview of their expression patterns; 2. NDDs associated with specific

genetic alterations in TFs, including Rett syndrome, Williams syndrome, and Pitt-Hopkins syndrome; 3. The correlation of environmental factors with alterations in TFs; 4. The changes in TFs in multifactorial disorders - focusing on ASD and Schizophrenia - demonstrating that genetic and environmental risk factors can propagate similar alterations; 5. TFs that are not strictly associated with specific disorders but seem to impact important aspects of NDDs in general, like language development; and 6. Integrative perspectives regarding TFs and NDDs.

1.1 An Overview about Transcription Factors

TFs are proteins with DNA-binding properties that orchestrate the transcriptional machinery, regulating rate, time, location, and several other conditions involved in gene expression. The specific transcriptome from each cell type is governed by a particular set of TFs, which defines cellular identities and programming (Cevallos et al., 2020).

Besides the DNA-binding sites, TFs can contain ligand-binding sites, protein-protein interaction sites, and enzymatic activity domains (Lambert et al., 2018). These features are grouped as effector domains since they actively mediate the functions of the TFs, enabling them to perform several actions such as responding to stimuli, dimerization, regulation of RNA-polymerases functions, and modulation of DNA access by indirect interference on histone modifications (Xin and Rohs, 2018). In humans, over 1,600 TFs have already been described (Lambert et al., 2018), grouped into classes by similarities in the DNA-binding domains. Approximately 90% of the TFs in humans are included in one of the three major classes: Basic Domain, Zinc Coordinating Domain, and Helix-turn-helix Domain (Wingender et al., 2015).

The several contributions of TFs in fundamental biological pathways (like cell cycle, neurodevelopment, and immune activation, for example) highlight the importance of time, location, and context throughout biological development. In *Drosophila* studies, this issue is demonstrated by *Hox* (Homeobox) TFs (which regulates the structure of body plan), since alterations in the transcription of *Hox* along body segments generate abrupt abnormalities like ectopic growth of legs (Kaufman et al., 1980) or duplicated thorax (Weatherbee et al., 1998). In humans, extreme alterations like the described in *Drosophila* are probably incompatible with life; nonetheless, subtle alterations may lead to important impacts - mutations in *TP53* (tumor protein p53), for example, can induce major deregulation of the cell cycle,

resulting in tumor growth (Blagih et al., 2020). Similarly, several single nucleotide polymorphisms (SNP) in TFs were already related to psychiatric disorders (Pearl et al., 2019).

All of the TFs addressed in this review are summarized in Table 1, with information regarding their main DNA-binding domains and the regions or specific cell types where these TFs present higher expression in embryonic tissue (focusing on the nervous system and immune system). In Figure 2, the peak of expression of each TF was demonstrated in the two regions that presented complete information regarding the time course of expression: forebrain and cerebellum. All information was obtained from LifeMap Discovery™ (Edgar et al., 2013) and “Evo-devo mammalian app” (Cardoso-Moreira et al., 2019).

2. Genetic-associated neurodevelopmental disorders

This section discusses the association among NDDs and specific genetic alterations in TFs (mutations, deletions, and other disturbances), focusing on the mechanisms linking TFs and pathophysiology pathways.

2.1 Rett syndrome

Rett syndrome (RTT), the second leading cause of female intellectual disability, is a progressive NDD, affecting one in 10,000 females (Rosenberg and Pascual, 2014). In most cases, RTT is caused by mutations in the *MECP2* gene (methyl-CpG binding protein 2) (Shahbazian and Zoghbi, 2001), and, in a smaller proportion, in the *FOXG1* gene (forkhead box G1 protein), both described as TFs (Ma et al., 2016).

The protein MeCP2 mostly represses gene expression by modifying chromatin access (Ip et al., 2018). Mutations in this gene notoriously impact neurodevelopment (Gonzales and LaSalle, 2010), skeletal muscle growth (Conti et al., 2015), liver metabolism (Kyle et al., 2016), heart function (Wang et al., 2018), and other organs. Males with mutations in MECP2 are often stillborn or do not live past infancy, explaining the higher prevalence in females (Weaving et al., 2005).

Animal models of *Mecp2* deletion or haploinsufficiency improved the understanding of possible outcomes resulting from the loss of this protein activity. *Mecp2*-deficient mice exhibited altered content of GABA and glutamate (in different brain regions in postnatal life) (El-Khoury et al., 2014) and also their receptors (in the CA3 region of the hippocampus) (Calfa et al., 2015), in addition to the loss of the

characteristic barrel field organization in the somatosensory cortex (Lee et al., 2017). The presence of sensory impairments was also observed in zebrafish lacking *mecp2*, probably related to SEMA5B (semaphorin 5B) and ROBO2 (roundabout guidance receptor 2) downregulated expression since these proteins are essential to neuron migration and cortex formation (Leong et al., 2015).

These data emphasize the contribution of MeCP2 in the maintenance of the excitatory/inhibitory balance and the typical organization of the central nervous system (CNS). In this context, deletion of *Mecp2* in mice disrupted the perineuronal net associated with parvalbumin-positive neurons (PV+), inducing enhancement of thalamocortical excitatory inputs to PV+ and, consequently, increasing the inhibitory activity of these cells, which may be related to the “cortex silencing” feature described in RTT patients (Sigal et al., 2019). Silencing or deletion of *Mecp2* impaired long-term memory and learning in the hippocampus due to alterations in chromatin organization of CA1 neurons (Gulmez Karaca et al., 2018) and reduced neuronal connectivity between dentate gyrus and entorhinal cortex (Sun et al., 2019). Moreover, mitochondrial-oxygen consumption is enhanced in hippocampal neurons from *Mecp2*-deficient mice, increasing reactive oxygen species (ROS) and probably impairing the functions of these cells (Can et al., 2019).

Glial cells were also observed to be involved in these models. Astrocytes containing *Mecp2* mutations showed decreased expression of the TF Nr2f2 (nuclear receptor subfamily 2 group F member), besides other relevant genes associated with glutamate metabolism and ion transporters, such as lipocalin-2 and chromogranin B (Delépine et al., 2015). Interestingly, astrocytes derived from RTT patients cannot support neuronal development in co-culture (Williams et al., 2014) since disruptions in MeCP2 decrease the expression of EAAT1/2 glutamate transporters and increase the expression of glutamine synthetase, triggering glutamatergic excitotoxicity (Jin et al., 2017). Microglia derived from *Mecp2*-null mice displayed decreased synaptic pruning ability (Schafer et al., 2016), and metabolic alterations regarding glutamate uptake and ROS generation (Jin et al., 2015).

In oligodendrocytes, the total absence of MeCP2, or even its knockdown, induces alterations in cellular morphology, physiology, and survival (Lipi et al., 2018), and increases several myelin genes, like myelin basic protein (*Mbp*), proteolipid protein (*Plp*), myelin oligodendrocyte glycoprotein (*Mog*), and myelin-associated

oligodendrocyte basic protein (*Mobp*) (Sharma et al., 2015), suggesting an important role of MeCP2 in myelination processes.

The serotonergic system is also affected by *Mecp2* knockout: a 75-fold increased expression of the serotonin receptor 5b (5-ht5b) was observed in the brainstem of *Mecp2*^{-/-} mice, and this alteration disrupted the expected downregulation of this receptor in the following steps of neurodevelopment (Vogelgesang et al., 2017). Interestingly, *Mecp2*-deficient mice also presented alterations in breathing phenotype patterns, which is affected by the 5-ht5b expression (Vogelgesang et al., 2018), emphasizing the relation between serotonin system impairments and MeCP2.

The mutation in the *FOXG1* gene induces severe intellectual, motor, and language disabilities (Ma et al., 2016). Mice with *Foxg1* haploinsufficiency demonstrated enhanced expression of inhibitory synaptic markers (glutamate decarboxylase 67 (GAD67) and GABA AR- α 1) and reduced excitatory synaptic markers (VGLUT1, GluA1, GluN1, and PSD-95) in cell culture and mice embryo. In adults, all markers were reduced, indicating a time-dependent action of FOXG1 throughout synaptic neurodevelopment (Patriarchi et al., 2016). Beyond that, an electrophysiological analysis showed cortical hyperexcitability with increased expression of VGLUT and reduced expression of KCC2, indicating a contribution of FOXG1 in the excitatory/inhibitory balance (Wong et al., 2019).

2.2. Pitt-Hopkins syndrome

Pitt-Hopkins syndrome (PTHS) is a condition marked by ID, psychomotor delay, and, in many cases, ASD features (Goodspeed et al., 2018). Despite being first described in 1978 (Pitt and Hopkins, 1978), the cause of PTHS was only elucidated in 2007 (Amiel et al., 2007; Brockschmidt et al., 2007; Zweier et al., 2007): specific mutations in *TCF4* (transcription factor 4). This member of the basic helix-loop-helix TF family (bHLH) regulates gene expression by forming homodimers and heterodimers that can play different roles depending on their dimerization partners (Jones, 2004). Several TFs can dimerize with TCF4 in the brain, such as ATHO1/MATH1 (atonal homolog 1), ASH1/ASCL1 (achaete-scute homolog 1), and NEUROD1 (neuronal differentiation 1) (Navarrete et al., 2013). The brain expression of TCF4 seems to be evolutionarily conserved in humans, rhesus monkeys, and mice. *Tcf4* haploinsufficiency in mice, for example, replicated anomalies found in PTHS

patients, especially in the regulation of neuronal migration (Jung et al., 2018). Furthermore, the specific knockout of *Tcf4* in the CNS of mice induced whole hippocampal architecture impairments and, in the cortex, delayed neural progenitor differentiation and resulted in neuronal morphology alterations in later stages of development (Schoof et al., 2020).

Recently, these hippocampal disturbances were associated with altered neural migration caused by a disruption in radial glia fibers, possibly mediated by WNT pathway protein *wnt7b* (Wang et al., 2020). Finally, four different mouse models of PTHS highlighted the link between the deficits in the hippocampus-related behaviors and the exaggerated long-term potentiation (LTP) due to increased activation of NMDA receptors in this region (Thaxton et al., 2018).

2.3 Other Genetic Disorders

The SOX (SRY-related HMG-box) proteins have a fundamental role in the developmental regulation (Pillai-Kastoori et al., 2015). Although already described as altered in several disorders, some critical alterations in SOX genes result in distinct conditions categorized as separated syndromes. For example, mutations in *SOX5* are related to Lamb-Shaffer syndrome, characterized by ID and speech delay (Lamb et al., 2012); mutations in *SOX10* are associated with Waardenburg–Hirschprung disease, which is marked by neurosensory deafness (Pingault et al., 1998), and, finally, *SOX9* mutations are related to campomelic dysplasia, also associated with hearing loss (Kwok et al., 1995).

Williams syndrome (WS) is a disorder characterized by mild ID and specific cognitive profiles caused by deletions in 7q11.23, a region that includes the *GTF2i* and *GTF2ird* (general transcription factor) genes (Morris, 2017). In mice, knockout of *Gtf2ird* induced alterations in other important TFs associated with neurodevelopment, like *Hey1* (Hes related family BHLH transcription factor with YRPW motif 1), *Myf6* (myogenic factor 6), *Myog* (myogenin), *Dlx2* (distal-less homeobox 2), *Lhx2* (LIM homeobox 2), *Pou3f3* (POU class 3 homeobox 3), *Sox2*, and *Foxp3* (forkhead box protein P3) (Corley et al., 2016). Either partial or total loss of *GTF2ird* in mice impaired serotonin signaling in the prefrontal cortex. Neurons from layer V of this region demonstrated significantly larger inhibitory outward currents in response to serotonin, which may be associated with the reduced basal anxiety and increased sociability observed in WS individuals (Proulx et al., 2010). Finally, selective deletion of *Gtf2i* in

excitatory forebrain neurons resulted in clinical features of WS and significant impairments in myelination – intervention with a remyelinating drug rescued both oligodendrocytes and behavioral impairments (Barak et al., 2019).

Coffin-Siris syndrome (CSS) is a NDD characterized by ID, facial dysmorphology, microcephaly, and feeding difficulties (Iwamoto et al., 2003). Deletions involving *SOX11* TF were associated with microcephaly, developmental delay, and shared dysmorphic features with CSS. Beyond that, knockdown of *Sox11* in *Xenopus morphants* resulted in diminished head size, confirming this intriguing relation between *SOX11* and microcephaly (Kosho et al., 2014). Interestingly, it was demonstrated that the Zika virus infection of SH-SY5Y neuroblastoma cell line induced important up-regulation of miR (145 and 148a) that target *Sox11*, adding evidence to the role of *SOX11* in microcephaly (Castro et al., 2019).

Dravet syndrome (DS) is a severe type of refractory epilepsy with early life symptoms. The syndrome is characterized by age-related progression of seizures, cognitive decline, and movement disorders (Akiyama et al., 2010). About 80% of the DS cases are caused by a *de novo* mutation in the sodium voltage-gated channel alpha subunit 1 (*SCN1A*) gene, resulting in Nav1.1 haploinsufficiency (Chopra and Isom, 2014). Human transcriptome analysis demonstrated specific dysregulations of genes associated with chromatin structure, mitotic progression, neural plasticity, and excitability in GABAergic neurons derived from patients, with up-regulation of the TFs FOXM1 and E2F (Transcription Factor E2F1), important regulators of histone modifications and cell cycle (Schuster et al., 2019).

The compilation of all TFs described in the “Genetic-associated neurodevelopmental disorders” section was submitted to Reactome® analysis (Wu and Haw, 2017), resulting in a demonstration of enriched biological pathways associated with this group. Table 2 highlights the most relevant, confirming well-known pathways and suggesting possible new fields of study in this context.

3. Environmental factors and TFs in Psychiatric Disorders

Since the discovery of the lac operon system in *E. coli* – the first demonstration of how the transcription machinery works in different environmental contexts (Jacob and Monod, 1961) – several other examples were described in different organisms like fungi (Vicente-franqueira et al., 2018), plants (Song et al., 2016), and animals (Pat

Willmer, 2004) in situations like temperature variation, stress response, immune system modulation and others.

The challenge behind the search for risk factors in psychiatric disorders is understanding how different interactions may converge to a similar outcome. Environmental factors can cause a significant impact on the onset of NDDs along with genetic risk factors (discussed in section 2). Alterations in TFs may be a common point in this multifactorial universe of NDD triggering. In this section, environmental risk factors are discussed, focusing on possible roles in NDDs and psychiatric disorders.

3.1 Maternal Immune Activation

Maternal immune activation (MIA) is associated with the onset of disorders such as ASD and schizophrenia (Fontes-Dutra et al., 2020). MIA induction by poly(I:C) exposure enhanced PAX6 (paired box 6) expression in mice embryos resulting in cell cycle impairments, and increased number of cortical neurons expressing COUP-TF interacting protein 2 (CTIP2) in deeper layers (V and VI) (Ben-Reuven and Reiner, 2019). In a complementary finding, *in vitro* exposure of neuronal progenitors to high doses of IL-6 (mimicking MIA) increased STAT3 (signal transducer and activator of transcription 3) phosphorylation and reduced the differentiation of neurons that express CTIP2 and TBR1 (T-box brain transcription factor 1) (Zuiki et al., 2017). We hypothesize that these differences occur due to the TFs activated in each model: enhanced PAX6 expression, a pivotal regulator of neuronal processes, is associated with increased CTIP2⁺ cells since this TF is a major regulator of deeper cortical layers. On the other hand, IL-6 leads to the activation of STAT3, which, in neural progenitors, was already associated with increased astrogliogenesis and suppressed neurogenesis (Hong and Song, 2015, Chen et al., 2014), explaining the decreased number of neuronal cells expressing CTIP2 and TBR1.

MIA-induced by poly(I:C) in mice increased REST/RE-1 (RE-1 silencing transcription factor) expression, resulting in decreased expression of KCC2 cotransporter, delaying the switch of GABA function from excitatory to inhibitory in mice embryos (Corradini et al., 2018). In addition, a decreased forebrain expression of ARX (aristaless related homeobox), was associated with PV⁺-neurons impairments (Nakamura et al., 2019) in the same model. In an LPS-induced MIA, the fetus presented reduced expression of the TFs *Dlx* 1, 2, and 5 (distal-less homeobox), which are involved in the generation and migration of GABAergic interneurons (Oskvig et al.,

2012). Finally, MIA-induced microglial activation was influenced by the decreased expression of the TF *Pu.1* (transcription factor PU.1) - in this case, epigenetic changes impaired the expression of this TF (Mattei et al., 2017; Yeh and Ikezu, 2019).

Some viral infections are also described as environmental risk factors during pregnancy. For example, the STAT-binding V protein, an important virulence factor in the rubella infection, can impair the functions of STAT, a TF involved in interferon signaling and synaptic plasticity processes (Ramachandran et al., 2008). Also, the rubella virus itself can interfere in the expression of *Rax* (retina and anterior neural fold homeobox) and *Six3* (sine oculis homeobox homolog) TFs (Bilz et al., 2019), importantly related to eye and brain development. In neural progenitor cell culture, the cytomegalovirus early protein 1 (IE1) decreased *Sox2* expression by inhibiting phosphorylation of STAT3 (Wu et al., 2018) and downregulated *Hes1* (Hes family BHLH transcription factor 1) (Liu et al., 2017; Wu et al., 2018), leading to cell cycle and migration disturbances.

3.2 Effects of Teratogens

The environmental risk factors during pregnancy (Lein, 2015) also include chemical treatments such as the antiepileptic valproic acid (VPA), a well-demonstrated risk factor to ASD (Christensen et al., 2013). Adult hippocampal neural progenitors exposed to VPA *in vitro* increased the expression of *NEUROD1*, a TF involved in neuro/glial differentiation (Hsieh et al., 2004). In a complementary way, mice embryos exposed to VPA upregulated *Pou3f1* and *Sox4*, downregulated *Egr2* (growth response protein 2) (Okada et al., 2005), and altered the expressions of neurogenin 2 (NGN2), *NEUROD1*, and *PAX6* (Kim et al., 2014) in a time-dependent way. Interestingly, *PAX6* alterations (like increased acetylated histone binding to the gene promoter region), which were more prominent, are related to the VPA histone deacetylase (HDAC) inhibition feature (Kim et al., 2014). Moreover, postnatal analysis of mice exposed to VPA during pregnancy showed decreased expression of *Hes1* and *Pax6* mRNA in the cerebral cortex, suggesting a possible long-term effect of these TFs in brain development (Kawada et al., 2018). The set of evidence emphasizes the major impact of VPA in the TF machinery associated with cell cycle, apoptosis of neural tube cells, histone modulation, and brain organization.

Ethanol (Et-OH) consumption during pregnancy causes fetal alcohol syndrome (Gupta et al., 2016), a disorder that shares several features with ASD. Similar to VPA,

Et-OH impairs *Pax6* expression in murine embryos (Aronne et al., 2008) and disrupts correct cell lineage differentiation, mainly by modulation of POU5F1 and SOX2 (Sánchez-Alvarez et al., 2013). In a study using zebrafish embryos exposed to Et-OH, besides *sox2*, sixty TFs associated with gastrulation processes demonstrated altered expression (mostly downregulated) (Sarmah et al., 2020). Interestingly, both human progenitor neural cells and mouse embryos demonstrated abnormal activation of HSF1 (heat-shock transcription factor 1), leading to neuronal migration impairments and periventricular heterotopia (Ishii et al., 2017).

Folate intake during pregnancy is necessary to prevent neural tube-associated alterations like spina bifida and myelomeningocele (Pachón et al., 2013); however, the regulation of dosage is essential since high doses are potentially deleterious (Mudryj et al., 2016). An *in vitro* study demonstrated that folate receptors, which have TF function, regulate the expression of other TFs involved in neurodevelopment like *Sox2* and *Klf4* (kruppel like factor 4) (Mohanty et al., 2016). Interestingly, in a neural tube defect animal model based on the deletion of *Pax3*, supplementation with folate restored the proliferative status of the neuroepithelium, demonstrating a possible common pathway regarding PAX3 and folate signaling (Sudiwala et al., 2019). Analysis of DNA methylation patterns in blood and tissue from the human umbilical cord demonstrated that folate deficiency during pregnancy is associated with methylation alterations in HOX, LIM, PAX, and TBOX TF families (Sakurai et al., 2019). On the other hand, excessive supplementation in mice induced dysregulated expression of *Fos* (FBJ osteosarcoma oncogene), *Maff* (MAF B ZIP Transcription Factor F), and EGR2, in addition to inducing behavioral and weight alterations (Chu et al., 2019).

3.3 Lesion Events

Perinatal complications like fetal or early postnatal hypoxia are also associated with neurodevelopmental impairments and expression changes in TFs, especially in the hypoxia-induced factors (HIF) (Dengler et al., 2014). The expression of HIF-2 α , *in vitro*, upregulated the solute carrier transporter 7a5 (SLC7A5) in differentiated neuronal cells, followed by impaired transport of branched-chain amino acids in the brain (Onishi et al., 2019) - a feature already described in ASD (Maynard and Manzini, 2017). While early postnatal hypoxia in mice decreased expression of Olig2 (oligodendrocyte transcription factor 2) (van Tilborg et al., 2018), transient hypoxia in

postnatal day 7 induced a complex time-course pattern of high and low expression of Olig2, Ascl1, and Nkx2-2 (NK2 Homeobox 2) TFs, followed by oligodendrocyte maturation impairment (Affeldt et al., 2017). Finally, GWAS comparison of schizophrenia and hypoxic-ischemic response associated genes in humans demonstrated significant overlap of changes in TFs like TCF4 and ZEB2 (zinc finger E-box binding homeobox 2) (Schmidt-Kastner et al., 2020). The compilation of all TF described in the “Environmental factors and TF in Psychiatric Disorders” section was submitted to Reactome® (Wu and Haw, 2017) analysis resulting in a demonstration of enriched biological pathways associated with this group. In Table 3, the most relevant are highlighted, demonstrating important overlays with ASD and schizophrenia.

4. NDD-associated multifactorial disorders

This section discusses ASD and schizophrenia, two disorders with an intricate contribution of both genetic and environmental risk factors. The diversity of effects in the TFs may be associated with the broad spectrum within the disorders and the interaction between genes and environment throughout the neurodevelopmental timeline.

4.1 Autism Spectrum Disorder (ASD) and TFs

ASD is a multifactorial NDD determined by a set of characteristics, including stereotyped or restricted behaviors and impairments on social interaction and communication (American Psychiatric Association, 2013). Genetic studies analyzing populations or families with ASD cases already demonstrated many alterations in TFs associated with neurodevelopment. One study comparing autistic subjects with unaffected siblings, focused on 64 genes implicated in neurodevelopment, highlighted mutation events in nine genes, three being TFs: *TBR1*, *ADNP* (activity-dependent neuroprotector homeobox), and *PAX5* (O’Roak et al., 2014).

Alterations in *TBR1* are classically related to ASD (O’Roak et al., 2012), and, more recently, mutations in this gene were also associated with neocortical malformations in humans (like pachygyria) (Nambot et al., 2020; Vegas et al., 2018). Furthermore, in animal models, loss-of-function or deletion of *TBR1* resulted in connectivity issues in layer VI neurons from the neocortex (Fazel Darbandi et al., 2018). These cells also presented disrupted expression of the laminar identity markers

(Bedogni et al., 2010), indicating the contribution of TBR1 during neuronal migration and cortical organization.

Critical mutations on *ADNP* are described in the Helsmoortel-Van der Aa syndrome, a rare condition with substantial overlap with ASD (Arnett et al., 2018). *ADNP* can play essential roles in autophagy (Sragovich et al., 2017), cell cycle regulation (Mollinedo et al., 2019), neuronal migration, and maturation (Helsmoortel et al., 2014). In animal models and clinical studies, supplementation with peptides derived from *ADNP* demonstrated interesting neuroprotective results (regulation of glutamatergic synapses and microtubule conservation, for example) in ASD (Gozes et al., 2009; Javitt et al., 2012; Sragovich et al., 2019).

Finally, *PAX5* has recently emerged as a gene associated with ASD, with incipient descriptions of its function during neurodevelopment. The deletion of *PAX5* in GABAergic neurons led to malformations in the ventricles, triggering a hydrocephalus-like condition, which may imply that this factor is pivotal in processes like neuron maturation and cytoarchitecture organization (Ohtsuka et al., 2013).

In the Lamb-Shaffer syndrome, a disorder associated with autistic traits, several microdeletions and truncating variants in *SOX5*, were observed (Zawerton et al., 2020). The attenuation in the expression of the *SOX5* gene in different brain regions seems to be related to splicing alterations and the generation of regulatory molecules like lncRNA (Parikshak et al., 2016). *Sox5*-null mice displayed an immature pattern of layer VI neuron expression, as well as impairments on corticothalamic connectivity, demonstrating important roles of this factor on corticogenesis (Kwan et al., 2008).

The impairments of several neurotransmitter systems in ASD are widely described and these changes may involve several TFs. Biallelic disruptions in *RARB* (retinoic acid receptor beta) and *FEV* (fifth ewing variant protein) were identified as altered in ASD (Doan et al., 2019). *RARB* targets were altered both in animal models and humans, demonstrating the translation in *RARB* alterations mediating the retinoic acid pathway (Moreno-Ramos et al., 2015), while *FEV* is mainly expressed in raphe nuclei (Iyo et al., 2005), especially in serotonergic neurons (Maurer et al., 2004), being necessary for both the differentiation and the synthesis of serotonin. Finally, a meta-analysis of GWAS studies demonstrated significant alterations in the *PITX3* (paired like homeodomain 3) gene (The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017), a TF that is related to the differentiation of dopaminergic neurons (and dopamine synthesis) in the midbrain, and was already

described in the context of Parkinson disease (Li et al., 2009) and ocular developmental defects (Zazo Seco et al., 2018).

Recently, new TFs were described in the context of ASD, including SHOX (short stature homeobox) (Tropeano et al., 2016), a TF associated with short stature disorders (Fukami et al., 2016), and ZNF292 (zinc finger protein 292), both TFs with important expression in the developing brain (Mirzaa et al., 2020) (Durand et al., 2011). The possible roles of these TFs in NDD are still to be unveiled.

Moreover, alterations in the interaction components of TFs were described as relevant in the context of ASD. A specific SNP was associated with less DNA binding of MAZ (MYC associated zinc finger protein), resulting in lower expression of oxytocin receptor (OXTR) gene and possibly contributing to impairments in the oxytocin signaling (de Oliveira Pereira Ribeiro et al., 2018), suggesting a new mechanism behind oxytocin questions in ASD. In addition, an up-regulation of *ATF6* (activating transcription factor 6) was observed in the *postmortem* hippocampus of ASD patients (Dong et al., 2018). This TF interacts with misfolded proteins, inducing chaperone transcription (Adachi et al., 2008).

4.1.1 TF roles in the neuroimmune component of ASD

In addition to the neurodevelopmental impairments, changes in the immune system (including neuroinflammation) play an important role in ASD, being often described as a hallmark of this disorder (Deckmann et al., 2018; Gottfried et al., 2015; Masi et al., 2017; Siniscalco et al., 2018). Interestingly, several TFs also mediate these neuroimmunological issues. Recently, NRF2 (nuclear factor, erythroid 2-like 2) - a basic leucine zipper TF that protects the immune cells against inflammation and pro-oxidating agents - was downregulated in monocytes of ASD subjects, whereas inflammatory (NF κ B, IL-6, IL-1 β) and nitrate stress (iNOS, nitrotyrosine) parameters were increased (Nadeem et al., 2020).

The T-bet (T-box transcription factor 21), GATA3 (GATA-binding protein 3), STAT3, ROR γ t (RAR-related orphan receptor gamma), and FOXP3 TFs play an important role in Th1 (T-bet), Th2 (GATA3), Th17 (STAT3/ROR γ t) and Treg (FOXP3) commitment lineages from naïve CD4⁺ T cells (Deckmann et al., 2018). Peripheral blood mononuclear cells (PBMC) from ASD patients demonstrated lower levels of FOXP3 and higher levels of ROR γ t/STAT 3, T-bet, and GATA3, together indicating a deficit in Treg differentiation and an imbalance of TFs related to Th1/Th2/Th17

response (Ahmad et al., 2017c). Besides that, HELIOS (expressed by FOXP3⁺ T cells and associated with T cell differentiation) was downregulated, both in mRNA and protein expression levels, suggesting that this TF is pivotal in the ASD immune imbalance (Ahmad et al., 2018e). Likewise, granulocyte-macrophage colony-stimulating factor (GM-CSF) expressed by CD45 cells was increased in children with ASD, whilst numbers of CD45⁺HELIOS⁺ and CD45⁺Stat6⁺ cells were lower, corroborating the involvement of TFs in the regulation of the immune system and demonstrating the need for further investigations (Ahmad et al., 2020).

Another interesting animal model to ASD study is the BTBR T⁺ Itpr3tf/J (BTBR), a genetic model that presents low levels of social behavior and high levels of repetitive behavior (Ryan et al., 2019). CD8⁺ T cells from BTBR animals produced higher levels of IL-17A, RORγT, IL-22, T-bet, and STAT3 and lower levels of inducible costimulator (ICOS) and FOXP3. CD4⁺ T cells, in turn, produced elevated levels IL-17A, IL-21, IL-22, IFN-γ, T-bet, RORγt, and STAT3, and diminished levels of FOXP3 and HELIOS (Ahmad et al., 2018b, Ahmad et al., 2018c, Ansari et al., 2017). Alterations in mRNA and protein expression levels of IL-17A, RORγT, IL-22, T-bet, STAT3, pSTAT-3, IL-10, and FOXP3 were observed in the brain tissue (Ahmad et al., 2019).

BTBR mice also exhibited decreased CD4⁺IL-21⁺, CD4⁺IL-22⁺, CD4⁺GATA3⁺, and CD4⁺T-bet⁺, and increased CD4⁺CTLA-4⁺ (cytotoxic T lymphocyte-associated gene-4) expression in spleen cells, in addition to increased mRNA and protein expression levels of IL-21, IL-22, GATA3, and T-bet in brain tissue (Ahmad et al., 2017a). Departing from previous evidence, BTBR mice showed lower levels of FOXP3⁺ and higher levels of T-bet⁺, GATA-3⁺, and RORγt⁺ production in CD4⁺ T cells (Bakheet et al., 2017), shedding light on how the BTBR animal model reproduces the complexity in immune impairments observed in ASD subjects.

When the neuroimmune response mediated by toll-like receptors (TLR), NF-κB signaling, nitric oxide synthase (iNOS), and cyclooxygenase (COX-2) expression was evaluated, results showed elevated CD4⁺TLR2⁺, CD4⁺TLR3⁺, CD4⁺TLR4⁺, CD4⁺NF-κB⁺, and CD4⁺iNOS⁺ levels in spleen cells and increased TLR2, TLR3, TLR4, NF-κB, iNOS, and COX-2 mRNA expression levels in brain tissue (Ahmad et al., 2018a). Further, BTBR mice showed increased levels of IL-6⁺, TNF-α⁺, IFN-γ⁺, and STAT3⁺ in CD4⁺ spleen cells, and increased both mRNA expression and protein expression of IL-6, TNF-α, IFN-γ, JAK1, and STAT3 in brain tissue (Ahmad et al., 2018d). Altogether, these recent studies demonstrate an important connection

between TFs and the neuroimmune alterations present in ASD, with interesting evidence of diminished Treg and increased Th1/Th17 responses, suggesting new targets for study.

4.1.2 Complementary evidence of TF in ASD animal models

Animal models are pivotal to understand the biological pathways altered as a result of genetic issues. CHD8 haploinsufficiency in mice triggered ASD-like behaviors, such as repetitive behavior and impaired sociability. CHD8 acts by remodeling the chromatin through ATP-dependent activity, regulating the expression of many genes, such as β -catenin (Katayama et al., 2016), which has a pivotal role in the canonical WNT signaling pathway - directly implicated in ASD pathophysiology (Kwan et al., 2016). In addition, CHD8 mutations were associated with neurodevelopmental delay and abnormal activation of REST - a known neuronal gene regulator capable of physically interacting with CHD8 (Katayama et al., 2016). This is particularly interesting since it suggests a significant association between two genes in ASD, a chromatin remodeler (CHD8) and a TF (REST). Thus, the ASD pathophysiology could (at least partially) be explained by the remodeling of chromatin, facilitating the transcription of specific genes that may be related to the onset of this disorder.

Brain alterations related to changes in TFs include cortical and hippocampal structure, synaptic composition, and neuronal maturity and function – critical events in several psychiatric conditions. This is the case of EN2 (engrailed homeobox 2), a TF with conflicting associations with ASD in humans (Benayed et al., 2009; Gharani et al., 2004; Yang et al., 2008). In mice, knockout of *En2* resulted in several ASD-like behavioral alterations, including loss of sociability and impairments in fear conditioning and water maze learning (Brielmaier et al., 2012). In the same model, a reduction in the mRNA expression of GABAergic markers in the cortex and hippocampus (Sgadò et al., 2013) was observed, suggesting that these impairments might be time and layer-dependent (Allegra et al., 2014), which should be considered in the studies with humans. In addition, recent evidence demonstrates alterations in sensory features in *En2*-null mice, including impaired processing of taste (Gupta et al., 2018) and reduced connectivity in the somatosensory cortex, combined with increased activity of the basolateral amygdala after sensory tasks (Chelini et al., 2019). These data indicate a possible increased aversion component in the context of non-aversive sensory stimuli,

which is typical in ASD (Balasco et al., 2020). Finally, other aspects like decreased serotonin content (more critical at a young age) in the cerebellar cortex (Viaggi et al., 2015) and monoamine system impairment were already described (Genestine et al., 2015).

In rodent models, conditional alteration of *Tshz3* (teashirt zinc finger homeodomain 3) is explored as a translational approach to the 19q12q13.1 heterozygous deletion syndrome, a condition that shares similarities with ASD (Chowdhury et al., 2014). In this scenario, the haploinsufficiency of *Tshz3* in mice decreased the interest in social novelty and increased stereotypy, downregulated genes associated with dendritic extension, neuronal glutamate release, and increased LTP in corticostriatal connections (Caubit et al., 2016). Moreover, approximately 50% of the affected genes have a human ortholog described in ASD, highlighting glutamatergic synapses as a key subject in this model (Chabbert et al., 2019).

The presence of an SNP in a regulatory element, called I56i, identified in ASD patients (Hamilton et al., 2005) decreased DLX5/6 transcriptional activity in GABAergic interneurons from embryonic to postnatal life (Poitras et al., 2010), impairing cell migration, maturation, and survival (Lindtner et al., 2019). Another TF demonstrated significant action in these neurons: FOXP1 upregulation increased the number of GABAergic neurons in organoids derived from ASD patient cells (Mariani et al., 2015). In mice embryos, heterozygous loss of FOXP1 impaired dendritic morphology and neuronal migration in cortical neurons (Li et al., 2019b).

VPA-exposed rat offspring showed increased PAX6 expression, with higher postnatal glutamatergic neuronal differentiation, possibly related to the VPA-induced HDAC inhibition (Kim et al., 2014). Moreover, propionic acid-exposed animals decreased the expression of TCF4 in the hippocampus, resulting in granule cell impairments (Choi et al., 2018). TCF4 alterations, although more prominent in schizophrenia, have relevance in ASD: gain of function of TCF4 impairs the prefrontal cortex, with disruption of columnar organization of layers II/III, as observed in ASD patients (Page et al., 2018b). Moreover, a chromatin immunoprecipitation study demonstrated that TCF4 also binds to different sites associated with ASD (Forrest et al., 2018).

The compilation of all TF described in the “Autism Spectrum Disorder and TFs” section was submitted to Reactome® (Wu and Haw, 2017) analysis resulting in a demonstration of enriched biological pathways associated with this group. Table 4

highlights the most relevant, like the immune system, gene transcription, protein metabolism, cell signaling, and development.

4.2. Schizophrenia and TFs

Schizophrenia is a disorder characterized by the presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (American Psychiatric Association, 2013).

The *SOX11* gene was identified as a candidate gene for greater susceptibility to schizophrenia in a GWAS study in the Chinese Han population (Sun et al., 2020). *SOX11* is expressed early in development, playing roles in cell fate, survival, and differentiation during neurodevelopment and organogenesis (Angelozzi and Lefebvre, 2019; Chew and Gallo, 2009). Moreover, a meta-analysis of GWAS found an overlap in regions implicated in schizophrenia and ASD in *FOXP3* and ATPase plasma membrane Ca²⁺ transporting 2 (*ATP2B2*) genes (The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017). This is particularly interesting since *FOXP3* is an essential regulator of the immune system (Taylor et al., 2020), and *ATP2B2* regulates intracellular calcium homeostasis, necessary for appropriate synaptic connections (Yang et al., 2013).

In addition, the GWAS study pointed to genetic correlations of neurodevelopmental genes such as exostosin glycosyltransferase 1 (*EXT1*), astrotactin 2 (*ASTN2*), mono-ADP ribosylhydrolase 2 (*MACROD2*), and HDAC4 with schizophrenia and ASD. *EXT1* gene is related to heparan sulfate synthesis, presenting a higher expression profile during the early postnatal period in the brain (mainly in the cortex and hippocampus formation) and around birth in the cerebellum (Inatani and Yamaguchi, 2003). Altered copy number variations (CNV) of the *ASTN2* gene - involved in recycling vesicles in cerebellar neurons, (Behesti et al., 2018) - are associated with NDDs, such as ASD. *MACROD2* regulates the processes involved in mono-ADP-ribosylation (Žaja et al., 2020). It is expressed in neuronal cells at embryonic day 16.5 and reaches the peak of expression at postnatal day 8, especially in the cortical layers II–V, and then gradually decreases through P30 (Ito et al., 2018). Lastly, HDAC4 plays a significant role in gene expression regulation related to synaptic plasticity, neuronal survival, and neurodevelopment (Ronan et al., 2013; Wu et al., 2016).

Several *postmortem* studies elucidated important region-specific features in the context of psychosis and schizophrenia. SP1 and SP4 (Sp transcription factor) are zinc-finger TFs with increased levels in the hippocampus and the cerebellum of chronic schizophrenia patients (Pinacho et al., 2014). The blockage of NMDAR caused similar alterations in these factors, suggesting involvement in glutamatergic pathways. Moreover, SP4 has been described as a GABAAR regulator, highlighting the possible influence on E/I balance (Pinacho et al., 2015).

A recent study showed differential expression patterns and rare variants in genes related to neural cell genesis and glial differentiation in individuals with schizophrenia (Chen et al., 2018). One of these genes was the *Pou3f2* gene, a TF involved in cognitive function and adult hippocampal neurogenesis (Hashizume et al., 2018). Interneurons also seem to be affected by disturbances in TFs: an analysis of the prefrontal cortex from schizophrenia patients demonstrated an elevation in the expression of *MAFB* and the coactivator PGC-1 α (Volk et al., 2016), which are deeply related to PV and SST development and function, suggesting possible immaturity of these cells or compensatory mechanisms.

NPAS4 (neuronal PAS domain protein 4) is a brain-specific TF that can modulate schizophrenia symptoms (Alachkar et al., 2018; Shepard et al., 2019). This protein is present in both excitatory and inhibitory neurons, regulating the excitability by increasing the activity of the interneurons in neural circuits (Spiegel et al., 2014). The deficiency of NPAS4 affects the expression of many GABAergic targets in the prefrontal cortex (PFC), such as PV and GAD67 (Shepard et al., 2017). When combining NPAS4 deficiency and adolescent stress, mice showed altered performance in cognitive flexibility on the extra-dimensional set shift task and altered expression in GABAergic markers (Page et al., 2018a).

Npas4 wild-type mice showed a decreased percentage of PV cells in PFC after adolescent stress when compared to heterozygous mice (Page et al., 2018a). Moreover, the relation between NPAS4 expression and behavioral alterations was confirmed using transgenic Cre-Lox mice, elucidating the contributions of NPAS4 in the regulation of excitatory and inhibitory balance, as well as in behavior in schizophrenia animal models (Shepard et al., 2019).

LHX6 presents a cysteine-rich zinc-binding domain, the LIM domain, whereas SOX6 presents a conserved high mobility group (HMG) DNA-binding in the minor groove of DNA. Altogether, both LHX6 and SOX6 regulate crucial neurodevelopmental

processes, such as specification, migration, and maturation of PV and SST neurons (Volk et al., 2012). In *postmortem* samples of PFC from individuals diagnosed with schizophrenia, reduced mRNA levels of *Lhx6* and *Gad67* were found, but there were no significant differences of *Sox6* and calretinin (Volk et al., 2012). Furthermore, in a cohort of schizophrenia individuals, reduced levels of *Lhx6* and *Gad67* mRNA levels were observed in the cortex. In parallel, the same study evaluated monkeys throughout postnatal life, pointing out declining levels of LHX6 from perinatal to prepubertal life (Volk and Lewis, 2014). These crucial data highlight the important roles of LHX6 in GABAergic alterations in the pathophysiology of schizophrenia.

Another signaling pathway implicated in many NDDs is the JAK/STAT1, with roles regarding the activation of a proinflammatory profile in circulating immune cells (Ahmad et al., 2017b; Sharma et al., 2017). Recently, a study measuring the activation of this pathway in individuals with psychosis, early in the illness and hospitalized with acute exacerbation of psychosis, showed that JAK-STAT1 related gene expression is suppressed in both groups. The expression normalized in individuals with chronic or longer illness duration, indicating a temporal and contextual regulatory profile of JAK/STAT1 signaling pathway and highlighting roles of the immune system in the pathophysiology of schizophrenia (Melbourne et al., 2019).

Like animal models, *in silico* approaches can provide relevant information and mechanistic evidence about the roles of TF in neurodevelopment. A recent study, which analyzed neuronal migration and corticogenesis data, identified eight functional modules involving Disrupted-in-schizophrenia 1 (DISC1) gene and its interacting proteins that regulate neuronal migration processes, such as STAT3, TCF3, and TAL1 (John et al., 2019).

4.2.1 The prominent role of TCF4 in schizophrenia

In the context of schizophrenia, one TF has particular relevance: TCF4. TCF4 is known to be intimately related to PTHS (Amiel et al., 2007), and interestingly, in schizophrenia, many altered biological pathways have a significant association with this TF. Since the late 2000s, when the first study associating alterations in TCF4 and schizophrenia was released (Stefansson et al., 2009), several other studies consolidated and demonstrated the relevance of TCF4 in psychotic episodes and bipolar disorder (Gao et al., 2020; Hall et al., 2014; Ripke et al., 2014; Steinberg et al., 2011).

In animal models, it was demonstrated that overexpression of TCF4 in mice resulted in sensorimotor and fear conditioning impairments, highlighting the relevance of TCF4 in cognitive processes (Brzózka et al., 2010, Brzózka et al., 2016; Brzózka and Rossner, 2013). Analysis of *Tcf4* polymorphisms in humans with schizophrenia confirmed the influence of this TF in processes like verbal declarative memory (Lennertz et al., 2011), attention-related tasks (Zhu et al., 2013), problem-solving tasks (Albanna et al., 2014), and lower cognitive performance (Hui et al., 2015). In addition, TCF4 mRNA levels were related to positive- and negative-symptoms (Wirgenes et al., 2012), and cognitive impairments (Alizadeh et al., 2017), consolidating the role of this TF in high-functioning integrative processes.

Knockdown of *Tcf4* in neural-lineage cells increased transcription of genes related to cell cycle control, specifically proliferation (Hill et al., 2017). Besides that, phosphorylation promoted by protein kinase A (PKA) also seems to be related to the TCF4 activity both *in vitro* and *in vivo* in response to Ca^{2+} influx (Sepp et al., 2017). Likewise, the WNT/ β -Catenin pathway also influences the transcription and activity of *Tcf4* since the activation of WNT/ β -Catenin mediated by pharmacological intervention increased TCF4 mRNA levels (Hennig et al., 2017). Some evidence involving changes in WNT/ β -Catenin pathway and schizophrenia includes shortening of cell cycle (Fan et al., 2012), weakening of the blood-brain-barrier associated with alterations in PKA (Nishiura et al., 2017), and disruptions in glutamatergic signaling (Uematsu et al., 2015; Zhao et al., 2019). Complementary evidence of disruption in the WNT pathway includes hyperactivation in the presence of DISC-1 (Brandon et al., 2009), imbalance between canonical and non-canonical signaling, and altered mRNA levels of WNT-related genes (Hoseth et al., 2018). Therefore, TCF4 may be the convergent point of relevant alterations in the context of neurodevelopment, synaptic plasticity, and cell signaling.

The necessity to understand how TCF4 works in the context of other genomic alterations in schizophrenia was clarified by wide chromatin immunoprecipitation (ChIP) assays and *in silico* approaches. The identification of TCF4 in a ChIP assay in SH-SY5Y cells demonstrated that this TF is majorly related to genes involved in axonal and neuronal development, especially those expressed in the pyramidal neurons of the somatosensory cortex. Additionally, the results also confirmed prior studies that suggested targets of TCF4 by using interference RNA techniques or *postmortem* transcriptomic analysis of patients with schizophrenia (Xia et al., 2018). A

transcriptional analysis of the dorsal PFC and olfactory neuroepithelium of schizophrenia subjects demonstrated that TCF4 is a major regulator in transcriptional networks in both regions. When comparing cell lineages with TCF4 knockdown, the impact on these networks was increased in neuronal progenitor lineages compared to mature glutamatergic neurons, suggesting that TCF4 may be pivotal in early developmental processes (Torshizi et al., 2019).

TCF4 studies faced a vital limitation in animal models: homozygous knockout was extremely deleterious, resulting in the death soon after birth (Forrest et al., 2013). *Tcf4* haploinsufficiency in mice resulted in substantial behavior impairments, such as in social interaction, vocalization, fear conditioning, learning, and memory, which are improved by inhibiting or silencing HDAC function, suggesting a possible pathway involved in TCF4 action (Kennedy et al., 2016). A comparison between human and mouse embryos demonstrated that TCF4 is expressed in the same regions across time in both species (initially in transient regions of proliferation and then in neurons during migration) and has similar regulation by associated TF TCF3. TCF4 haploinsufficiency was also related to impairments on neuronal migration, cortical composition, and synaptic structure (Li et al., 2019a). Similarities between humans, rhesus monkeys, and mice regarding TCF4 alterations demonstrated structural brain abnormalities similar to PTHS (Jung et al., 2018).

Interestingly, a study with *Drosophila* demonstrated that silencing of *TCF4* orthologue *Da* resulted in synaptic and locomotor impairments (Tamberg et al., 2020). These results highlight the important conservation of TCF4 function in several species, especially regarding neurodevelopment. Although the animal models may be more related to PTHS, their insights about pathways involved in schizophrenia are fundamental to guide further investigations in this theme.

Genetic alterations are not unusual, and the interactions between may underlie several impairments. Disruption in two TFs relevant to schizophrenia (TNR1 and TCF4) resulted in a similar outcome in mouse primary neuronal cultures: decreased synaptic content and neuronal proliferation, probably associated with disruptions in syntaxin-mediated neurotransmitter release pathway (Rosato et al., 2019). Likewise, using *in silico* approaches, six genes (*CNTN4*, *GPM6A*, *MMP16*, *PSMA4*, *GATAD2A*, and *TCF4* - the last two are TF) are highlighted as a significant cluster associated with schizophrenia - when knockdown of this group was replicated in SH-SY5Y cells, major issues regarding proliferation were observed. This set of evidence brings attention to

the fact that polygenetic risks need to be considered to better understand the condition (Ma et al., 2018).

The compilation of all TF described in the “Schizophrenia and TFs” section was submitted to Reactome® (Wu and Haw, 2017) analysis resulting in a demonstration of enriched biological pathways associated with this group. Table 5 highlights the most relevant, like the immune system, gene transcription, cell signaling, and development.

5. Intellectual Disabilities (ID) and TFs

In this section, TFs related to ID, language impairments, and other characteristics not necessarily strictly associated with specific disorders are discussed since the pathways involved may be relevant in several conditions.

FOX proteins are a highly conserved group of TFs with many different functions including cell cycle regulation, energetic metabolism, and stress resistance (Golson and Kaestner, 2016). A subset of this group, FOXP, have important relations with cognitive processes, especially language and speech development (Hamdan et al., 2010; Lai et al., 2001).

Researchers observed an association of a family-related language impairment (which included speech and written alterations) with a missense mutation on the *FOXP2* gene that disrupted the DNA-binding domain (Lai et al., 2001). Since then, the “KE family” improved the understanding of the pathways behind language, and alterations in *FOXP2* were analyzed in several other disorders, including ASD and schizophrenia (Oswald et al., 2017). The mechanisms related to FOXP2 activity are still unclear; however, important animal studies brought insights regarding this theme.

An analysis in zebra finch demonstrated that both humans and songbirds have similar patterns of FOXP2 brain expression throughout development, especially in regions associated with sensorimotor integration, which are important in both species for the modulation of vocal expression (Teramitsu et al., 2004). Studies with *Foxp2*-mutations in mice showed important alterations in the basal ganglia regarding dopamine levels, synaptic plasticity, and neuronal morphology (Enard, 2011). Disruptions on cortico-basal ganglia circuits may be related to MEF2C (myocyte-specific enhancer binding factor 2C) TF, which represses striatal synaptic and spinogenesis and is repressed by FOXP2; thus, defects in FOXP2 may lead to a disinhibition of MEF2C (Chen et al., 2016). Additionally, FOXP2 also seems to increase GABAergic inhibition on D1 positive neurons in striatum, impairing the

dopaminergic signaling (van Rhijn et al., 2018) and playing important role in the maturation of excitatory cortical neurons (Hickey et al., 2019).

In the behavioral field, FOXP2 alterations were associated with social impairments (Medvedeva et al., 2019), probably related to modifications in the pattern of ultrasonic vocalizations (Chabout et al., 2016; Gaub et al., 2016). Interestingly, modifications in FOXP2 restricted to other structures like cartilage also caused impairments on vocalizations and motor skills, indicating a convergent role of this TF in brain circuitry and skeletal development (Xu et al., 2018).

FOXP1 descriptions in the context of psychiatric disorders started in 2009, with a report that a chromosomal deletion in this TF was associated with speech delay, muscular tone alterations, and malformations (Pariani et al., 2009). Although similar to FOXP2, when observing language impairments, FOXP1 demonstrated an important association with ID, autistic-like features, and epilepsy, which highlighted its global spectrum of action. Interestingly, recent articles observed that similar alterations in *FOXP1* and *FOXP2* resulted in different phenotypes: while FOXP2 seemed to be restricted to verbal impairments, FOXP1 was confirmed to cause more broad and severe issues in the context of the NDDs (Sollis et al., 2017). The fact that FOXP1 also interferes in language may be explained by its interaction with FOXP2: even when altered by mutations, FOXP1 retained the ability to interact with FOXP2, which may end up disrupting FOXP2 action (Sollis et al., 2016).

Homozygous brain loss of FOXP1 in an animal model resulted in a decreased number of neurons in the striatum and excitatory/inhibitory imbalance in the CA1 area of the hippocampus, as well as autistic-like behaviors including stereotypy and social impairments (Bacon et al., 2015). In addition, *FOXP1* deletion seems to disrupt the expression of genes related to synaptic plasticity, LTP, and spatial learning in the hippocampus and genes related to the identity of neurons of the somatosensory cortex (Araujo et al., 2017). Important alterations found in models with total or partial *FOXP1* deletion include reduced pup ultrasonic vocalization, and loss of the sex-associated differences in these vocalizations (probably by an interesting relation of FOXP1 and androgen hormones) (Fröhlich et al., 2017), in addition to motor issues related to gastrointestinal function (Fröhlich et al., 2019). Moreover, the ASD-related nonsense mutation in FOXP1 induced autophagy and impaired neuronal migration and dendritic morphology (Li et al., 2019b). Taken together, the present data highlight the variety of functions of FOXP1 in neurodevelopment - which probably are associated with

hippocampal and striatal function - suggesting that alterations in this TF may lead to a chain reaction that affects other TFs.

BCL11b (BAF chromatin remodeling complex subunit) is a zinc finger TF with important roles in the development of the immune system, especially the T lymphocytes lineage. Heterozygous mutation in this gene was associated with a severe combined immunodeficiency identified as Immunodeficiency 49, in which the patient presents features like cranial malformation and absence of corpus callosum (Punwani et al., 2016). Further studies demonstrated the presence of impaired speech, motor development, and intellectual disabilities in multiple types of mutations, with severity being associated with alterations within the DNA-binding site (Lessel et al., 2018; Prasad et al., 2020; Qiao et al., 2019). Although little is known about BCL11b specific mechanisms in NDDs, its function is already described in the context of spinal and neocortex development and hippocampal neurogenesis (Simon et al., 2020). Since this TF appears to be a link between immune and neurological development, understanding its functions in psychiatric disorders like ASD and schizophrenia is likely to be a very promising field of study.

6. Integrative Perspectives

The complexity regarding each cell fate involves a coordinated expression profile that can be altered in many ways. We observed that genetic structural alterations in TFs impair their functions significantly, especially when the DNA-binding domain is affected. Environmental factors also impair the functionality of TFs; however, the issue here seems to occur at the transcription level, probably altered by processes like epigenetic modifications and cell reprogramming.

The timing of the alteration also influences the major outcomes. By observing Figure 2, we can see that the TFs have important peaks of expression in the first or second trimester of pregnancy. In these moments, processes like neural proliferation and migration, microglia migration, astrocyte proliferation, oligodendrocyte formation, and synaptogenesis are guided by a strict time course of TFs expression. If a genetic alteration limits the TF, we can expect that all processes and other factors associated with it will be disorganized, inducing significant consequences. For environmental risk factors, the outcomes would primarily depend on 1) the duration of the risk factor exposure; 2) the number of pathways associated with the TF that are affected, and 3) the impacts on upstream and downstream elements. For example, if a relevant TF in

progenitor cells is affected, we expect considerable impacts in the whole lineage; conversely, if the alteration happens in more mature cells, we expect more specific impacts like the inability to develop full functionality.

Finally, the place or cellular type of occurrence indicates the most likely outcomes. Table 1 demonstrated that several TFs are highly expressed in embryo-fetal neural structures, especially in progenitor cells that will generate oligodendrocytes, astrocytes, GABAergic neurons, motor neurons, and others. For example, if a TF is highly expressed in the ganglionic eminence, we expect that alterations would induce significant impairments in GABAergic interneurons, the major population of cells originating from this region. Moreover, the basal expression of a TF is also fundamental to maintain cell programming, so alterations in other moments (for example, later periods of fetal life) may induce more subtle alterations that still have important effects.

In Figure 3, we observe the several interactions between all the TFs provided by String Database (Szklarczyk et al., 2019), highlighting that interference in one TF can disrupt many others – directly and indirectly. TFs like TCF4, PAX6, STAT, GATA, FOXP3, which are cited in several contexts (affected by environmental factors and also described in genetic and multifactorial disorders), are key points in the interaction map. Moreover, on the left side of the image, we can observe the distribution of the factors among the disorders, demonstrating important common points of TF involvement. Finally, from a biological pathway point of view, we can observe that, although the disorders are affected by different TFs, similar pathways are described (Tables 2-5), including transcription regulation, interleukin signaling, WNT/ β -catenin signaling, cellular proliferation, activation of HOX genes and others, suggesting points of convergence in NDDs.

Thus, taken together, the body of evidence points to the fact that the broad spectrum of phenotypes observed in multifactorial disorders like ASD and schizophrenia may be associated with the alterations in TFs induced both by genetic and environmental triggers. Together with more specific studies of time-course and place of expression, the association among TFs will improve the understanding of major common points in the biological pathways, improving the knowledge about pathophysiology and possible therapeutic approaches in NDDs.

7. Concluding remarks

The complexity behind neurodevelopmental disorders and risk factors demands *in vivo*, *in vitro*, and *in silico* approaches to understand how biological pathways are disturbed in a context of genetic and environmental influences. The TFs comprise a diverse group of proteins with the ability to modulate RNA transcription, demonstrating an impressive time- and location-dependent organization, besides plasticity and susceptibility to possible context alterations. The present review compiled relevant data on literature regarding the expression and roles played by TFs during development in different NDDs and neuropsychiatric disorders, considering a multifactorial approach. Upon the observation of environmental risk factors and genome interactions, essential to the understanding of the final phenotypes of each disorder, we conclude that 1) TFs emerge as a point of convergence in NDDs, modulating neuroimmune alterations, disrupting processes like neuronal maturation, and causing anatomical changes; and 2) The analysis of TFs in psychiatric disorders is essential to shed light on molecular features of development still unknown and to expand the horizons for pharmacological interventions that can significantly improve the life quality of the affected individuals and their relatives.

8. Authors Contributions

JST and CG conceptualized the review. All authors contributed to the article and approved the submitted version.

9. Funding

National Institute of Science and Technology on Neuroimmunomodulation – INCT-NIM; National Council of Technological and Scientific Development (CNPq) and Coordination for the Improvement of Higher Education Personnel (CAPES).

10. Acknowledgements

Conflict of Interest: The authors declare that they have no conflict of interest. The authors would like to thank the reviewers for the careful revision and constructive suggestions made in order to improve the content of our manuscript and Dr. Craig Bertram, UCLan – UK, for the careful revision of the text and the contributions that significantly improved the readability of the article.

11. References

- Adachi, Y., Yamamoto, K., Okada, T., Yoshida, H., Harada, A., Mori, K., 2008. ATF6 is a transcription factor specializing in the regulation of quality control proteins in the endoplasmic reticulum. *Cell Struct. Funct.* 33, 75–89.
<https://doi.org/10.1247/csf.07044>
- Affeldt, B.M., Obenaus, A., Chan, J., Pardo, A.C., 2017. Region specific oligodendrocyte transcription factor expression in a model of neonatal hypoxic injury. *Int. J. Dev. Neurosci.* 61, 1–11.
<https://doi.org/10.1016/j.ijdevneu.2017.05.001>
- Ahmad, S.F., Ansari, M.A., Nadeem, A., Alzahrani, M.Z., Bakheet, S.A., Attia, S.M., 2018a. Resveratrol Improves Neuroimmune Dysregulation Through the Inhibition of Neuronal Toll-Like Receptors and COX-2 Signaling in BTBR T+ Itpr3tf/J Mice. *NeuroMolecular Med.* 20, 133–146.
<https://doi.org/10.1007/s12017-018-8483-0>
- Ahmad, S.F., Ansari, M.A., Nadeem, A., Bakheet, S.A., AL-Ayadhi, L.Y., Alasmari, A.F., Alanazi, M.M., Al-Mazroua, H.A., Attia, S.M., 2020. Involvement of CD45 cells in the development of autism spectrum disorder through dysregulation of granulocyte-macrophage colony-stimulating factor, key inflammatory cytokines, and transcription factors. *Int. Immunopharmacol.* 83.
<https://doi.org/10.1016/j.intimp.2020.106466>
- Ahmad, Sheikh F., Ansari, M.A., Nadeem, A., Bakheet, S.A., Almutairi, M.M., Attia, S.M., 2017a. Adenosine A2A receptor signaling affects IL-21/IL-22 cytokines and GATA3/T-bet transcription factor expression in CD4+ T cells from a BTBR T+ Itpr3tf/J mouse model of autism. *J. Neuroimmunol.* 311, 59–67.
<https://doi.org/10.1016/j.jneuroim.2017.08.002>
- Ahmad, S.F., Ansari, M.A., Nadeem, A., Bakheet, S.A., Alshammari, M.A., Attia, S.M., 2018b. Protection by tyrosine kinase inhibitor, tyrphostin AG126, through the suppression of IL-17A, ROR γ t, and T-bet signaling, in the BTBR mouse model of autism. *Brain Res. Bull.* 142, 328–337.
<https://doi.org/10.1016/j.brainresbull.2018.08.020>
- Ahmad, S.F., Ansari, M.A., Nadeem, A., Bakheet, S.A., Alshammari, M.A., Khan, M.R., Alsaad, A.M.S., Attia, S.M., 2018c. S3I-201, a selective Stat3 inhibitor, restores neuroimmune function through upregulation of Treg signaling in autistic BTBR T+ Itpr3tf/J mice. *Cell. Signal.* 52, 127–136.
<https://doi.org/10.1016/j.cellsig.2018.09.006>
- Ahmad, S.F., Ansari, M.A., Nadeem, A., Bakheet, S.A., Alzahrani, M.Z., Alshammari, M.A., Alanazi, W.A., Alasmari, A.F., Attia, S.M., 2018d. Resveratrol attenuates pro-inflammatory cytokines and activation of JAK1-STAT3 in BTBR T+ Itpr3tf/J autistic mice. *Eur. J. Pharmacol.* 829, 70–78.
<https://doi.org/10.1016/j.ejphar.2018.04.008>
- Ahmad, Sheikh F., Nadeem, A., Ansari, M.A., Bakheet, S.A., Al-Ayadhi, L.Y., Attia, S.M., 2017b. Upregulation of IL-9 and JAK-STAT signaling pathway in children with autism. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 79, 472–480.
<https://doi.org/10.1016/j.pnpbp.2017.08.002>
- Ahmad, S.F., Nadeem, A., Ansari, M.A., Bakheet, S.A., AL-Ayadhi, L.Y., Attia, S.M., 2018e. Downregulation in Helios transcription factor signaling is associated with immune dysfunction in blood leukocytes of autistic children. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 85, 98–104.

<https://doi.org/10.1016/j.pnpbp.2018.04.011>

- Ahmad, S.F., Nadeem, A., Ansari, M.A., Bakheet, S.A., Al-Mazroua, H.A., Khan, M.R., Alasmari, A.F., Alanazi, W.A., As Sobeai, H.M., Attia, S.M., 2019. The histamine-4 receptor antagonist JNJ7777120 prevents immune abnormalities by inhibiting ROR γ t/T-bet transcription factor signaling pathways in BTBR T+
lpr3tf/J mice exposed to gamma rays. *Mol. Immunol.* 114, 561–570.
<https://doi.org/10.1016/j.molimm.2019.09.007>
- Ahmad, Sheikh Fayaz, Zoheir, K.M.A., Ansari, M.A., Nadeem, A., Bakheet, S.A., AL-Ayadhi, L.Y., Alzahrani, M.Z., Al-Shabanah, O.A., Al-Harbi, M.M., Attia, S.M., 2017. Dysregulation of Th1, Th2, Th17, and T regulatory cell-related transcription factor signaling in children with autism. *Mol. Neurobiol.* 54, 4390–4400. <https://doi.org/10.1007/s12035-016-9977-0>
- Akiyama, M., Kobayashi, K., Yoshinaga, H., Ohtsuka, Y., 2010. A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia* 51, 1043–1052.
<https://doi.org/10.1111/j.1528-1167.2009.02466.x>
- Alachkar, A., Wang, L., Yoshimura, R., Hamzeh, A.R., Wang, Z., Sanathara, N., Lee, S.M., Xu, X., Abbott, G.W., Civelli, O., 2018. Prenatal one-carbon metabolism dysregulation programs schizophrenia-like deficits. *Mol. Psychiatry*.
<https://doi.org/10.1038/mp.2017.164>
- Albanna, A., Choudhry, Z., Harvey, P.O., Fathalli, F., Cassidy, C., Sengupta, S.M., Iyer, S.N., Rho, A., Lepage, M., Malla, A., Joober, R., 2014. TCF4 gene polymorphism and cognitive performance in patients with first episode psychosis. *Schizophr. Res.* 152, 124–129.
<https://doi.org/10.1016/j.schres.2013.10.038>
- Alizadeh, F., Tavakkoly-Bazzaz, J., Bozorgmehr, A., Azarnezhad, A., Tabrizi, M., Shahsavand Ananloo, E., 2017. Association of transcription factor 4 (TCF4) gene mRNA level with schizophrenia, its psychopathology, intelligence and cognitive impairments. *J. Neurogenet.* 31, 344–351.
<https://doi.org/10.1080/01677063.2017.1396330>
- Allegra, M., Genovesi, S., Maggia, M., Cenni, M.C., Zunino, G., Sgad $\tilde{A}$ ², P., Caleo, M., Bozzi, Y., 2014. Altered GABAergic markers, increased binocularity and reduced plasticity in the visual cortex of Engrailed-2 knockout mice. *Front. Cell. Neurosci.* 8, 163. <https://doi.org/10.3389/fncel.2014.00163>
- American Psychiatric, 2013. DSM 5, American Journal of Psychiatry.
<https://doi.org/10.1176/appi.books.9780890425596.744053>
- Amiel, J., Rio, M., De Pontual, L., Redon, R., Malan, V., Boddaert, N., Plouin, P., Carter, N.P., Lyonnet, S., Munnich, A., Colleaux, L., 2007. Mutations in TCF4, encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. *Am. J. Hum. Genet.* 80, 988–993.
<https://doi.org/10.1086/515582>
- Angelozzi, M., Lefebvre, V., 2019. SOXopathies: Growing Family of Developmental Disorders Due to SOX Mutations. *Trends Genet.*
<https://doi.org/10.1016/j.tig.2019.06.003>
- Ansari, M.A., Nadeem, A., Attia, S.M., Bakheet, S.A., Raish, M., Ahmad, S.F., 2017. Adenosine A2A receptor modulates neuroimmune function through Th17/retinoid-related orphan receptor gamma t (ROR γ t) signaling in a BTBR T+
lpr3tf/J mouse model of autism. *Cell. Signal.* 36, 14–24.
<https://doi.org/10.1016/j.cellsig.2017.04.014>
- Araujo, D.J., Toriumi, X.K., Escamilla, C.O., Kulkarni, A., Anderson, A.G., Harper,

- X.M., Usui, X.N., Ellegood, X.J., Lerch, J.P., Birnbaum, S.G., Tucker, H.O., Powell, C.M., Konopka, G., 2017. Cellular/Molecular Foxp1 in Forebrain Pyramidal Neurons Controls Gene Expression Required for Spatial Learning and Synaptic Plasticity. <https://doi.org/10.1523/JNEUROSCI.1005-17.2017>
- Arnett, A.B., Rhoads, C.L., Hoekzema, K., Turner, T.N., Gerdts, J., Wallace, A.S., Bedrosian-Sermone, S., Eichler, E.E., Bernier, R.A., 2018. The autism spectrum phenotype in ADNP syndrome. *Autism Res.* 11, 1300–1310. <https://doi.org/10.1002/aur.1980>
- Aronne, M.P., Evrard, S.G., Mirochnic, S., Brusco, A., 2008. Prenatal ethanol exposure reduces the expression of the transcriptional factor Pax6 in the developing rat brain, in: *Annals of the New York Academy of Sciences*. Blackwell Publishing Inc., pp. 478–498. <https://doi.org/10.1196/annals.1432.006>
- Bacon, C., Schneider, M., Le Magueresse, C., Froehlich, H., Sticht, C., Gluch, C., Monyer, H., Rappold, G.A., 2015. Brain-specific Foxp1 deletion impairs neuronal development and causes autistic-like behaviour. *Mol. Psychiatry* 20, 632–639. <https://doi.org/10.1038/mp.2014.116>
- Bakheet, S.A., Alzahrani, M.Z., Ansari, M.A., Nadeem, A., Zoheir, K.M.A., Attia, S.M., Al-Ayadhi, L.Y., Ahmad, S.F., 2017. Resveratrol Ameliorates Dysregulation of Th1, Th2, Th17, and T Regulatory Cell-Related Transcription Factor Signaling in a BTBR T + tf/J Mouse Model of Autism. *Mol. Neurobiol.* 54, 5201–5212. <https://doi.org/10.1007/s12035-016-0066-1>
- Balasco, L., Provenzano, G., Bozzi, Y., 2020. Sensory Abnormalities in Autism Spectrum Disorders: A Focus on the Tactile Domain, From Genetic Mouse Models to the Clinic. *Front. Psychiatry*. <https://doi.org/10.3389/fpsy.2019.01016>
- Barak, B., Zhang, Z., Liu, Y., Nir, A., Trangle, S.S., Ennis, M., Levandowski, K.M., Wang, D., Quast, K., Boulting, G.L., Li, Y., Bayarsaihan, D., He, Z., Feng, G., 2019. Neuronal deletion of Gtf2i, associated with Williams syndrome, causes behavioral and myelin alterations rescuable by a remyelinating drug. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-019-0380-9>
- Bedeschi, M.F., Marangi, G., Calvello, M.R., Ricciardi, S., Leone, F.P.C., Baccarin, M., Gueneri, S., Orteschi, D., Murdolo, M., Lattante, S., Frangella, S., Keena, B., Harr, M.H., Zackai, E., Zollino, M., 2017. Impairment of different protein domains causes variable clinical presentation within Pitt-Hopkins syndrome and suggests intragenic molecular syndromology of TCF4. *Eur. J. Med. Genet.* 60, 565–571. <https://doi.org/10.1016/j.ejmg.2017.08.004>
- Bedogni, F., Hodge, R.D., Elsen, G.E., Nelson, B.R., Daza, R.A.M., Beyer, R.P., Bammler, T.K., Rubenstein, J.L.R., Hevner, R.F., 2010. Tbr1 regulates regional and laminar identity of postmitotic neurons in developing neocortex. *Proc. Natl. Acad. Sci. U. S. A.* 107, 13129–13134. <https://doi.org/10.1073/pnas.1002285107>
- Behesti, H., Fore, T.R., Wu, P., Horn, Z., Leppert, M., Hull, C., Hattena, M.E., 2018. ASTN2 modulates synaptic strength by trafficking and degradation of surface proteins. *Proc. Natl. Acad. Sci. U. S. A.* 115, E9717–E9726. <https://doi.org/10.1073/pnas.1809382115>
- Ben-Reuven, L., Reiner, O., 2019. Dynamics of cortical progenitors and production of subcerebral neurons are altered in embryos of a maternal inflammation model for autism. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-019-0594-y>
- Benayed, R., Choi, J., Matteson, P.G., Gharani, N., Kamdar, S., Brzustowicz, L.M., Millonig, J.H., 2009. Autism-Associated Haplotype Affects the Regulation of the Homeobox Gene, ENGRAILED 2. *Biol. Psychiatry* 66, 911–917.

- <https://doi.org/10.1016/j.biopsych.2009.05.027>
- Bilz, N.C., Willscher, E., Binder, H., Böhnke, J., Stanifer, M.L., Hübner, D., Boulant, S., Liebert, U.G., Claus, C., 2019. Teratogenic Rubella Virus Alters the Endodermal Differentiation Capacity of Human Induced Pluripotent Stem Cells. *Cells* 8. <https://doi.org/10.3390/cells8080870>
- Blagih, J., Buck, M.D., Vousden, K.H., 2020. p53, cancer and the immune response. *J. Cell Sci.* <https://doi.org/10.1242/jcs.237453>
- Brandon, N.J., Millar, J.K., Korth, C., Sive, H., Singh, K.K., Sawa, A., 2009. Understanding the role of DISC1 in psychiatric disease and during normal development, in: *Journal of Neuroscience. Society for Neuroscience*, pp. 12768–12775. <https://doi.org/10.1523/JNEUROSCI.3355-09.2009>
- Brielmaier, J., Matteson, P.G., Silverman, J.L., Senerth, J.M., Kelly, S., Genestine, M., Millonig, J.H., DiCicco-Bloom, E., Crawley, J.N., 2012. Autism-relevant social abnormalities and cognitive deficits in engrailed-2 knockout mice. *PLoS One* 7. <https://doi.org/10.1371/journal.pone.0040914>
- Brzózka, M.M., Radyushkin, K., Wichert, S.P., Ehrenreich, H., Rossner, M.J., 2010. Cognitive and Sensorimotor Gating Impairments in Transgenic Mice Overexpressing the Schizophrenia Susceptibility Gene Tcf4 in the Brain. *Biol. Psychiatry* 68, 33–40. <https://doi.org/10.1016/j.biopsych.2010.03.015>
- Brzózka, M.M., Rossner, M.J., 2013. Deficits in trace fear memory in a mouse model of the schizophrenia risk gene TCF4. *Behav. Brain Res.* 237, 348–356. <https://doi.org/10.1016/j.bbr.2012.10.001>
- Brzózka, M.M., Rossner, M.J., de Hoz, L., 2016. Tcf4 transgenic female mice display delayed adaptation in an auditory latent inhibition paradigm. *Eur. Arch. Psychiatry Clin. Neurosci.* 266, 505–512. <https://doi.org/10.1007/s00406-015-0643-8>
- Calfa, G., Li, W., Rutherford, J.M., Pozzo-Miller, L., 2015. Excitation/inhibition imbalance and impaired synaptic inhibition in hippocampal area CA3 of Mecp2 knockout mice. *Hippocampus* 25, 159–168. <https://doi.org/10.1002/hipo.22360>
- Can, K., Menzfeld, C., Rinne, L., Rehling, P., Kügler, S., Golubiani, G., Dudek, J., Müller, M., 2019. Neuronal redox-imbalance in Rett syndrome affects mitochondria as well as cytosol, and is accompanied by intensified mitochondrial O₂ consumption and ROS release. *Front. Physiol.* 10. <https://doi.org/10.3389/fphys.2019.00479>
- Cardoso-Moreira, M., Halbert, J., Valloton, D., Velten, B., Chen, C., Shao, Y., Liechti, A., Ascensão, K., Rummel, C., Ovchinnikova, S., Mazin, P. V., Xenarios, I., Harshman, K., Mort, M., Cooper, D.N., Sandi, C., Soares, M.J., Ferreira, P.G., Afonso, S., Carneiro, M., Turner, J.M.A., VandeBerg, J.L., Fallahshahroudi, A., Jensen, P., Behr, R., Lisgo, S., Lindsay, S., Khaitovich, P., Huber, W., Baker, J., Anders, S., Zhang, Y.E., Kaessmann, H., 2019. Gene expression across mammalian organ development. *Nature*. <https://doi.org/10.1038/s41586-019-1338-5>
- Castro, F.L., Geddes, V.E.V., Monteiro, F.L.L., Gonçalves, R.M.D.T., Campanati, L., Pezzuto, P., Paquin-Proulx, D., Schamber-Reis, B.L., Azevedo, G.S., Gonçalves, A.L., Cunha, D.P., Moreira, M.E.L., Vasconcelos, Z.F.M., Chimeli, L., Melo, A., Tanuri, A., Nixon, D.F., Ribeiro-Alves, M., Aguiar, R.S., 2019. MicroRNAs 145 and 148a Are Upregulated During Congenital Zika Virus Infection. *ASN Neuro.* <https://doi.org/10.1177/1759091419850983>
- Caubit, X., Gubellini, P., Andrieux, J., Roubertoux, P.L., Metwaly, M., Jacq, B., Fatmi, A., Had-Aissouni, L., Kwan, K.Y., Salin, P., Carlier, M., Liedén, A., Rudd,

- E., Shinawi, M., Vincent-Delorme, C., Cuisset, J.M., Lemaitre, M.P., Abderrehamane, F., Duban, B., Lemaitre, J.F., Woolf, A.S., Bockenhauer, D., Severac, D., Dubois, E., Zhu, Y., Sestan, N., Garratt, A.N., Kerkerian-Le Goff, L., Fasano, L., 2016. TSHZ3 deletion causes an autism syndrome and defects in cortical projection neurons. *Nat. Genet.* 48, 1359–1369. <https://doi.org/10.1038/ng.3681>
- Cevallos, R.R., Edwards, Y.J.K., Parant, J.M., Yoder, B.K., Hu, K., 2020. Human transcription factors responsive to initial reprogramming predominantly undergo legitimate reprogramming during fibroblast conversion to iPSCs. *Sci. Rep.* <https://doi.org/10.1038/s41598-020-76705-y>
- Chabbert, D., Caubit, X., Roubertoux, P.L., Carlier, M., Habermann, B., Jacq, B., Salin, P., Metwaly, M., Frahm, C., Fatmi, A., Garratt, A.N., Severac, D., Dubois, E., Kerkerian-Le Goff, L., Fasano, L., Gubellini, P., 2019. Postnatal Tshz3 Deletion Drives Altered Corticostriatal Function and Autism Spectrum Disorder-like Behavior. *Biol. Psychiatry* 86, 274–285. <https://doi.org/10.1016/j.biopsych.2019.03.974>
- Chabout, J., Sarkar, A., Patel, S.R., Radden, T., Dunson, D.B., Fisher, S.E., Jarvis, E.D., 2016. A Foxp2 mutation implicated in human speech deficits alters sequencing of ultrasonic vocalizations in adult male mice. *Front. Behav. Neurosci.* 10. <https://doi.org/10.3389/fnbeh.2016.00197>
- Chang, X., Lima, L. de A., Liu, Y., Li, J., Li, Q., Sleiman, P.M.A., Hakonarson, H., 2018. Common and Rare Genetic Risk Factors Converge in Protein Interaction Networks Underlying Schizophrenia. *Front. Genet.* 9, 434. <https://doi.org/10.3389/fgene.2018.00434>
- Chelini, G., Zerbi, V., Cimino, L., Grigoli, A., Markicevic, M., Libera, F., Robbiati, S., Gadler, M., Bronzoni, S., Miorelli, S., Galbusera, A., Gozzi, A., Casarosa, S., Provenzano, G., Bozzi, Y., 2019. Aberrant somatosensory processing and connectivity in mice lacking engrailed-2. *J. Neurosci.* 39, 1525–1538. <https://doi.org/10.1523/JNEUROSCI.0612-18.2018>
- Chen, C., Meng, Q., Xia, Y., Ding, C., Wang, L., Dai, R., Cheng, L., Gunaratne, P., Gibbs, R.A., Min, S., Coarfa, C., Reid, J.G., Zhang, C., Jiao, C., Jiang, Y., Giase, G., Thomas, A., Fitzgerald, D., Brunetti, T., Shieh, A., Xia, C., Wang, Yongjun, Wang, Yunpeng, Badner, J.A., Gershon, E.S., White, K.P., Liu, C., 2018. The transcription factor POU3F2 regulates a gene coexpression network in brain tissue from patients with psychiatric disorders. *Sci. Transl. Med.* 10, eaat8178. <https://doi.org/10.1126/scitranslmed.aat8178>
- Chen, E., Xu, D., Lan, X., Jia, B., Sun, L., Zheng, J., Peng, H., 2013. A Novel Role of the STAT3 Pathway in Brain Inflammation-induced Human Neural Progenitor Cell Differentiation. *Curr. Mol. Med.* 13, 1474–1484. <https://doi.org/10.2174/15665240113139990076>
- Chen, Y.C., Kuo, H.Y., Bornschein, U., Takahashi, H., Chen, S.Y., Lu, K.M., Yang, H.Y., Chen, G.M., Lin, J.R., Lee, Y.H., Chou, Y.C., Cheng, S.J., Chien, C.T., Enard, W., Hevers, W., Pääbo, S., Graybiel, A.M., Liu, F.C., 2016. Foxp2 controls synaptic wiring of corticostriatal circuits and vocal communication by opposing Mef2c. *Nat. Neurosci.* 19, 1513–1522. <https://doi.org/10.1038/nn.4380>
- Chew, L.J., Gallo, V., 2009. The Yin and Yang of Sox proteins: Activation and repression in development and disease. *J. Neurosci. Res.* <https://doi.org/10.1002/jnr.22128>
- Choi, J., Lee, S., Won, J., Jin, Y., Hong, Yunkyung, Hur, T.Y., Kim, J.H., Lee, S.R.,

- Hong, Yonggeun, 2018. Pathophysiological and neurobehavioral characteristics of a propionic acid-mediated autism-like rat model. *PLoS One* 13. <https://doi.org/10.1371/journal.pone.0192925>
- Chopra, R., Isom, L.L., 2014. Untangling the dravet syndrome seizure network: The changing face of a rare genetic epilepsy. *Epilepsy Curr.* 14, 86–89. <https://doi.org/10.5698/1535-7597-14.2.86>
- Chowdhury, S., Bandholz, A.M., Parkash, S., Dyack, S., Rideout, A.L., Leppig, K.A., Thiese, H., Wheeler, P.G., Tsang, M., Ballif, B.C., Shaffer, L.G., Torchia, B.S., Ellison, J.W., Rosenfeld, J.A., 2014. Phenotypic and molecular characterization of 19q12q13.1 deletions: A report of five patients. *Am. J. Med. Genet. Part A* 164, 62–69. <https://doi.org/10.1002/ajmg.a.36201>
- Christensen, J., Grønborg, T.K., Sørensen, M.J., Schendel, D., Parner, E.T., Pedersen, L.H., Vestergaard, M., 2013. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. *JAMA* 309, 1696. <https://doi.org/10.1001/jama.2013.2270>
- Chu, D., Li, L., Jiang, Y., Tan, J., Ji, J., Zhang, Y., Jin, N., Liu, F., 2019. Excess Folic Acid Supplementation Before and During Pregnancy and Lactation Activates Fos Gene Expression and Alters Behaviors in Male Mouse Offspring. *Front. Neurosci.* 13, 313. <https://doi.org/10.3389/fnins.2019.00313>
- Conti, V., Gandaglia, A., Galli, F., Tirone, M., Bellini, E., Campana, L., Kilstrup-Nielsen, C., Rovere-Querini, P., Brunelli, S., Landsberger, N., 2015. MeCP2 affects skeletal muscle growth and morphology through non cell-autonomous mechanisms. *PLoS One* 10. <https://doi.org/10.1371/journal.pone.0130183>
- Corley, S.M., Canales, C.P., Carmona-Mora, P., Mendoza-Reinos, V., Beverdam, A., Hardeman, E.C., Wilkins, M.R., Palmer, S.J., 2016. RNA-Seq analysis of Gtf2ird1 knockout epidermal tissue provides potential insights into molecular mechanisms underpinning Williams-Beuren syndrome. *BMC Genomics* 17, 450. <https://doi.org/10.1186/s12864-016-2801-4>
- Corradini, I., Focchi, E., Rasile, M., Morini, R., Desiato, G., Tomasoni, R., Lizier, M., Ghirardini, E., Fesce, R., Morone, D., Barajon, I., Antonucci, F., Pozzi, D., Matteoli, M., 2018. Maternal Immune Activation Delays Excitatory-to-Inhibitory Gamma-Aminobutyric Acid Switch in Offspring. *Biol. Psychiatry* 83, 680–691. <https://doi.org/10.1016/j.biopsych.2017.09.030>
- Dai, H., Wang, Z., 2014. Histone Modification Patterns and Their Responses to Environment. *Curr. Environ. Heal. reports* 1, 11–21. <https://doi.org/10.1007/s40572-013-0008-2>
- Danielson, M.L., Bitsko, R.H., Ghandour, R.M., Holbrook, J.R., Kogan, M.D., Blumberg, S.J., 2018. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. *J. Clin. Child Adolesc. Psychol.* <https://doi.org/10.1080/15374416.2017.1417860>
- de Oliveira Pereira Ribeiro, L., Vargas-Pinilla, P., Kappel, D.B., Longo, D., Ranzan, J., Becker, M.M., dos Santos Riesgo, R., Schuler-Faccini, L., Roman, T., Schuch, J.B., 2018. Evidence for Association Between OXTR Gene and ASD Clinical Phenotypes. *J. Mol. Neurosci.* 65, 213–221. <https://doi.org/10.1007/s12031-018-1088-0>
- Deckmann, I., Schwingel, G.B., Fontes-Dutra, M., Bambini-Junior, V., Gottfried, C., 2018. Neuroimmune Alterations in Autism: A Translational Analysis Focusing on the Animal Model of Autism Induced by Prenatal Exposure to Valproic Acid. *Neuroimmunomodulation* 25, 285–299. <https://doi.org/10.1159/000492113>
- Delépine, C., Nectoux, J., Letourneur, F., Baud, V., Chelly, J., Billuart, P., Bienvenu, J., 2018. A large family with a de novo mutation in the OXTR gene and ASD. *J. Clin. Invest.* 128, 1000–1008. <https://doi.org/10.1172/JCI120000>

- T., 2015. Astrocyte Transcriptome from the Mecp2308-Truncated Mouse Model of Rett Syndrome. *NeuroMolecular Med.* 17, 353–363. <https://doi.org/10.1007/s12017-015-8363-9>
- Dengler, V.L., Galbraith, M.D., Espinosa, J.M., 2014. Transcriptional regulation by hypoxia inducible factors. *Crit. Rev. Biochem. Mol. Biol.* <https://doi.org/10.3109/10409238.2013.838205>
- Doan, R.N., Lim, E.T., De Rubeis, S., Betancur, C., Cutler, D.J., Chiochetti, A.G., Overman, L.M., Soucy, A., Goetze, S., Freitag, C.M., Daly, M.J., Walsh, C.A., Buxbaum, J.D., Yu, T.W., 2019. Recessive gene disruptions in autism spectrum disorder. *Nat. Genet.* 51, 1092–1098. <https://doi.org/10.1038/s41588-019-0433-8>
- Dong, D., Zielke, H.R., Yeh, D., Yang, P., 2018. Cellular stress and apoptosis contribute to the pathogenesis of autism spectrum disorder. *Autism Res.* 11, 1076–1090. <https://doi.org/10.1002/aur.1966>
- Durand, C., Roeth, R., Dweep, H., Vlatkovic, I., Decker, E., Schneider, K.U., Rappold, G., 2011. Alternative Splicing and Nonsense-Mediated RNA Decay Contribute to the Regulation of SHOX Expression. *PLoS One* 6, e18115. <https://doi.org/10.1371/journal.pone.0018115>
- Edgar, R., Mazor, Y., Rinon, A., Blumenthal, J., Golan, Y., Buzhor, E., Livnat, I., Ben-Ari, S., Lieder, I., Shitrit, A., Gilboa, Y., Ben-Yehudah, A., Edri, O., Shraga, N., Bogoch, Y., Leshansky, L., Aharoni, S., West, M.D., Warshawsky, D., Shtrichman, R., 2013. LifeMap Discovery™: The Embryonic Development, Stem Cells, and Regenerative Medicine Research Portal. *PLoS One.* <https://doi.org/10.1371/journal.pone.0066629>
- El-Khoury, R., Panayotis, N., Matagne, V., Ghata, A., Villard, L., Roux, J.C., 2014. GABA and glutamate pathways are spatially and developmentally affected in the brain of Mecp2-deficient mice. *PLoS One* 9. <https://doi.org/10.1371/journal.pone.0092169>
- Enard, W., 2011. FOXP2 and the role of cortico-basal ganglia circuits in speech and language evolution. *Curr. Opin. Neurobiol.* <https://doi.org/10.1016/j.conb.2011.04.008>
- Fan, Y., Abrahamsen, G., McGrath, J.J., MacKay-Sim, A., 2012. Altered cell cycle dynamics in schizophrenia. *Biol. Psychiatry* 71, 129–135. <https://doi.org/10.1016/j.biopsych.2011.10.004>
- Fazel Darbandi, S., Robinson Schwartz, S.E., Qi, Q., Catta-Preta, R., Pai, E.L.L., Mandell, J.D., Everitt, A., Rubin, A., Krasnoff, R.A., Katzman, S., Tastad, D., Nord, A.S., Willsey, A.J., Chen, B., State, M.W., Sohal, V.S., Rubenstein, J.L.R., 2018. Neonatal Tbr1 Dosage Controls Cortical Layer 6 Connectivity. *Neuron* 100, 831-845.e7. <https://doi.org/10.1016/j.neuron.2018.09.027>
- Feigenson, K.A., Kusnecov, A.W., Silverstein, S.M., 2014. Inflammation and the two-hit hypothesis of schizophrenia. *Neurosci. Biobehav. Rev.* <https://doi.org/10.1016/j.neubiorev.2013.11.006>
- Fontes-Dutra, M., Rabelo, B., Santos-Terra, J., Deckmann, I., Schwingel, G.B., Gottfried, C., 2020. Maternal Immune Activation and Neuropsychiatric Disorders: The Intricate Puzzle of Autism Spectrum Disorder. *Springer, Cham*, pp. 167–205. https://doi.org/10.1007/978-3-030-39335-9_11
- Forrest, M.P., Hill, M.J., Kavanagh, D.H., Tansey, K.E., Waite, A.J., Blake, D.J., 2018. The psychiatric risk gene transcription factor 4 (TCF4) regulates neurodevelopmental pathways associated with schizophrenia, Autism, and intellectual disability. *Schizophr. Bull.* 44, 1100–1110.

- <https://doi.org/10.1093/schbul/sbx164>
- Forrest, M.P., Waite, A.J., Martin-Rendon, E., Blake, D.J., 2013. Knockdown of Human TCF4 Affects Multiple Signaling Pathways Involved in Cell Survival, Epithelial to Mesenchymal Transition and Neuronal Differentiation. *PLoS One* 8, 73169. <https://doi.org/10.1371/journal.pone.0073169>
- Fröhlich, H., Kollmeyer, M.L., Linz, V.C., Stuhlinger, M., Groneberg, D., Reigl, A., Zizer, E., Friebe, A., Niesler, B., Rappold, G., 2019. Gastrointestinal dysfunction in autism displayed by altered motility and Achalasia in *Foxp1*^{+/-} mice. *Proc. Natl. Acad. Sci. U. S. A.* 116, 22237–22245. <https://doi.org/10.1073/pnas.1911429116>
- Fröhlich, H., Rafiullah, R., Schmitt, N., Abele, S., Rappold, G.A., 2017. *Foxp1* expression is essential for sex-specific murine neonatal ultrasonic vocalization. *Hum. Mol. Genet.* 26, 1511–1521. <https://doi.org/10.1093/hmg/ddx055>
- Fukami, M., Seki, A., Ogata, T., 2016. SHOX Haploinsufficiency as a Cause of Syndromic and Nonsyndromic Short Stature. *Mol. Syndromol.* <https://doi.org/10.1159/000444596>
- Gao, J.Y., Ma, P., Li, Y., Yan, C.X., Zhang, Q., Yang, X.X., Shi, Q., Zhang, B., Wen, X.P., 2020. Association between a TCF4 Polymorphism and Susceptibility to Schizophrenia. *Biomed Res. Int.* 2020. <https://doi.org/10.1155/2020/1216303>
- Gaub, S., Fisher, S.E., Ehret, G., 2016. Ultrasonic vocalizations of adult male *Foxp2*-mutant mice: Behavioral contexts of arousal and emotion. *Genes, Brain Behav.* 15, 243–259. <https://doi.org/10.1111/gbb.12274>
- Genestine, M., Lin, L., Durens, M., Yan, Y., Jiang, Y., Prem, S., Bailoor, K., Kelly, B., Sonsalla, P.K., Matteson, P.G., Silverman, J., Crawley, J.N., Millonig, J.H., DiCicco-Bloom, E., 2015. Engrailed-2 (*En2*) deletion produces multiple neurodevelopmental defects in monoamine systems, forebrain structures and neurogenesis and behavior. *Hum. Mol. Genet.* 24, 5805–5827. <https://doi.org/10.1093/hmg/ddv301>
- Gharani, N., Benayed, R., Mancuso, V., Brzustowicz, L.M., Millonig, J.H., 2004. Association of the homeobox transcription factor, ENGRAILED 2, 3, with autism spectrum disorder. *Mol. Psychiatry.* <https://doi.org/10.1038/sj.mp.4001498>
- Golson, M.L., Kaestner, K.H., 2016. Fox transcription factors: From development to disease. *Dev.* 143, 4558–4570. <https://doi.org/10.1242/dev.112672>
- Gonzales, M.L., LaSalle, J.M., 2010. The role of MeCP2 in brain development and neurodevelopmental disorders. *Curr. Psychiatry Rep.* <https://doi.org/10.1007/s11920-010-0097-7>
- Goodspeed, K., Newsom, C., Morris, M.A., Powell, C., Evans, P., Golla, S., 2018. Pitt-Hopkins Syndrome: A Review of Current Literature, Clinical Approach, and 23-Patient Case Series. *J. Child Neurol.* <https://doi.org/10.1177/0883073817750490>
- Gottfried, C., Bambini-Junior, V., Francis, F., Riesgo, R., Savino, W., 2015. The impact of neuroimmune alterations in autism spectrum disorder. *Front. Psychiatry* 6. <https://doi.org/10.3389/fpsy.2015.00121>
- Gozes, I., Stewart, A., Morimoto, B., Fox, A., Sutherland, K., Schmechel, D., 2009. Addressing Alzheimers Disease Tangles: From NAP to AL-108. *Curr. Alzheimer Res.* 6, 455–460. <https://doi.org/10.2174/156720509789207895>
- Gulmez Karaca, K., Brito, D.V.C., Zeuch, B., Oliveira, A.M.M., 2018. Adult hippocampal MeCP2 preserves the genomic responsiveness to learning required for long-term memory formation. *Neurobiol. Learn. Mem.* 149, 84–97. <https://doi.org/10.1016/j.nlm.2018.02.010>

- Gupta, A., Li, X., DiCicco-Bloom, E., Bello, N.T., 2018. Altered salt taste response and increased tongue epithelium *Scnna1* expression in adult *Engrailed-2* null mice. *Physiol. Behav.* 194, 410–419. <https://doi.org/10.1016/j.physbeh.2018.06.030>
- Hall, M.H., Levy, D.L., Salisbury, D.F., Haddad, S., Gallagher, P., Lohan, M., Cohen, B., Öngür, D., Smoller, J.W., 2014. Neurophysiologic effect of GWAS derived schizophrenia and bipolar risk variants. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 165, 9–18. <https://doi.org/10.1002/ajmg.b.32212>
- Hamdan, F.F., Daoud, H., Rochefort, D., Piton, A., Gauthier, J., Langlois, M., Foomani, G., Dobrzeniecka, S., Krebs, M.O., Joober, R., Lafrenire, R.G., Lacaille, J.C., Mottron, L., Drapeau, P., Beauchamp, M.H., Phillips, M.S., Fombonne, E., Rouleau, G.A., Michaud, J.L., 2010. De novo mutations in *FOXP1* in cases with intellectual disability, autism, and language impairment. *Am. J. Hum. Genet.* 87, 671–678. <https://doi.org/10.1016/j.ajhg.2010.09.017>
- Hamilton, S.P., Woo, J.M., Carlson, E.J., Ghanem, N., Ekker, M., Rubenstein, J.L.R., 2005. Analysis of four *DLX* homeobox genes in autistic probands. *BMC Genet.* 6, 52. <https://doi.org/10.1186/1471-2156-6-52>
- Hashizume, K., Yamanaka, M., Ueda, S., 2018. *POU3F2* participates in cognitive function and adult hippocampal neurogenesis via mammalian-characteristic amino acid repeats. *Genes, Brain Behav.* 17, 118–125. <https://doi.org/10.1111/gbb.12408>
- Helsmoortel, C., Vulto-Van Silfhout, A.T., Coe, B.P., Vandeweyer, G., Rooms, L., Van Den Ende, J., Schuurs-Hoeijmakers, J.H.M., Marcelis, C.L., Willemsen, M.H., Vissers, L.E.L.M., Yntema, H.G., Bakshi, M., Wilson, M., Witherspoon, K.T., Malmgren, H., Nordgren, A., Annerén, G., Fichera, M., Bosco, P., Romano, C., De Vries, B.B.A., Kleefstra, T., Kooy, R.F., Eichler, E.E., Van Der Aa, N., 2014. A *SWI/SNF*-related autism syndrome caused by de novo mutations in *ADNP*. *Nat. Genet.* 46, 380–384. <https://doi.org/10.1038/ng.2899>
- Hendricks, T.J., Fyodorov, D. V., Wegman, L.J., Lelutiu, N.B., Pehek, E.A., Yamamoto, B., Silver, J., Weeber, E.J., Sweatt, J.D., Deneris, E.S., 2003. *Pet-1* ETS gene plays a critical role in 5-HT neuron development and is required for normal anxiety-like and aggressive behavior. *Neuron* 37, 233–247. [https://doi.org/10.1016/S0896-6273\(02\)01167-4](https://doi.org/10.1016/S0896-6273(02)01167-4)
- Hennig, K.M., Fass, D.M., Zhao, W.-N., Sheridan, S.D., Fu, T., Erdin, S., Stortchevoi, A., Lucente, D., Cody, J.D., Sweetser, D., Gusella, J.F., Talkowski, M.E., Haggarty, S.J., 2017. *WNT/β-Catenin* Pathway and Epigenetic Mechanisms Regulate the Pitt-Hopkins Syndrome and Schizophrenia Risk Gene *TCF4*. *Mol. Neuropsychiatry* 3, 53–71. <https://doi.org/10.1159/000475666>
- Hickey, S.L., Berto, S., Konopka, G., 2019. Chromatin Decondensation by *FOXP2* Promotes Human Neuron Maturation and Expression of Neurodevelopmental Disease Genes. *Cell Rep.* 27, 1699–1711.e9. <https://doi.org/10.1016/j.celrep.2019.04.044>
- Hill, M.J., Killick, R., Navarrete, K., Maruszak, A., McLaughlin, G.M., Williams, B.P., Bray, N.J., 2017. Knockdown of the schizophrenia susceptibility gene *TCF4* alters gene expression and proliferation of progenitor cells from the developing human neocortex. *J. Psychiatry Neurosci.* 42, 181–188. <https://doi.org/10.1503/jpn.160073>
- Hong, S., Song, M.R., 2015. Signal transducer and activator of transcription-3 maintains the stemness of radial glia at mid-neurogenesis. *J. Neurosci.* 35, 1011–1023. <https://doi.org/10.1523/JNEUROSCI.2119-14.2015>

- Hoseth, E.Z., Krull, F., Dieset, I., Mørch, R.H., Hope, S., Gardsjord, E.S., Steen, N.E., Melle, I., Brattbakk, H.R., Steen, V.M., Aukrust, P., Djurovic, S., Andreassen, O.A., Ueland, T., 2018. Exploring the Wnt signaling pathway in schizophrenia and bipolar disorder. *Transl. Psychiatry* 8, 55. <https://doi.org/10.1038/s41398-018-0102-1>
- Hou, P.S., hAilín, D., Vogel, T., Hanashima, C., 2020. Transcription and Beyond: Delineating FOXP1 Function in Cortical Development and Disorders. *Front. Cell. Neurosci.* <https://doi.org/10.3389/fncel.2020.00035>
- Hsieh, J., Nakashima, K., Kuwabara, T., Mejia, E., Gage, F.H., 2004. Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells. *Proc. Natl. Acad. Sci. U. S. A.* 101, 16659–16664. <https://doi.org/10.1073/pnas.0407643101>
- Inatani, M., Yamaguchi, Y., 2003. Gene expression of EXT1 and EXT2 during mouse brain development. *Dev. Brain Res.* 141, 129–136. [https://doi.org/10.1016/S0165-3806\(03\)00010-5](https://doi.org/10.1016/S0165-3806(03)00010-5)
- Ip, J.P.K., Mellios, N., Sur, M., 2018. Rett syndrome: Insights into genetic, molecular and circuit mechanisms. *Nat. Rev. Neurosci.* <https://doi.org/10.1038/s41583-018-0006-3>
- Ishii, S., Torii, M., Son, A.I., Rajendraprasad, M., Morozov, Y.M., Kawasaki, Y.I., Salzberg, A.C., Fujimoto, M., Brennand, K., Nakai, A., Mezger, V., Gage, F.H., Rakic, P., Hashimoto-Torii, K., 2017. Variations in brain defects result from cellular mosaicism in the activation of heat shock signalling. *Nat. Commun.* 8, 1–15. <https://doi.org/10.1038/ncomms15157>
- Ito, H., Morishita, R., Mizuno, M., Kawamura, N., Tabata, H., Nagata, K., 2018. Biochemical and Morphological Characterization of a Neurodevelopmental Disorder-Related Mono-ADP-Ribosylhydrolase, MACRO Domain Containing 2. *Dev. Neurosci.* 40, 278–287. <https://doi.org/10.1159/000492271>
- Iwamoto, O., Koga, C., Matsumoto, H., Terasaki, S., Kusukawa, J., Kameyama, T., 2003. Coffin Siris Syndrome. *Asian J. Oral Maxillofac. Surg.* 15, 205–207. [https://doi.org/10.1016/S0915-6992\(03\)80044-4](https://doi.org/10.1016/S0915-6992(03)80044-4)
- Iyo, A.H., Porter, B., Deneris, E.S., Austin, M.C., 2005. Regional distribution and cellular localization of the ETS-domain transcription factor, FEV, mRNA in the human postmortem brain. *Synapse* 57, 223–228. <https://doi.org/10.1002/syn.20178>
- Jacob, F., Monod, J., 1961. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.* [https://doi.org/10.1016/S0022-2836\(61\)80072-7](https://doi.org/10.1016/S0022-2836(61)80072-7)
- Jacob, F.D., Ramaswamy, V., Andersen, J., Bolduc, F. V., 2009. Atypical Rett syndrome with selective FOXP1 deletion detected by comparative genomic hybridization: Case report and review of literature. *Eur. J. Hum. Genet.* 17, 1577–1581. <https://doi.org/10.1038/ejhg.2009.95>
- Javitt, D.C., Buchanan, R.W., Keefe, R.S.E., Kern, R., McMahon, R.P., Green, M.F., Lieberman, J., Goff, D.C., Csernansky, J.G., McEvoy, J.P., Jarskog, F., Seidman, L.J., Gold, J.M., Kimhy, D., Nolan, K.S., Barch, D.S., Ball, M.P., Robinson, J., Marder, S.R., 2012. Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia. *Schizophr. Res.* 136, 25–31. <https://doi.org/10.1016/j.schres.2011.11.001>
- Jin, L.W., Horiuchi, M., Wulff, H., Liu, X.B., Cortopassi, G.A., Erickson, J.D., Maezawa, I., 2015. Dysregulation of Glutamine Transporter SNAT1 in Rett Syndrome Microglia: A Mechanism for Mitochondrial Dysfunction and Neurotoxicity. *J. Neurosci.* 35, 2516–2529.

- <https://doi.org/10.1523/JNEUROSCI.2778-14.2015>
- Jin, X.R., Chen, X.S., Xiao, L., 2017. MeCP2 deficiency in neuroglia: New progress in the pathogenesis of rett syndrome. *Front. Mol. Neurosci.*
<https://doi.org/10.3389/fnmol.2017.00316>
- John, J.P., Thirunavukkarasu, P., Ishizuka, K., Parekh, P., Sawa, A., 2019. An in-silico approach for discovery of microRNA-TF regulation of DISC1 interactome mediating neuronal migration. *npj Syst. Biol. Appl.*
<https://doi.org/10.1038/s41540-019-0094-3>
- Jones, S., 2004. An overview of the basic helix-loop-helix proteins. *Genome Biol.*
<https://doi.org/10.1186/gb-2004-5-6-226>
- Jung, M., Häberle, B.M., Tschakowsky, T., Wittmann, M.T., Balta, E.A., Stadler, V.C., Zweier, C., Dörfler, A., Gloeckner, C.J., Lie, D.C., 2018. Analysis of the expression pattern of the schizophrenia-risk and intellectual disability gene TCF4 in the developing and adult brain suggests a role in development and plasticity of cortical and hippocampal neurons. *Mol. Autism* 9.
<https://doi.org/10.1186/s13229-018-0200-1>
- Katayama, Y., Nishiyama, M., Shoji, H., Ohkawa, Y., Kawamura, A., Sato, T., Suyama, M., Takumi, T., Miyakawa, T., Nakayama, K.I., 2016. CHD8 haploinsufficiency results in autistic-like phenotypes in mice. *Nature*.
<https://doi.org/10.1038/nature19357>
- Kaufman, T.C., Lewis, R., Wakimoto, B., 1980. Cytogenetic analysis of chromosome 3 in *Drosophila melanogaster*: The homoeotic gene complex in polytene chromosome interval 84A-B. *Genetics*.
- Kawada, K., Mimori, S., Okuma, Y., Nomura, Y., 2018. Involvement of endoplasmic reticulum stress and neurite outgrowth in the model mice of autism spectrum disorder. *Neurochem. Int.* 119, 115–119.
<https://doi.org/10.1016/j.neuint.2017.07.004>
- Kennedy, A.J., Rahn, E.J., Paulukaitis, B.S., Savell, K.E., Kordasiewicz, H.B., Wang, J., Lewis, J.W., Posey, J., Strange, S.K., Guzman-Karlsson, M.C., Phillips, S.E., Decker, K., Motley, S.T., Swayze, E.E., Ecker, D.J., Michael, T.P., Day, J.J., Sweatt, J.D., 2016. Tcf4 Regulates Synaptic Plasticity, DNA Methylation, and Memory Function. *Cell Rep.* 16, 2666–2685.
<https://doi.org/10.1016/j.celrep.2016.08.004>
- Kim, K.C., Lee, D.K., Go, H.S., Kim, P., Choi, C.S., Kim, J.W., Jeon, S.J., Song, M.R., Shin, C.Y., 2014. Pax6-dependent cortical glutamatergic neuronal differentiation regulates autism-like behavior in prenatally valproic acid-exposed rat offspring. *Mol. Neurobiol.* <https://doi.org/10.1007/s12035-013-8535-2>
- Kosho, T., Miyake, N., Carey, J.C., 2014. Coffin-Siris syndrome and related disorders involving components of the BAF (mSWI/SNF) complex: Historical review and recent advances using next generation sequencing. *Am. J. Med. Genet. Part C Semin. Med. Genet.* 166, 241–251.
<https://doi.org/10.1002/ajmg.c.31415>
- Kwan, K.Y., Lam, M.M.S., Krsnik, Ž., Kawasawa, Y.I., Lefebvre, V., Šestan, N., 2008. SOX5 postmitotically regulates migration, postmigratory differentiation, and projections of subplate and deep-layer neocortical neurons. *Proc. Natl. Acad. Sci. U. S. A.* 105, 16021–16026.
<https://doi.org/10.1073/pnas.0806791105>
- Kwan, V., Unda, B.K., Singh, K.K., 2016. Wnt signaling networks in autism spectrum disorder and intellectual disability. *J. Neurodev. Disord.*
<https://doi.org/10.1186/s11689-016-9176-3>

- Kwok, C., Weller, P.A., Guioli, S., Foster, J.W., Mansour, S., Zuffardi, O., Punnett, H.H., Dominguez-Steglich, M.A., Brook, J.D., Young, I.D., Goodfellow, P.N., Schafer, A.J., 1995. Mutations in SOX9, the gene responsible for campomelic dysplasia and autosomal sex reversal. *Am. J. Hum. Genet.* 57, 1028–1036.
- Lai, C.S.L., Fisher, S.E., Hurst, J.A., Vargha-Khadem, F., Monaco, A.P., 2001. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature*. <https://doi.org/10.1038/35097076>
- Lamb, A.N., Rosenfeld, J.A., Neill, N.J., Talkowski, M.E., Blumenthal, I., Girirajan, S., Keelean-Fuller, D., Fan, Z., Pouncey, J., Stevens, C., Mackay-Loder, L., Terespolsky, D., Bader, P.I., Rosenbaum, K., Vallee, S.E., Moeschler, J.B., Ladda, R., Sell, S., Martin, J., Ryan, S., Jones, M.C., Moran, R., Shealy, A., Madan-Khetarpal, S., Mcconnell, J., Surti, U., Delahaye, A., Heron-Longe, B., Pipiras, E., Benzacken, B., Passemard, S., Verloes, A., Isidor, B., Le Caignec, C., Glew, G.M., Opheim, K.E., Descartes, M., Eichler, E.E., Morton, C.C., Gusella, J.F., Schultz, R.A., Ballif, B.C., Shaffer, L.G., 2012. Haploinsufficiency of SOX5 at 12p12.1 is associated with developmental delays with prominent language delay, behavior problems, and mild dysmorphic features. *Hum. Mutat.* 33, 728–740. <https://doi.org/10.1002/humu.22037>
- Lambert, S.A., Jolma, A., Campitelli, L.F., Das, P.K., Yin, Y., Albu, M., Chen, X., Taipale, J., Hughes, T.R., Weirauch, M.T., 2018. The Human Transcription Factors. *Cell*. <https://doi.org/10.1016/j.cell.2018.01.029>
- Lee, L.J., Tsytsarev, V., Erzurumlu, R.S., 2017. Structural and functional differences in the barrel cortex of Mecp2 null mice. *J. Comp. Neurol.* 525, 3951–3961. <https://doi.org/10.1002/cne.24315>
- Lein, P.J., 2015. Overview of the Role of Environmental Factors in Neurodevelopmental Disorders, in: *Environmental Factors in Neurodevelopmental and Neurodegenerative Disorders*. <https://doi.org/10.1016/B978-0-12-800228-5.00001-7>
- Leong, W.Y., Lim, Z.H., Korzh, V., Pietri, T., Goh, E.L.K., 2015. Methyl-CpG binding protein 2 (Mecp2) regulates sensory function through Sema5b and Robo2. *Front. Cell. Neurosci.* 9. <https://doi.org/10.3389/fncel.2015.00481>
- Lessel, D., Gehbauer, C., Bramswig, N.C., Schluth-Bolard, C., Venkataramanappa, S., van Gassen, K.L.I., Hempel, M., Haack, T.B., Baresic, A., Genetti, C.A., Funari, M.F.A., Lessel, I., Kuhlmann, L., Simon, R., Liu, P., Denecke, J., Kuechler, A., De Kruijff, I., Shoukier, M., Lek, M., Mullen, T., Lüdecke, H.J., Lerario, A.M., Kobbe, R., Krieger, T., Demeer, B., Lebrun, M., Keren, B., Nava, C., Buratti, J., Afenjar, A., Shinawi, M., Guillen Sacoto, M.J., Gauthier, J., Hamdan, F.F., Laberge, A.M., Campeau, P.M., Louie, R.J., Cathey, S.S., Prinz, I., Jorge, A.A.L., Terhal, P.A., Lenhard, B., Wieczorek, D., Strom, T.M., Agrawal, P.B., Britsch, S., Tolosa, E., Kubisch, C., 2018. BCL11B mutations in patients affected by a neurodevelopmental disorder with reduced type 2 innate lymphoid cells. *Brain* 141, 2299–2311. <https://doi.org/10.1093/brain/awy173>
- Li, J., Dani, J.A., Le, W., 2009. The Role of Transcription Factor Pitx3 in Dopamine Neuron Development and Parkinson's Disease.
- Li, X., Han, X., Tu, X., Zhu, D., Feng, Y., Jiang, T., Yang, Y., Qu, J., Chen, J.G., 2019. An Autism-Related, Nonsense Foxp1 Mutant Induces Autophagy and Delays Radial Migration of the Cortical Neurons. *Cereb. Cortex* 29, 3193–3208. <https://doi.org/10.1093/cercor/bhy185>
- Lindtner, S., Catta-Preta, R., Tian, H., Su-Feher, L., Price, J.D., Dickel, D.E., Greiner, V., Silberberg, S.N., McKinsey, G.L., McManus, M.T., Pennacchio,

- L.A., Visel, A., Nord, A.S., Rubenstein, J.L.R., 2019. Genomic Resolution of DLX-Orchestrated Transcriptional Circuits Driving Development of Forebrain GABAergic Neurons. *Cell Rep.* 28, 2048-2063.e8. <https://doi.org/10.1016/j.celrep.2019.07.022>
- Maenner, M.J., Shaw, K.A., Baio, J., Washington, A., Patrick, M., DiRienzo, M., Christensen, D.L., Wiggins, L.D., Pettygrove, S., Andrews, J.G., Lopez, M., Hudson, A., Baroud, T., Schwenk, Y., White, T., Rosenberg, C.R., Lee, L.C., Harrington, R.A., Huston, M., Hewitt, A., Esler, A., Hall-Lande, J., Poynter, J.N., Hallas-Muchow, L., Constantino, J.N., Fitzgerald, R.T., Zahorodny, W., Shenouda, J., Daniels, J.L., Warren, Z., Vehorn, A., Salinas, A., Durkin, M.S., Dietz, P.M., 2020. Prevalence of autism spectrum disorder among children aged 8 Years-Autism and developmental disabilities monitoring network, 11 Sites, United States, 2016. *MMWR Surveill. Summ.* <https://doi.org/10.15585/MMWR.SS6904A1>
- Mariani, J., Coppola, G., Zhang, P., Abyzov, A., Provini, L., Tomasini, L., Amenduni, M., Szekely, A., Palejev, D., Wilson, M., Gerstein, M., Grigorenko, E.L., Chawarska, K., Pelphrey, K.A., Howe, J.R., Vaccarino, F.M., 2015. FOXP1-Dependent Dysregulation of GABA/Glutamate Neuron Differentiation in Autism Spectrum Disorders. *Cell* 162, 375–390. <https://doi.org/10.1016/j.cell.2015.06.034>
- Masi, A., Glozier, N., Dale, R., Guastella, A.J., 2017. The Immune System, Cytokines, and Biomarkers in Autism Spectrum Disorder. *Neurosci. Bull.* <https://doi.org/10.1007/s12264-017-0103-8>
- Mattei, D., Ivanov, A., Ferrai, C., Jordan, P., Guneykaya, D., Buonfiglioli, A., Schaafsma, W., Przanowski, P., Deuther-Conrad, W., Brust, P., Hesse, S., Patt, M., Sabri, O., Ross, T.L., Eggen, B.J.L., Boddeke, E.W.G.M., Kaminska, B., Beule, D., Pombo, A., Kettenmann, H., Wolf, S.A., 2017. Maternal immune activation results in complex microglial transcriptome signature in the adult offspring that is reversed by minocycline treatment. *Transl. Psychiatry* 7, e1120–e1120. <https://doi.org/10.1038/tp.2017.80>
- Maurer, P., Rorive, S., D'Exaerde, A.D.K., Schiffmann, S.N., Salmon, I., De Launoit, Y., 2004. The Ets transcription factor Fev is specifically expressed in the human central serotonergic neurons. *Neurosci. Lett.* 357, 215–218. <https://doi.org/10.1016/j.neulet.2003.12.086>
- Maynard, T.M., Manzini, M.C., 2017. Balancing Act: Maintaining Amino Acid Levels in the Autistic Brain. *Neuron*. <https://doi.org/10.1016/j.neuron.2017.01.015>
- McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiol. Rev.* <https://doi.org/10.1093/epirev/mxn001>
- Medvedeva, V.P., Rieger, M.A., Vieth, B., Mombereau, C., Ziegenhain, C., Ghosh, T., Cressant, A., Enard, W., Granon, S., Dougherty, J.D., Groszer, M., 2019. Altered social behavior in mice carrying a cortical Foxp2 deletion. *Hum. Mol. Genet.* 28, 701–717. <https://doi.org/10.1093/hmg/ddy372>
- Melbourne, J.K., Rosen, C., Feiner, B., Pang, Y., Sharma, R.P., 2019. The JAK-STAT1 transcriptional signature in peripheral immune cells reveals alterations related to illness duration and acuity in psychosis. *Brain. Behav. Immun.* 77, 37–45. <https://doi.org/10.1016/j.bbi.2018.11.317>
- Mirzaa, G.M., Chong, J.X., Piton, A., Popp, B., Foss, K., Guo, H., Harripaul, R., Xia, K., Scheck, J., Aldinger, K.A., Sajjan, S.A., Tang, S., Bonneau, D., Beck, A., White, J., Mahida, S., Harris, J., Smith-Hicks, C., Hoyer, J., Zweier, C., Reis, A.,

- Thiel, C.T., Jamra, R.A., Zeid, N., Yang, A., Farach, L.S., Walsh, L., Payne, K., Rohena, L., Velinov, M., Ziegler, A., Schaefer, E., Gatinois, V., Geneviève, D., Simon, M.E.H., Kohler, J., Rotenberg, J., Wheeler, P., Larson, A., Ernst, M.E., Akman, C.I., Westman, R., Blanchet, P., Schillaci, L.A., Vincent-Delorme, C., Gripp, K.W., Mattioli, F., Guyader, G. Le, Gerard, B., Mathieu-Dramard, M., Morin, G., Sasanfar, R., Ayub, M., Vasli, N., Yang, S., Person, R., Monaghan, K.G., Nickerson, D.A., van Binsbergen, E., Enns, G.M., Dries, A.M., Rowe, L.J., Tsai, A.C.H., Svihovec, S., Friedman, J., Agha, Z., Qamar, R., Rodan, L.H., Martinez-Agosto, J., Ockeloen, C.W., Vincent, M., Sunderland, W.J., Bernstein, J.A., Eichler, E.E., Vincent, J.B., Bamshad, M.J., 2020. De novo and inherited variants in ZNF292 underlie a neurodevelopmental disorder with features of autism spectrum disorder. *Genet. Med.* <https://doi.org/10.1038/s41436-019-0693-9>
- Mohanty, V., Shah, A., Allender, E., Siddiqui, M.R., Monick, S., Ichi, S., Mania-Farnell, B., G. McLone, D., Tomita, T., Mayanil, C.S., 2016. Folate Receptor Alpha Upregulates *Oct4*, *Sox2* and *Klf4* and Downregulates miR-138 and miR-let-7 in Cranial Neural Crest Cells. *Stem Cells* 34, 2721–2732. <https://doi.org/10.1002/stem.2421>
- Mollinedo, P., Kapitanisky, O., Gonzalez-Lamuño, D., Zaslavsky, A., Real, P., Gozes, I., Gandarillas, A., Fernandez-Luna, J.L., 2019. Cellular and animal models of skin alterations in the autism-related ADNP syndrome. *Sci. Rep.* 9. <https://doi.org/10.1038/s41598-018-36859-2>
- Moreno-Ramos, O.A., Olivares, A.M., Haider, N.B., De Autismo, L.C., Lattig, M.C., 2015. Whole-exome sequencing in a south American cohort links ALDH1A3, FOXN1 and retinoic acid regulation pathways to autism spectrum disorders. *PLoS One* 10. <https://doi.org/10.1371/journal.pone.0135927>
- Morris-Rosendahl, D.J., Crocq, M.A., 2020. Neurodevelopmental disorders-the history and future of a diagnostic concept. *Dialogues Clin. Neurosci.* <https://doi.org/10.31887/DCNS.2020.22.1/macrocq>
- Morris, C.A., 2017. Williams Syndrome.
- Mudryj, A.N., De Groh, M., Aukema, H.M., Yu, N., 2016. Folate intakes from diet and supplements may place certain Canadians at risk for folic acid toxicity. *Br. J. Nutr.* 116, 1236–1245. <https://doi.org/10.1017/S000711451600307X>
- Nadeem, A., Ahmad, S.F., AL-Ayadhi, L.Y., Attia, S.M., Al-Harbi, N.O., Alzahrani, K.S., Bakheet, S.A., 2020. Differential regulation of Nrf2 is linked to elevated inflammation and oxidative stress in monocytes of children with autism. *Psychoneuroendocrinology* 113. <https://doi.org/10.1016/j.psyneuen.2019.104554>
- Nakamura, J.P., Schroeder, A., Hudson, M., Jones, N., Gillespie, B., Du, X., Notaras, M., Swaminathan, V., Reay, W.R., Atkins, J.R., Green, M.J., Carr, V.J., Cairns, M.J., Sundram, S., Hill, R.A., 2019. The maternal immune activation model uncovers a role for the Arx gene in GABAergic dysfunction in schizophrenia. *Brain. Behav. Immun.* 81, 161–171. <https://doi.org/10.1016/j.bbi.2019.06.009>
- Nambot, S., Faivre, L., Mirzaa, G., Thevenon, J., Bruel, A.L., Mosca-Boidron, A.L., Masurel-Paulet, A., Goldenberg, A., Le Meur, N., Charollais, A., Mignot, C., Petit, F., Rossi, M., Metreau, J., Layet, V., Amram, D., Boute-Bénéjean, O., Bhoj, E., Cousin, M.A., Kruisselbrink, T.M., Lanpher, B.C., Klee, E.W., Fiala, E., Grange, D.K., Meschino, W.S., Hiatt, S.M., Cooper, G.M., Olivie, H., Smith, W.E., Dumas, M., Lehman, A., Adam, S., du Souich, C., Elliott, A.M., Mwenifumbo, J., Nelson, T.N., van Karnebeek, C., Friedman, J.M., Inglese, C.,

- Nizon, M., Guerrini, R., Vetro, A., Kaplan, E.S., Miramar, D., Van Gils, J., Fergelot, P., Bodamer, O., Herkert, J.C., Pajusalu, S., Öunap, K., Filiano, J.J., Smol, T., Piton, A., Gérard, B., Chantot-Bastaraud, S., Bienvenu, T., Li, D., Juusola, J., Devriendt, K., Bilan, F., Poé, C., Chevarin, M., Jouan, T., Tisserant, E., Riviére, J.B., Tran Mau-Them, F., Philippe, C., Duffourd, Y., Dobyns, W.B., Hevner, R., Thauvin-Robinet, C., 2020. De novo TBR1 variants cause a neurocognitive phenotype with ID and autistic traits: report of 25 new individuals and review of the literature. *Eur. J. Hum. Genet.* 28, 770–782. <https://doi.org/10.1038/s41431-020-0571-6>
- Nan, X., Cross, S., Bird, A., 1998. Gene silencing by methyl-CpG-binding proteins. *Novartis Found. Symp.* <https://doi.org/10.1002/9780470515501.ch2>
- Navarrete, K., Pedroso, I., De Jong, S., Stefansson, H., Steinberg, S., Stefansson, K., Ophoff, R.A., Schalkwyk, L.C., Collier, D.A., 2013. TCF4 (e2-2; ITF2): A schizophrenia-associated gene with pleiotropic effects on human disease. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* <https://doi.org/10.1002/ajmg.b.32109>
- Nishiura, K., Ichikawa-Tomikawa, N., Sugimoto, K., Kunii, Y., Kashiwagi, K., Tanaka, M., Yokoyama, Y., Hino, M., Sugino, T., Yabe, H., Takahashi, H., Kakita, A., Imura, T., Chiba, H., 2017. PKA activation and endothelial claudin-5 breakdown in the schizophrenic prefrontal cortex. *Oncotarget* 8, 93382–93391. <https://doi.org/10.18632/oncotarget.21850>
- O’Roak, B.J., Stessman, H.A., Boyle, E.A., Witherspoon, K.T., Martin, B., Lee, C., Vives, L., Baker, C., Hiatt, J.B., Nickerson, D.A., Bernier, R., Shendure, J., Eichler, E.E., 2014. Recurrent de novo mutations implicate novel genes underlying simplex autism risk. *Nat. Commun.* 5, 5595. <https://doi.org/10.1038/ncomms6595>
- Ohtsuka, N., Badurek, S., Busslinger, M., Benes, F.M., Minichiello, L., Rudolph, U., 2013. GABAergic neurons regulate lateral ventricular development via transcription factor Pax5. *Genesis* 51, 234–245. <https://doi.org/10.1002/dvg.22370>
- Okada, A., Kushima, K., Aoki, Y., Bialer, M., Fujiwara, M., 2005. Identification of early-responsive genes correlated to valproic acid-induced neural tube defects in mice. *Birth Defects Res. Part A - Clin. Mol. Teratol.* 73, 229–238. <https://doi.org/10.1002/bdra.20131>
- Onishi, Y., Hiraiwa, M., Kamada, H., Iezaki, T., Yamada, T., Kaneda, K., Hinoi, E., 2019. Hypoxia affects Slc7a5 expression through HIF-2 α in differentiated neuronal cells. *FEBS Open Bio* 9, 241–247. <https://doi.org/10.1002/2211-5463.12559>
- Oskvig, D.B., Elkahloun, A.G., Johnson, K.R., Phillips, T.M., Herkenham, M., 2012. Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. *Brain. Behav. Immun.* 26, 623–634. <https://doi.org/10.1016/j.bbi.2012.01.015>
- Oswald, F., Klöble, P., Ruland, A., Rosenkranz, D., Hinz, B., Butter, F., Ramljak, S., Zechner, U., Herlyn, H., 2017. The FOXP2-Driven network in developmental disorders and neurodegeneration. *Front. Cell. Neurosci.* 11, 212. <https://doi.org/10.3389/fncel.2017.00212>
- Pachón, H., Kancherla, V., Handforth, B., Tyler, V., Bauwens, L., 2013. Folic acid fortification of wheat flour: A cost-effective public health intervention to prevent birth defects in Europe. *Nutr. Bull.* 38, 201–209.

- <https://doi.org/10.1111/nbu.12023>
- Page, C.E., Alexander, J., Shepard, R., Coutellier, L., 2018. Npas4 deficiency interacts with adolescent stress to disrupt prefrontal GABAergic maturation and adult cognitive flexibility. *Genes, Brain Behav.* 17. <https://doi.org/10.1111/gbb.12459>
- Page, S.C., Hamersky, G.R., Gallo, R.A., Rannals, M.D., Calcaterra, N.E., Campbell, M.N., Mayfield, B., Briley, A., Phan, B.N., Jaffe, A.E., Maher, B.J., 2018. The schizophrenia-and autism-associated gene, transcription factor 4 regulates the columnar distribution of layer 2/3 prefrontal pyramidal neurons in an activity-dependent manner. *Mol. Psychiatry* 23, 304–315. <https://doi.org/10.1038/mp.2017.37>
- Pariani, M.J., Spencer, A., Graham, J.M., Rimoin, D.L., 2009. A 785 kb deletion of 3p14.1p13, including the FOXP1 gene, associated with speech delay, contractures, hypertonia and blepharophimosis. *Eur. J. Med. Genet.* 52, 123–127. <https://doi.org/10.1016/j.ejmg.2009.03.012>
- Parikshak, N.N., Swarup, V., Belgard, T.G., Irimia, M., Ramaswami, G., Gandal, M.J., Hartl, C., Leppa, V., Ubieta, L.D.L.T., Huang, J., Lowe, J.K., Blencowe, B.J., Horvath, S., Geschwind, D.H., 2016. Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. *Nature* 540, 423–427. <https://doi.org/10.1038/nature20612>
- Park, J.M., Jo, S.H., Kim, M.Y., Kim, T.H., Ahn, Y.H., 2015. Role of transcription factor acetylation in the regulation of metabolic homeostasis. *Protein Cell.* <https://doi.org/10.1007/s13238-015-0204-y>
- Pat Willmer, G.S.I.J., 2004. *Environmental Physiology of Animals*, 2nd Edition | Wiley [WWW Document]. URL <https://www.wiley.com/en-us/Environmental+Physiology+of+Animals%2C+2nd+Edition-p-9781405107242> (accessed 12.16.20).
- Pearl, J.R., Colantuoni, C., Bergey, D.E., Funk, C.C., Shannon, P., Basu, B., Casella, A.M., Oshone, R.T., Hood, L., Price, N.D., Ament, S.A., 2019. Genome-Scale Transcriptional Regulatory Network Models of Psychiatric and Neurodegenerative Disorders. *Cell Syst.* 8, 122–135.e7. <https://doi.org/10.1016/j.cels.2019.01.002>
- Pillai-Kastoori, L., Wen, W., Morris, A.C., 2015. Keeping an eye on SOXC proteins. *Dev. Dyn.* <https://doi.org/10.1002/dvdy.24235>
- Pinacho, R., Saia, G., Meana, J.J., Gill, G., Ramos, B., 2015. Transcription factor SP4 phosphorylation is altered in the postmortem cerebellum of bipolar disorder and schizophrenia subjects. *Eur. Neuropsychopharmacol.* 25, 1650–1660. <https://doi.org/10.1016/j.euroneuro.2015.05.006>
- Pinacho, R., Valdizán, E.M., Pilar-Cuellar, F., Prades, R., Tarragó, T., Haro, J.M., Ferrer, I., Ramos, B., 2014. Increased SP4 and SP1 transcription factor expression in the postmortem hippocampus of chronic schizophrenia. *J. Psychiatr. Res.* 58, 189–196. <https://doi.org/10.1016/j.jpsychires.2014.08.006>
- Pingault, V., Bondurand, N., Kuhlbrodt, K., Goerich, D.E., Préhu, M.O., Puliti, A., Herbarth, B., Hermans-Borgmeyer, I., Legius, E., Matthijs, G., Amiel, J., Lyonnet, S., Ceccherini, I., Romeo, G., Smith, J.C., Read, A.P., Wegner, M., Goossens, M., 1998. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. *Nat. Genet.* 18, 171–173. <https://doi.org/10.1038/ng0298-171>
- Poitras, L., Yu, M., Lesage-Pelletier, C., MacDonald, R.B., Gagné, J.P., Hatch, G., Kelly, I., Hamilton, S.P., Rubenstein, J.L.R., Poirier, G.G., Ekker, M., 2010. An

- SNP in an ultraconserved regulatory element affects *Dlx5/Dlx6* regulation in the forebrain. *Development* 137, 3089–3097. <https://doi.org/10.1242/dev.051052>
- Prasad, M., Balci, T.B., Prasad, C., Andrews, J.D., Lee, R., Jurkiewicz, M.T., Napier, M.P., Colaiacovo, S., Guillen Sacoto, M.J., Karp, N., 2020. BCL11B-related disorder in two canadian children: Expanding the clinical phenotype. *Eur. J. Med. Genet.* 63. <https://doi.org/10.1016/j.ejmg.2020.104007>
- Proulx, É., Young, E.J., Osborne, L.R., Lambe, E.K., 2010. Enhanced prefrontal serotonin 5-HT_{1A} currents in a mouse model of Williams-Beuren syndrome with low innate anxiety. *J. Neurodev. Disord.* 2, 99–108. <https://doi.org/10.1007/s11689-010-9044-5>
- Punwani, D., Zhang, Y., Yu, J., Cowan, M.J., Rana, S., Kwan, A., Adhikari, A.N., Lizama, C.O., Mendelsohn, B.A., Fahl, S.P., Chellappan, A., Srinivasan, R., Brenner, S.E., Wiest, D.L., Puck, J.M., 2016. Multisystem Anomalies in Severe Combined Immunodeficiency with Mutant BCL11B. *N. Engl. J. Med.* 375, 2165–2176. <https://doi.org/10.1056/nejmoa1509164>
- Qiao, F., Wang, C., Luo, C., Wang, Y., Shao, B., Tan, J., Hu, P., Xu, Z., 2019. A De Novo heterozygous frameshift mutation identified in BCL11B causes neurodevelopmental disorder by whole exome sequencing. *Mol. Genet. Genomic Med.* 7. <https://doi.org/10.1002/mgg3.897>
- Ramachandran, A., Parisien, J.-P., Horvath, C.M., 2008. STAT2 Is a Primary Target for Measles Virus V Protein-Mediated Alpha/Beta Interferon Signaling Inhibition. *J. Virol.* 82, 8330–8338. <https://doi.org/10.1128/jvi.00831-08>
- Ripke, S., Neale, B.M., Corvin, A., Walters, J.T.R., Farh, K.H., Holmans, P.A., Lee, P., Bulik-Sullivan, B., Collier, D.A., Huang, H., Pers, T.H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S.A., Begemann, M., Belliveau, R.A., Bene, J., Bergen, S.E., Bevilacqua, E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N.G., Buckner, R.L., Byerley, W., Cahn, W., Cai, G., Campion, D., Cantor, R.M., Carr, V.J., Carrera, N., Catts, S. V., Chambert, K.D., Chan, R.C.K., Chen, R.Y.L., Chen, E.Y.H., Cheng, W., Cheung, E.F.C., Chong, S.A., Cloninger, C.R., Cohen, D., Cohen, N., Cormican, P., Craddock, N., Crowley, J.J., Curtis, D., Davidson, M., Davis, K.L., Degenhardt, F., Del Favero, J., Demontis, D., Dikeos, D., Dinan, T., Djurovic, S., Donohoe, G., Drapeau, E., Duan, J., Dudbridge, F., Durmishi, N., Eichhammer, P., Eriksson, J., Escott-Price, V., Essioux, L., Fanous, A.H., Farrell, M.S., Frank, J., Franke, L., Freedman, R., Freimer, N.B., Friedl, M., Friedman, J.I., Fromer, M., Genovese, G., Georgieva, L., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., Golimbet, V., Gopal, S., Gratten, J., De Haan, L., Hammer, C., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V., Hartmann, A.M., Henskens, F.A., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A., Hollegaard, M. V., Hougaard, D.M., Ikeda, M., Joa, I., Julià, A., Kahn, R.S., Kalaydjieva, L., Karachanak-Yankova, S., Karjalainen, J., Kavanagh, D., Keller, M.C., Kennedy, J.L., Khrunin, A., Kim, Y., Klovins, J., Knowles, J.A., Konte, B., Kucinskas, V., Kucinskiene, Z.A., Kuzelova-Ptackova, H., Kähler, A.K., Laurent, C., Keong, J.L.C., Lee, S.H., Legge, S.E., Lerer, B., Li, M., Li, T., Liang, K.Y., Lieberman, J., Limborska, S., Loughland, C.M., Lubinski, J., Lönngqvist, J., Macek, M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J., Marsal, S., Mattheisen, M., Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier, S., Meijer, C.J., Meleghe, B., Melle, I., Meshulam-Gatley, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mokrab, Y., Morris, D.W., Mors, O., Murphy, K.C., Murray, R.M., Myin-Germeys, I., Müller-Myhsok, B., Nelis, M., Nenadic, I.,

- Nertney, D.A., Nestadt, G., Nicodemus, K.K., Nikitina-Zake, L., Nisenbaum, L., Nordin, A., O'Callaghan, E., O'Dushlaine, C., O'Neill, F.A., Oh, S.Y., Olincy, A., Olsen, L., Van Os, J., Pantelis, C., Papadimitriou, G.N., Papiol, S., Parkhomenko, E., Pato, M.T., Paunio, T., Pejovic-Milovancevic, M., Perkins, D.O., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A., Pulver, A.E., Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M.A., Richards, A.L., Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R., Schall, U., Schubert, C.R., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman, L.J., Shi, J., Sigurdsson, E., Silagadze, T., Silverman, J.M., Sim, K., Slominsky, P., Smoller, J.W., So, H.C., Spencer, C.C.A., Stahl, E.A., Stefansson, H., Steinberg, S., Stogmann, E., Straub, R.E., Strengman, E., Strohmaier, J., Stroup, T.S., Subramaniam, M., Suvisaari, J., Svrakic, D.M., Szatkiewicz, J.P., Söderman, E., Thirumalai, S., Toncheva, D., Tosato, S., Veijola, J., Waddington, J., Walsh, D., Wang, D., Wang, Q., Webb, B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams, S., Witt, S.H., Wolen, A.R., Wong, E.H.M., Wormley, B.K., Xi, H.S., Zai, C.C., Zheng, X., Zimprich, F., Wray, N.R., Stefansson, K., Visscher, P.M., Adolfsson, R., Andreassen, O.A., Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Børglum, A.D., Cichon, S., Darvasi, A., Domenici, E., Ehrenreich, H., Esko, T., Gejman, P. V., Gill, M., Gurling, H., Hultman, C.M., Iwata, N., Jablensky, A. V., Jönsson, E.G., Kendler, K.S., Kirov, G., Knight, J., Lencz, T., Levinson, D.F., Li, Q.S., Liu, J., Malhotra, A.K., McCarroll, S.A., McQuillin, A., Moran, J.L., Mortensen, P.B., Mowry, B.J., Nöthen, M.M., Ophoff, R.A., Owen, M.J., Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D., Rietschel, M., Riley, B.P., Rujescu, D., Sham, P.C., Sklar, P., St Clair, D., Weinberger, D.R., Wendland, J.R., Werge, T., Daly, M.J., Sullivan, P.F., O'Donovan, M.C., 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*.
<https://doi.org/10.1038/nature13595>
- Ronan, J.L., Wu, W., Crabtree, G.R., 2013. From neural development to cognition: Unexpected roles for chromatin. *Nat. Rev. Genet.*
<https://doi.org/10.1038/nrg3413>
- Rosato, M., Stringer, S., Gebuis, T., Paliukhovich, I., Li, K.W., Posthuma, D., Sullivan, P.F., Smit, A.B., van Kesteren, R.E., 2019. Combined cellomics and proteomics analysis reveals shared neuronal morphology and molecular pathway phenotypes for multiple schizophrenia risk genes. *Mol. Psychiatry*.
<https://doi.org/10.1038/s41380-019-0436-y>
- Rosenberg, R.N., Pascual, J.M., 2014. *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease: Fifth Edition*, Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease: Fifth Edition.
- Sakurai, K., Shioda, K., Eguchi, A., Watanabe, M., Miyaso, H., Mori, C., Shioda, T., 2019. DNA methylome of human neonatal umbilical cord: Enrichment of differentially methylated regions compared to umbilical cord blood DNA at transcription factor genes involved in body patterning and effects of maternal folate deficiency or children's sex. *PLoS One* 14, e0214307.
<https://doi.org/10.1371/JOURNAL.PONE.0214307>
- Sánchez-Alvarez, R., Gayen, S., Vadigepalli, R., Anni, H., 2013. Ethanol Diverts Early Neuronal Differentiation Trajectory of Embryonic Stem Cells by Disrupting the Balance of Lineage Specifiers. *PLoS One* 8, e63794.
<https://doi.org/10.1371/journal.pone.0063794>
- Sarmah, S., Srivastava, R., McClintick, J.N., Janga, S.C., Edenberg, H.J., Marrs,

- J.A., 2020. Embryonic ethanol exposure alters expression of sox2 and other early transcripts in zebrafish, producing gastrulation defects. *Sci. Rep.* 10. <https://doi.org/10.1038/s41598-020-59043-x>
- Schafer, D.P., Heller, C.T., Gunner, G., Heller, M., Gordon, C., Hammond, T., Wolf, Y., Jung, S., Stevens, B., 2016. Microglia contribute to circuit defects in Mecp2 null mice independent of microglia-specific loss of Mecp2 expression. *Elife* 5. <https://doi.org/10.7554/eLife.15224>
- Schmidt-Kastner, R., Guloksuz, S., Kietzmann, T., van Os, J., Rutten, B.P.F., 2020. Analysis of GWAS-Derived Schizophrenia Genes for Links to Ischemia-Hypoxia Response of the Brain. *Front. Psychiatry* 11, 1. <https://doi.org/10.3389/fpsy.2020.00393>
- Schoof, M., Hellwig, M., Harrison, L., Holdhof, D., Lauffer, M.C., Niesen, J., Viridi, S., Indenbirken, D., Schüller, U., 2020. The basic helix-loop-helix transcription factor TCF4 impacts brain architecture as well as neuronal morphology and differentiation. *Eur. J. Neurosci.* 51, 2219–2235. <https://doi.org/10.1111/ejn.14674>
- Schuster, J., Laan, L., Klar, J., Jin, Z., Huss, M., Korol, S., Noraddin, F.H., Sobol, M., Birnir, B., Dahl, N., 2019. Transcriptomes of Dravet syndrome iPSC derived GABAergic cells reveal dysregulated pathways for chromatin remodeling and neurodevelopment. *Neurobiol. Dis.* 132, 104583. <https://doi.org/10.1016/j.nbd.2019.104583>
- Sepp, M., Vihma, H., Nurm, K., Urb, M., Page, S.C., Roots, K., Hark, A., Maher, B.J., Pruunsild, P., Timmusk, T., 2017. The intellectual disability and schizophrenia associated transcription factor TCF4 is regulated by neuronal activity and protein kinase A. *J. Neurosci.* 37, 10516–10527. <https://doi.org/10.1523/JNEUROSCI.1151-17.2017>
- Sgadò, P., Genovesi, S., Kalinovsky, A., Zunino, G., Macchi, F., Allegra, M., Murenu, E., Provenzano, G., Tripathi, P.P., Casarosa, S., Joyner, A.L., Bozzi, Y., 2013. Loss of GABAergic neurons in the hippocampus and cerebral cortex of Engrailed-2 null mutant mice: Implications for autism spectrum disorders. *Exp Neurol* 247, 496–505. <https://doi.org/10.1016/j.expneurol.2013.01.021>
- Shafique, S., Winn, L.M., 2020. Gestational exposure to valproic acid upregulates total Stat3 protein expression while downregulating phosphorylated Stat3 in CD-1 mouse embryos with neural tube defects. *Birth Defects Res.* 112, 555–568. <https://doi.org/10.1002/bdr2.1666>
- Shahbazian, M.D., Zoghbi, H.Y., 2001. Molecular genetics of Rett syndrome and clinical spectrum of MECP2 mutations. *Curr. Opin. Neurol.* <https://doi.org/10.1097/00019052-200104000-00006>
- Sharma, K., Singh, J., Pillai, P.P., Frost, E.E., 2015. Involvement of MeCP2 in Regulation of Myelin-Related Gene Expression in Cultured Rat Oligodendrocytes. *J. Mol. Neurosci.* 57, 176–184. <https://doi.org/10.1007/s12031-015-0597-3>
- Sharma, R.P., Rosen, C., Melbourne, J.K., Feiner, B., Chase, K.A., 2017. Activated phosphorylated STAT1 levels as a biologically relevant immune signal in schizophrenia. *Neuroimmunomodulation* 23, 224–229. <https://doi.org/10.1159/000450581>
- Shepard, R., Heslin, K., Coutellier, L., 2017. The transcription factor Npas4 contributes to adolescent development of prefrontal inhibitory circuits, and to cognitive and emotional functions: Implications for neuropsychiatric disorders. *Neurobiol. Dis.* 99, 36–46. <https://doi.org/10.1016/j.nbd.2016.12.012>

- Shepard, R., Heslin, K., Hagerdorn, P., Coutellier, L., 2019. Downregulation of Npas4 in parvalbumin interneurons and cognitive deficits after neonatal NMDA receptor blockade: relevance for schizophrenia. *Transl. Psychiatry*. <https://doi.org/10.1038/s41398-019-0436-3>
- Sigal, Y.M., Bae, H., Bogart, L.J., Hensch, T.K., Zhuang, X., 2019. Structural maturation of cortical perineuronal nets and their perforating synapses revealed by superresolution imaging. *Proc. Natl. Acad. Sci. U. S. A.* 116, 7071–7076. <https://doi.org/10.1073/pnas.1817222116>
- Simon, R., Wiegrefe, C., Britsch, S., 2020. Bcl11 Transcription Factors Regulate Cortical Development and Function. *Front. Mol. Neurosci.* <https://doi.org/10.3389/fnmol.2020.00051>
- Siniscalco, D., Schultz, S., Brigida, A.L., Antonucci, N., 2018. Inflammation and neuro-immune dysregulations in autism spectrum disorders. *Pharmaceuticals*. <https://doi.org/10.3390/ph11020056>
- Sollis, E., Deriziotis, P., Saitsu, H., Miyake, N., Matsumoto, N., Hoffer, M.J.V., Ruivenkamp, C.A.L., Alders, M., Okamoto, N., Bijlsma, E.K., Plomp, A.S., Fisher, S.E., 2017. Equivalent missense variant in the FOXP2 and FOXP1 transcription factors causes distinct neurodevelopmental disorders. *Hum. Mutat.* 38, 1542–1554. <https://doi.org/10.1002/humu.23303>
- Song, L., Huang, S.S.C., Wise, A., Castano, R., Nery, J.R., Chen, H., Watanabe, M., Thomas, J., Bar-Joseph, Z., Ecker, J.R., 2016. A transcription factor hierarchy defines an environmental stress response network. *Science* (80-.). 354. <https://doi.org/10.1126/science.aag1550>
- Spiegel, I., Mardinly, A.R., Gabel, H.W., Bazinet, J.E., Couch, C.H., Tzeng, C.P., Harmin, D.A., Greenberg, M.E., 2014. Npas4 regulates excitatory-inhibitory balance within neural circuits through cell-type-specific gene programs. *Cell* 157, 1216–1229. <https://doi.org/10.1016/j.cell.2014.03.058>
- Sragovich, S., Malishkevich, A., Piontkewitz, Y., Giladi, E., Touloumi, O., Lagoudaki, R., Grigoriadis, N., Gozes, I., 2019. The autism/neuroprotection-linked ADNP/NAP regulate the excitatory glutamatergic synapse. *Transl. Psychiatry* 9. <https://doi.org/10.1038/s41398-018-0357-6>
- Sragovich, S., Merenlender-Wagner, A., Gozes, I., 2017. ADNP Plays a Key Role in Autophagy: From Autism to Schizophrenia and Alzheimer's Disease. *BioEssays*. <https://doi.org/10.1002/bies.201700054>
- Stefansson, H., Ophoff, R.A., Steinberg, S., Andreassen, O.A., Cichon, S., Rujescu, D., Werge, T., Pietiläinen, O.P.H., Mors, O., Mortensen, P.B., Sigurdsson, E., Gustafsson, O., Nyegaard, M., Tuulio-Henriksson, A., Ingason, A., Hansen, T., Suvisaari, J., Lonnqvist, J., Paunio, T., Børghlum, A.D., Hartmann, A., Fink-Jensen, A., Nordentoft, M., Hougaard, D., Norgaard-Pedersen, B., Böttcher, Y., Olesen, J., Breuer, R., Möller, H.J., Giegling, I., Rasmussen, H.B., Timm, S., Mattheisen, M., Bitter, I., Réthelyi, J.M., Magnusdottir, B.B., Sigmundsson, T., Olason, P., Masson, G., Gulcher, J.R., Haraldsson, M., Fossdal, R., Thorgeirsson, T.E., Thorsteinsdottir, U., Ruggeri, M., Tosato, S., Franke, B., Strengman, E., Kiemeny, L.A., Melle, I., Djurovic, S., Abramova, L., Kaleda, V., Sanjuan, J., De Frutos, R., Bramon, E., Vassos, E., Fraser, G., Ettinger, U., Picchioni, M., Walker, N., Touloupoulou, T., Need, A.C., Ge, D., Lim Yoon, J., Shianna, K. V., Freimer, N.B., Cantor, R.M., Murray, R., Kong, A., Golimbet, V., Carracedo, A., Arango, C., Costas, J., Jönsson, E.G., Terenius, L., Agartz, I., Petursson, H., Nöthen, M.M., Rietschel, M., Matthews, P.M., Muglia, P., Peltonen, L., St Clair, D., Goldstein, D.B., Stefansson, K., Collier, D.A., Kahn,

- R.S., Linszen, D.H., Van Os, J., Wiersma, D., Bruggeman, R., Cahn, W., De Haan, L., Krabbendam, L., Myin-Germeys, I., 2009. Common variants conferring risk of schizophrenia. *Nature* 460, 744–747. <https://doi.org/10.1038/nature08186>
- Steinberg, S., de Jong, S., Andreassen, O.A., Werge, T., Børglum, A.D., Mors, O., Mortensen, P.B., Gustafsson, O., Costas, J., Pietiläinen, O.P.H., Demontis, D., Papiol, S., Huttenlocher, J., Mattheisen, M., Breuer, R., Vassos, E., Giegling, I., Fraser, G., Walker, N., Tuulio-Henriksson, A., Suvisaari, J., Lönngqvist, J., Paunio, T., Agartz, I., Melle, I., Djurovic, S., Strengman, E., Jürgens, G., Glenthøj, B., Terenius, L., Hougaard, D.M., Ørntoft, T., Wiuf, C., Didriksen, M., Hollegaard, M. V., Nordentoft, M., van Winkel, R., Kenis, G., Abramova, L., Kaleda, V., Arrojo, M., Sanjuán, J., Arango, C., Sperling, S., Rossner, M., Ribolsi, M., Magni, V., Siracusano, A., Christiansen, C., Kiemene, L.A., Veldink, J., van den Berg, L., Ingason, A., Muglia, P., Murray, R., Nöthen, M.M., Sigurdsson, E., Petursson, H., Thorsteinsdottir, U., Kong, A., Rubino, I.A., de Hert, M., Réthelyi, J.M., Bitter, I., Jönsson, E.G., Golimbet, V., Carracedo, A., Ehrenreich, H., Craddock, N., Owen, M.J., O'Donovan, M.C., Ruggeri, M., Tosato, S., Peltonen, L., Ophoff, R.A., Collier, D.A., St Clair, D., Rietschel, M., Cichon, S., Stefansson, H., Rujescu, D., Stefansson, K., 2011. Common variants at VRK2 and TCF4 conferring risk of schizophrenia. *Hum. Mol. Genet.* 20, 4076–4081. <https://doi.org/10.1093/hmg/ddr325>
- Sudiwala, S., Palmer, A., Massa, V., Burns, A.J., Dunlevy, L.P.E., De Castro, S.C.P.S.C.P., Savery, D., Leung, K.Y., Copp, A.J., Greene, N.D.E., 2019. Cellular mechanisms underlying Pax3-related neural tube defects and their prevention by folic acid. *DMM Dis. Model. Mech.* 12. <https://doi.org/10.1242/dmm.042234>
- Sun, C.P., Sun, D., Luan, Z.L., Dai, X., Bie, X., Ming, W.H., Sun, X.W., Huo, X.X., Lu, T.L., Zhang, D., 2020. Association of SOX11 Polymorphisms in distal 3'UTR with Susceptibility for Schizophrenia. *J. Clin. Lab. Anal.* 34. <https://doi.org/10.1002/jcla.23306>
- Sun, Y., Gao, Y., Tidei, J.J., Shen, M., Hoang, J.T., Wagner, D.F., Zhao, X., 2019. Loss of MeCP2 in immature neurons leads to impaired network integration. *Hum. Mol. Genet.* 28, 245–257. <https://doi.org/10.1093/hmg/ddy338>
- Szklarczyk, D., Gable, A.L., Lyon, D., Junge, A., Wyder, S., Huerta-Cepas, J., Simonovic, M., Doncheva, N.T., Morris, J.H., Bork, P., Jensen, L.J., Von Mering, C., 2019. STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res.* <https://doi.org/10.1093/nar/gky1131>
- Tamberg, L., Jaago, M., Säälk, K., Sirp, A., Tuvikene, J., Shubina, A., Kiir, C.S., Nurm, K., Sepp, M., Timmusk, T., Palgi, M., 2020. Daughterless, the Drosophila orthologue of TCF4, is required for associative learning and maintenance of the synaptic proteome. *DMM Dis. Model. Mech.* 13. <https://doi.org/10.1242/dmm.042747>
- Taylor, M.R., Roby, C.R., Elziny, S., Duricy, E., Taylor, T.M., Bowers, J.M., 2020. Age, but Not Sex, Modulates Foxp3 Expression in the Rat Brain across Development. *Neuroscience* 442, 87–99. <https://doi.org/10.1016/j.neuroscience.2020.06.032>
- Teramitsu, I., Kudo, L.C., London, S.E., Geschwind, D.H., White, S.A., 2004. Parallel FoxP1 and FoxP2 Expression in Songbird and Human Brain Predicts Functional Interaction. *J. Neurosci.* 24, 3152–3163. <https://doi.org/10.1523/JNEUROSCI.5589-03.2004>

- Thaxton, X.C., Kloth, A.D., Clark, E.P., Moy, S.S., Chitwood, R.A., Benjamin, X., Philpot, D., 2018. Neurobiology of Disease Common Pathophysiology in Multiple Mouse Models of Pitt-Hopkins Syndrome. <https://doi.org/10.1523/JNEUROSCI.1305-17.2017>
- The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Mol. Autism* 8, 21. <https://doi.org/10.1186/s13229-017-0137-9>
- Thiel, G., Ekici, M., Rössler, O.G., 2015. RE-1 silencing transcription factor (REST): A regulator of neuronal development and neuronal/endocrine function. *Cell Tissue Res.* <https://doi.org/10.1007/s00441-014-1963-0>
- Torshizi, A.D., Armoskus, C., Zhang, H., Forrest, M.P., Zhang, S., Souaiaia, T., Evgrafov, O. V., Knowles, J.A., Duan, J., Wang, K., 2019. Deconvolution of transcriptional networks identifies TCF4 as a master regulator in schizophrenia. *Sci. Adv.* 5. <https://doi.org/10.1126/sciadv.aau4139>
- Tropeano, M., Howley, D., Gazzellone, M.J., Wilson, C.E., Ahn, J.W., Stavropoulos, D.J., Murphy, C.M., Eis, P.S., Eli Hatchwell, E., Dobson, R.J.B., Robertson, D., Holder, M., Irving, M., Josifova, D., Nehammer, A., Ryten, M., Spain, D., Pitts, M., Bramham, J., Asherson, P., Curran, S., Vassos, E., Breen, G., Flinter, F., Ogilvie, C.M., Collier, D.A., Scherer, S.W., McAlonan, G.M., Murphy, D.G., 2016. Microduplications at the pseudoautosomal SHOX locus in autism spectrum disorders and related neurodevelopmental conditions. *J. Med. Genet.* 53, 536–547. <https://doi.org/10.1136/jmedgenet-2015-103621>
- Uematsu, K., Heiman, M., Zelenina, M., Padovan, J., Chait, B.T., Aperia, A., Nishi, A., Greengard, P., 2015. Protein kinase A directly phosphorylates metabotropic glutamate receptor 5 to modulate its function. *J. Neurochem.* 132, 677–686. <https://doi.org/10.1111/jnc.13038>
- van Rhijn, J.R., Fisher, S.E., Vernes, S.C., Nadif Kasri, N., 2018. Foxp2 loss of function increases striatal direct pathway inhibition via increased GABA release. *Brain Struct. Funct.* 223, 4211–4226. <https://doi.org/10.1007/s00429-018-1746-6>
- van Tilborg, E., Achterberg, E.J.M., van Kammen, C.M., van der Toorn, A., Groenendaal, F., Dijkhuizen, R.M., Heijnen, C.J., Vanderschuren, L.J.M.J., Benders, M.N.J.L., Nijboer, C.H.A., 2018. Combined fetal inflammation and postnatal hypoxia causes myelin deficits and autism-like behavior in a rat model of diffuse white matter injury. *Glia* 66, 78–93. <https://doi.org/10.1002/glia.23216>
- Vegas, N., Cavallin, M., Kleefstra, T., de Boer, L., Philbert, M., Maillard, C., Boddaert, N., Munnich, A., Hubert, L., Bery, A., Besmond, C., Bahi-Buisson, N., 2018. Mutations in TBR1 gene leads to cortical malformations and intellectual disability. *Eur. J. Med. Genet.* 61, 759–764. <https://doi.org/10.1016/j.ejmg.2018.09.012>
- Viaggi, C., Gerace, C., Pardini, C., Corsini, G.U., Vaglini, F., 2015. Serotonin abnormalities in Engrailed-2 knockout mice: New insight relevant for a model of Autism Spectrum Disorder. *Neurochem. Int.* 87, 34–42. <https://doi.org/10.1016/j.neuint.2015.05.004>
- Vicente-franqueira, R., Amich, J., Marín, L., Sánchez, C.I., Leal, F., Calera, J.A., 2018. The transcription factor ZafA regulates the homeostatic and adaptive response to Zinc starvation in *aspergillus fumigatus*. *Genes (Basel)*. 9. <https://doi.org/10.3390/genes9070318>
- Vogelgesang, S., Niebert, M., Bischoff, A.M., Hülsmann, S., Manzke, T., 2018.

- Persistent expression of serotonin receptor 5b alters breathing behavior in male MeCP2 knockout mice. *Front. Mol. Neurosci.* 11. <https://doi.org/10.3389/fnmol.2018.00028>
- Vogelgesang, S., Niebert, S., Renner, U., Möbius, W., Hülsmann, S., Manzke, T., Niebert, M., 2017. Analysis of the serotonergic system in a mouse model of Rett syndrome reveals unusual upregulation of serotonin receptor 5b. *Front. Mol. Neurosci.* 10. <https://doi.org/10.3389/fnmol.2017.00061>
- Volk, D.W., Edelson, J.R., Lewis, D.A., 2016. Altered expression of developmental regulators of parvalbumin and somatostatin neurons in the prefrontal cortex in schizophrenia. *Schizophr. Res.* 177, 3–9. <https://doi.org/10.1016/j.schres.2016.03.001>
- Volk, D.W., Lewis, D.A., 2014. Early developmental disturbances of cortical inhibitory neurons: Contribution to cognitive deficits in schizophrenia. *Schizophr. Bull.* 40, 952–957. <https://doi.org/10.1093/schbul/sbu111>
- Volk, D.W., Matsubara, T., Li, S., Sengupta, E.J., Georgiev, D., Minabe, Y., Sampson, A., Hashimoto, T., Lewis, D.A., 2012. Deficits in transcriptional regulators of cortical parvalbumin neurons in schizophrenia. *Am. J. Psychiatry* 169, 1082–1091. <https://doi.org/10.1176/appi.ajp.2012.12030305>
- Wang, C., Wang, F., Cao, Q., Li, Z., Huang, L., Chen, S., 2018. The effect of Mecp2 on heart failure. *Cell. Physiol. Biochem.* 47, 2380–2387. <https://doi.org/10.1159/000491610>
- Wang, Y., Lu, Z., Zhang, Yilan, Cai, Y., Yun, D., Tang, T., Cai, Z., Wang, C., Zhang, Yandong, Fang, F., Yang, Z., Behnisch, T., Xie, Y., 2020. Transcription Factor 4 Safeguards Hippocampal Dentate Gyrus Development by Regulating Neural Progenitor Migration. *Cereb. Cortex* 30, 3102–3115. <https://doi.org/10.1093/cercor/bhz297>
- Weatherbee, S.D., Halder, G., Kim, J., Hudson, A., Carroll, S., 1998. Ultrabithorax regulates genes at several levels of the wing-patterning hierarchy to shape the development of the *Drosophila* haltere. *Genes Dev.* <https://doi.org/10.1101/gad.12.10.1474>
- Weaving, L.S., Ellaway, C.J., Géczy, J., Christodoulou, J., 2005. Rett syndrome: Clinical review and genetic update. *J. Med. Genet.* <https://doi.org/10.1136/jmg.2004.027730>
- Williams, E.C., Zhong, X., Mohamed, A., Li, R., Liu, Y., Dong, Q., Ananiev, G.E., Choongmok, J.C., Lin, B.R., Lu, J., Chiao, C., Cherney, R., Li, H., Zhang, S.C., Chang, Q., 2014. Mutant astrocytes differentiated from Rett syndrome patients-specific iPSCs have adverse effects on wildtype neurons. *Hum. Mol. Genet.* 23, 2968–2980. <https://doi.org/10.1093/hmg/ddu008>
- Wingender, E., Schoeps, T., Haubrock, M., Dönitz, J., 2015. TFClass: A classification of human transcription factors and their rodent orthologs. *Nucleic Acids Res.* <https://doi.org/10.1093/nar/gku1064>
- Wirgenes, K. V., Sønderby, I.E., Haukvik, U.K., Mattingsdal, M., Tesli, M., Athanasiu, L., Sundet, K., Røssberg, J.I., Dale, A.M., Brown, A.A., Agartz, I., Melle, I., Djurovic, S., Andreassen, O.A., 2012. TCF4 sequence variants and mRNA levels are associated with neurodevelopmental characteristics in psychotic disorders. *Transl. Psychiatry* 2. <https://doi.org/10.1038/tp.2012.39>
- Wong, L.C., Singh, S., Wang, H.P., Hsu, C.J., Hu, S.C., Lee, W.T., 2019. FOXG1-related syndrome: From clinical to molecular genetics and pathogenic mechanisms. *Int. J. Mol. Sci.* <https://doi.org/10.3390/ijms20174176>
- Wu, C.-C., Jiang, X., Wang, X.-Z., Liu, X.-J., Li, X.-J., Yang, B., Ye, H.-Q., Harwardt,

- T., Jiang, M., Xia, H.-M., Wang, W., Britt, W.J., Paulus, C., Nevels, M., Luo, M.-H., 2018. Human Cytomegalovirus Immediate Early 1 Protein Causes Loss of SOX2 from Neural Progenitor Cells by Trapping Unphosphorylated STAT3 in the Nucleus. *J. Virol.* 92. <https://doi.org/10.1128/jvi.00340-18>
- Wu, G., Haw, R., 2017. Functional interaction network construction and analysis for disease discovery, in: *Methods in Molecular Biology*. Humana Press Inc., pp. 235–253. https://doi.org/10.1007/978-1-4939-6783-4_11
- Wu, Y., Hou, F., Wang, X., Kong, Q., Han, X., Bai, B., 2016. Aberrant expression of histone deacetylases 4 in cognitive disorders: Molecular mechanisms and a potential target. *Front. Mol. Neurosci.* <https://doi.org/10.3389/fnmol.2016.00114>
- Xia, H., Jahr, F.M., Kim, N.K., Xie, L., Shabalin, A.A., Bryois, J., Sweet, D.H., Kronfol, M.M., Palasuberniam, P., McRae, M.P., Riley, B.P., Sullivan, P.F., Van Den Oord, E.J., McClay, J.L., 2018. Building a schizophrenia genetic network: Transcription factor 4 regulates genes involved in neuronal development and schizophrenia risk. *Hum. Mol. Genet.* 27, 3246–3256. <https://doi.org/10.1093/hmg/ddy222>
- Xin, B., Rohs, R., 2018. Relationship between histone modifications and transcription factor binding is protein family specific. *Genome Res.* <https://doi.org/10.1101/gr.220079.116>
- Xu, S., Liu, P., Chen, Yuanxing, Chen, Yi, Zhang, W., Zhao, H., Cao, Y., Wang, F., Jiang, N., Lin, S., Li, B., Zhang, Z., Wei, Z., Fan, Y., Jin, Y., He, L., Zhou, R., Dekker, J.D., Tucker, H.O., Fisher, S.E., Yao, Z., Liu, Q., Xia, X., Guo, X., 2018. Foxp2 regulates anatomical features that may be relevant for vocal behaviors and bipedal locomotion. *Proc. Natl. Acad. Sci. U. S. A.* 115, 8799–8804. <https://doi.org/10.1073/pnas.1721820115>
- Yang, P., Lung, F.-W., Jong, Y.-J., Hsieh, H.-Y., Liang, C.-L., Juo, S.-H.H., 2008. Association of the Homeobox Transcription Factor Gene ENGRAILED 2 with Autistic Disorder in Chinese Children. *Neuropsychobiology* 57, 3–8. <https://doi.org/10.1159/000123115>
- Yang, W., Liu, J., Zheng, F., Jia, M., Zhao, L., Lu, T., Ruan, Y., Zhang, J., Yue, W., Zhang, D., Wang, L., 2013. The Evidence for Association of ATP2B2 Polymorphisms with Autism in Chinese Han Population. *PLoS One* 8. <https://doi.org/10.1371/journal.pone.0061021>
- Yeh, H., Ikezu, T., 2019. Transcriptional and Epigenetic Regulation of Microglia in Health and Disease. *Trends Mol. Med.* <https://doi.org/10.1016/j.molmed.2018.11.004>
- Žaja, R., Aydin, G., Lippok, B.E., Feederle, R., Lüscher, B., Feijs, K.L.H., 2020. Comparative analysis of MACROD1, MACROD2 and TARG1 expression, localisation and interactome. *Sci. Rep.* <https://doi.org/10.1038/s41598-020-64623-y>
- Zawerton, A., Mignot, C., Sigafos, A., Blackburn, P.R., Haseeb, A., McWalter, K., Ichikawa, S., Nava, C., Keren, B., Charles, P., Marey, I., Tabet, A.C., Levy, J., Perrin, L., Hartmann, A., Lesca, G., Schluth-Bolard, C., Monin, P., Dupuis-Girod, S., Guillen Sacoto, M.J., Schnur, R.E., Zhu, Z., Poisson, A., El Chehadeh, S., Alembik, Y., Bruel, A.L., Lehalle, D., Nambot, S., Moutton, S., Odent, S., Jaillard, S., Dubourg, C., Hilhorst-Hofstee, Y., Barbaro-Dieber, T., Ortega, L., Bhoj, E.J., Masser-Frye, D., Bird, L.M., Lindstrom, K., Ramsey, K.M., Narayanan, V., Fassi, E., Willing, M., Cole, T., Salter, C.G., Akilapa, R., Vandersteen, A., Canham, N., Rump, P., Gerkes, E.H., Klein Wassink-Ruiter, J.S., Bijlsma, E., Hoffer, M.J.V., Vargas, M., Wojcik, A., Cherk, F., Francannet,

- C., Rosenfeld, J.A., Machol, K., Scott, D.A., Bacino, C.A., Wang, X., Clark, G.D., Bertoli, M., Zvolinski, S., Thomas, R.H., Akay, E., Chang, R.C., Bressi, R., Sanchez Russo, R., Srouf, M., Russell, L., Goyette, A.M.E., Dupuis, L., Mendoza-Londono, R., Karimov, C., Joseph, M., Nizon, M., Cogné, B., Kuechler, A., Piton, A., Klee, E.W., Lefebvre, V., Clark, K.J., Depienne, C., 2020. Widening of the genetic and clinical spectrum of Lamb–Shaffer syndrome, a neurodevelopmental disorder due to SOX5 haploinsufficiency. *Genet. Med.* 22, 524–537. <https://doi.org/10.1038/s41436-019-0657-0>
- Zazo Seco, C., Plaisancié, J., Lupasco, T., Michot, C., Pechmeja, J., Delanne, J., Cottureau, E., Ayuso, C., Corton, M., Calvas, P., Ragge, N., Chassaing, N., 2018. Identification of PITX3 mutations in individuals with various ocular developmental defects. *Ophthalmic Genet.* 39, 314–320. <https://doi.org/10.1080/13816810.2018.1430243>
- Zhao, L.X., Ge, Y.H., Li, J.B., Xiong, C.H., Law, P.Y., Xu, J.R., Qiu, Y., Chen, H.Z., 2019. M1 muscarinic receptors regulate the phosphorylation of AMPA receptor subunit GluA1 via a signaling pathway linking cAMP-PKA and PI3K-Akt. *FASEB J.* 33, 6622–6631. <https://doi.org/10.1096/fj.201802351R>
- Zhu, X., Gu, H., Liu, Z., Xu, Z., Chen, X., Sun, X., Zhai, J., Zhang, Q., Chen, M., Wang, K., Deng, X., Ji, F., Liu, C., Li, J., Dong, Q., Chen, C., 2013. Associations between TCF4 gene polymorphism and cognitive functions in schizophrenia patients and healthy controls. *Neuropsychopharmacology* 38, 683–689. <https://doi.org/10.1038/npp.2012.234>
- Zuiki, M., Chiyonobu, T., Yoshida, M., Maeda, H., Yamashita, S., Kidowaki, S., Hasegawa, T., Gotoh, H., Nomura, T., Ono, K., Hosoi, H., Morimoto, M., 2017. Luteolin attenuates interleukin-6-mediated astrogliosis in human iPSC-derived neural aggregates: A candidate preventive substance for maternal immune activation-induced abnormalities. *Neurosci. Lett.* 653, 296–301. <https://doi.org/10.1016/j.neulet.2017.06.004>

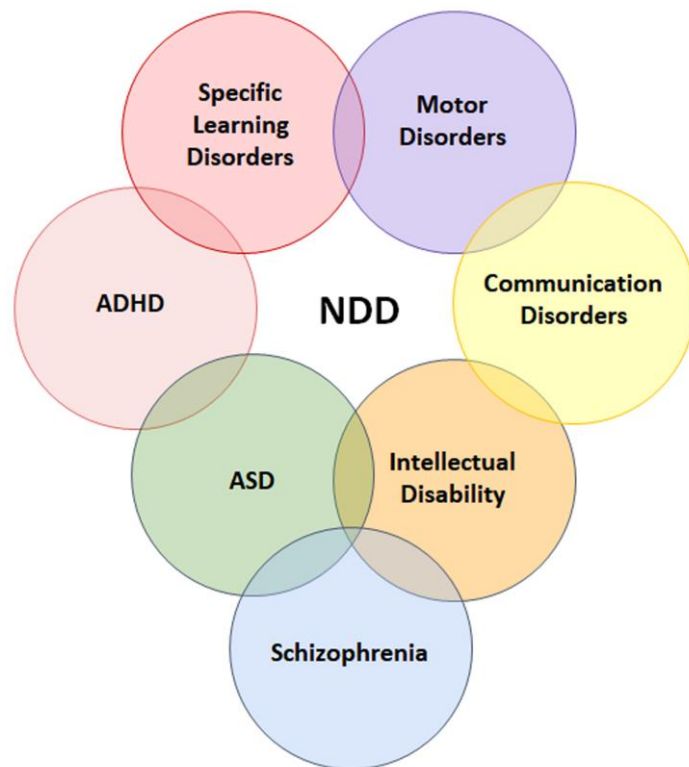


Figure 1: Diagram of neurodevelopmental disorders (NDD). Representation of the disorders included in the group of NDDs according to DSM-5, highlighting the chosen for this review.

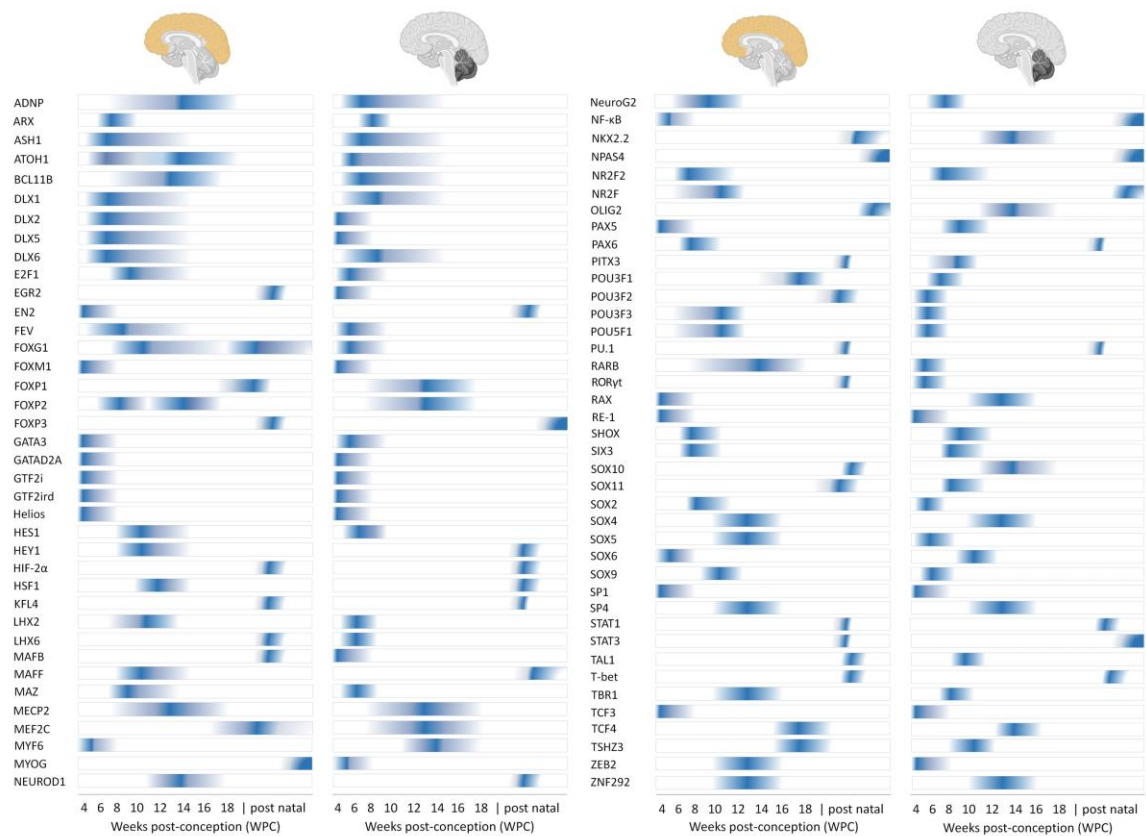


Figure 2: Time course of transcription factors expression. The double columns indicate patterns of expression in the human forebrain (left) and in the cerebellum (right). Blue gradient intensity is associated with expression peaks throughout time. Detailed information is available on Table 1. Adaptation from CARDOSO-MOREIRA, M. et al., 2019.

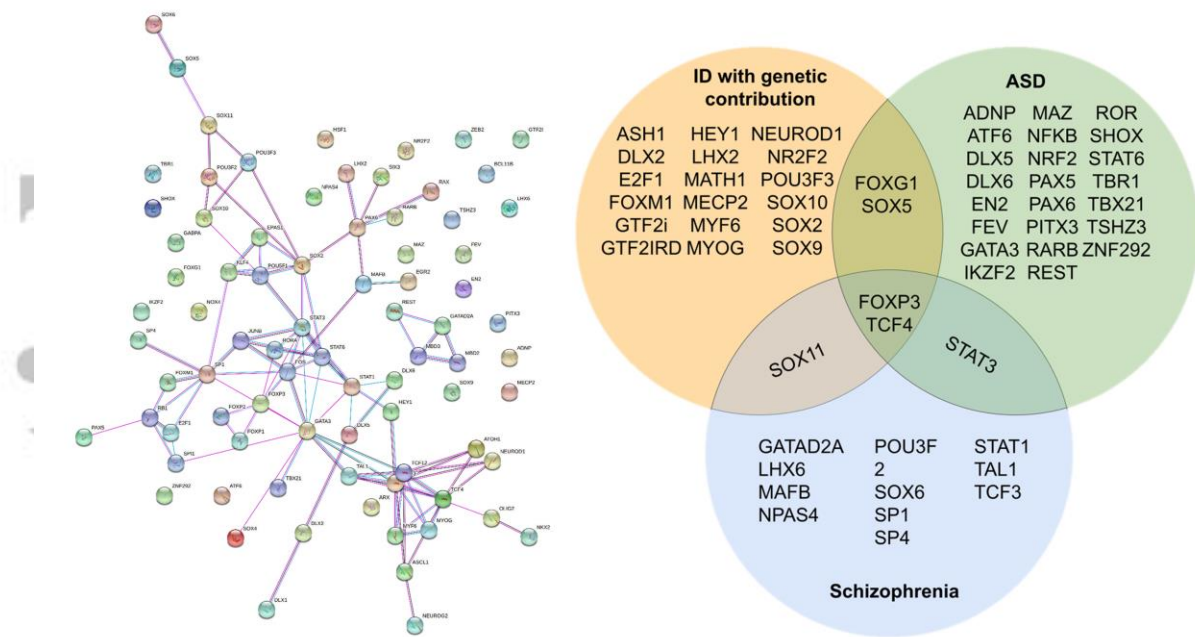


Figure 3: Interaction between transcription factors (TFs) distribution among the disorders. String Database map (Szklarczyk et al., 2019) demonstrates the interaction between all TFs listed in this review, while the Venn Diagram represents common and different points of TF involvement in the disorders discussed in this review. Black lines represent co-expression, cyan lines represent interactions observed in curated databases, and pink lines represent interactions observed experimentally.

Table 1: Compiled of all transcription factors addressed in this review.

Information regarding DNA-binding sites was obtained from a database provided by LAMBERT, S. A. et al., 2018. TFs are represented in alphabetical order according to their classes. Regions or cells with high expression of the factors in embryos were described (In this context, nervous system, immune system, and eye were considered since they are associated with the scope of the review). Some TFs do not present a peculiar pattern of expression in these regions (for example, if the expression remains at similar rates throughout development), so they are described as “Low expression specificity”. bHLH: basic helix-loop-helix; bZIP: basic leucine zipper domain; HMG: high mobility group box; WPC: weeks post conception; ZF: zinc finger. *GTF2i and GTF2ird had less information regarding time course of expression for humans, the represented data were obtained from mouse studies. Superscript numbers in the TFs indicate the section where they are cited and discussed. TFs complete denominations are described in Supplementary Table 1. ** The TF is considered a differential marker of the associated group of cells.

TF	Main DBD	Regions or Cells with high expression during embryo life
ASH1 / ASCL1 ^{2,3}	bHLH	Brain: Lateral, Medial and Caudal Ganglionic Eminence Progenitor Cells; d3**, d4** and d5** Neural Progenitor Cells; Anterior Entopeduncular Progenitor Cells Eye: Bipolar Precursor Cells; GABAergic Amacrine Cells; Rod Precursor Cells.
ATOH1/MATH1 ²	bHLH	Brain: Oligodendrocyte Precursor Cells**
HES1 ³	bHLH	Nervous System: Adult Oligodendrocyte Precursor Cells. Eye: Anterior Lens Epithelial Cells; Equatorial Lens Epithelial Cells; Late Retinal Progenitor Cells**; Muller Glia Precursor Cells**; Early Retinal Progenitor Cells**.
HEY1 ²	bHLH	Nervous System: Hypothalamus; Hippocampus; Thalamus; Cerebellum; Amygdala; Striatum; Medulla Oblongata; Cerebral Cortex; Pons
HIF-2α ³	bHLH	Low expression specificity
MYF6 ²	bHLH	Eye: All Amacrine Cells
MYOG ²	bHLH	Low expression specificity
NEUROD1 ^{2,3}	bHLH	Nervous System: Primitive Spinal Cord; Mesencephalic Ventricular Zone; Telencephalon; Diencephalon; Metencephalic Alar Plate; Spinal Ventral Columns; Cerebellar Ventricular Zone; Spinal Dorsal Columns; Metencephalic Basal Plate; Epithalamus; Pituitary Gland; Cerebellum; Midbrain tegmentum; Lateral Ventricle Eye: All Amacrine Cells; Bipolar Precursor Cells; Cone Precursor Cells; Mature Rod Bipolar Cells; Rod Precursor Cells; Mature Rod Cells;

NEUROG2 ³	bHLH	Nervous System: Meso-diencephalic Dopaminergic Precursor Cells **; Motor Neural Progenitor Cells Eye: Cholinergic Amacrine Cells; Bipolar Precursor Cells; Displaced Amacrine Cells; GABAergic Amacrine Cells; Dopaminergic Amacrine Cells
NPAS4 ⁵	bHLH	Nervous System: Amygdala, Anterior Cingulate Cortex, Caudate, Frontal Cortex, Hippocampus, Hypothalamus, Nucleus Accumbens, Putamen, Substantia Nigra, Cerebellar Cortex
OLIG2 ³	bHLH	Nervous System: Oligodendrocyte Precursor Cells; MN Progenitor Cells**; Lateral, Medial** and Central Ganglionic Eminence Progenitor Cells; Anterior Entopeduncular Progenitor Cells; Neocortical Radial Glia Cells; Protoplasmic Astrocyte Cells
TAL1 ⁵	bHLH	Nervous System: V2 Neural Progenitor Cells**
TCF3 ⁵	bHLH	Nervous System: Oligodendrocyte Precursor Cells Immune System: Small Pre B-Cells; Pro B-Cells; B-cell Progenitor Cells; Large Pre B-Cells; Immature B-Cells
TCF4 ^{2,4,6}	bHLH	Nervous System: Hypothalamus; Thalamus; Striatum; Medulla Oblongata; Cerebral Cortex; Midbrain tegmentum Eye: Amacrine Cells Immune System: pre Conventional Dendritic Cells; Plasmacytoid Dendritic cells; Mature B-Cells
MAFB ⁵	bZIP	Nervous System: Roof Plate Cells; Cranial Neural Crest Cells. Eye: Anterior Lens Epithelial Cells
MAFF ³	bZIP	Nervous System: Cerebral Cortex, Hippocampus, Basal Ganglia, Cerebellum Immune Cells: Granulocytes, NK cells
NRF2 ⁴	bZIP	Low expression specificity
BCL11B ⁶	C2H2 ZF	Immune System: T Helper Cells; T-Cytotoxic Cells; Double Negative 2 Thymocytes
EGR2 ³	C2H2 ZF	Nervous System: Myelinating Schwann Cells**
Helios/ IKZF2 ⁴	C2H2 ZF	Immune System: T cells, B cells, Granulocytes
KLF4 ³	C2H2 ZF	Immune System: Macrophages
MAZ ⁴	C2H2 ZF	Low expression specificity
RE-1 or REST ^{3,4}	C2H2 ZF	Low expression specificity
SP1 ⁵	C2H2 ZF	Eye: Fetal Corneal Basal Epithelial Cells; Keratocytes; Endothelial Cells; Keratoblasts
SP4 ⁵	C2H2 ZF	Nervous System: Hypothalamus; Hippocampus; Thalamus; Cerebellum; Amygdala; Striatum; Medulla Oblongata; Cerebral Cortex; Pons
TSHZ3 ⁴	C2H2 ZF	Immune System: Natural Killer Cells, Neutrophil
ZNF292 ⁴	C2H2 ZF	Immune System: pre-Conventional Dendritic Cells

ZEB2³	C2H2 ZF; Homeodomain	Nervous System: Myelinating Oligodendrocyte Cells
E2F1²	E2F	No differential expression during embryo stages
FEV⁴	Ets	Nervous System: Hypothalamus; Cerebellum; Amygdala; Cerebral Cortex; Midbrain tegmentum; Midbrain; Lateral funiculus; Midbrain; Basal Forebrain; Pons+Medulla;Septum;
PU.1³	Ets	Immune System: Small Pre B-Cells; Pro B-Cells Granulocytes; Osteoclast Precursor Cells**; B-cell Progenitor Cells
FOXP1^{2,4}	Forkhead	Nervous System: Telencephalic Progenitor Cells**; Mature Endothelial Cells
FOXM1²	Forkhead	No differential expression during embryo stages
FOXP1⁶	Forkhead	Nervous System: Lateral motor column neuron-like cells
FOXP2⁶	Forkhead	No differential expression during embryo stages
FOXP3^{2,4,5}	Forkhead	Nervous System: Hypothalamus Eye: Retina Immune System: CD4+ lymphocyte
GATA3⁴	GATA	Immune System: Hematopoietic Stem Cells**; Common Lymphoid Progenitor Cells**
GATAD2A⁵	GATA	No differential expression during embryo stages
GTF2ⁱ²	GTF2I-like	No differential expression during embryo stages
GTF2ird²	GTF2I-like	No differential expression during embryo stages
SOX10²	HMG/Sox	Nervous System: Oligodendrocyte Precursor Cells**; Schwann Precursor Cells**Diencephalic Neural Crest Cells**; Mesencephalic Neural Crest Cells**; Rhombencephalic Neural Crest Cells**
SOX11^{2,5}	HMG/Sox	No differential expression during embryo stages
SOX2^{2,3}	HMG/Sox	Nervous System: Bergmann Glia; Adult Neural Stem Cells Eye: Late Retinal Progenitor Cells Preplacodal Lens Ectoderm Cells Early Retinal Progenitor Cells Lens Placode Cells
SOX4³	HMG/Sox	Nervous System: Telencephalon; Metencephalic Alar Plate; Spinal Dorsal Columns; Metencephalic Basal Plate Immune System: Plasmacytoid Dendritic cells; Megakaryocyte-Erythroid Precursor Cells; Conventional Dendritic Cells II
SOX5^{2,4}	HMG/Sox	Nervous System: Oligodendrocyte Precursor Cells
SOX6⁵	HMG/Sox	Nervous System: Adult Dopaminergic Neurons; Adult Oligodendrocyte Precursor Cells; Oligodendrocyte Precursor Cells
SOX9²	HMG/Sox	Nervous System: Late MN Progenitor Cells; d3, d4 and d5 Neural Progenitor Cells; Bergmann Glia; Adult Neural Stem Cells; Endothelial Cells; Oligodendrocyte Precursor Cells; Eye: Late Retinal Progenitor Cells; Mature Muller Glia Cells; Mature Retinal Pigmented Epithelium Cells;

ADNP⁴	Homeodomain	No differential expression during embryo stages
ARX³	Homeodomain	Nervous System: Floor Plate Cells Late Floor Plate Cells
DLX1³	Homeodomain	Nervous System: Lateral Ganglionic Eminence Progenitor Cells; Anterior Entopeduncular Progenitor Cells; Caudal Ganglionic Eminence Progenitor Cells; Medial Ganglionic Eminence Progenitor Cells; Endothelial Cells; Mesencephalic Neural Crest Cells; Cranial Neural Crest Cells;
DLX2^{2,3}	Homeodomain	Nervous System: Lateral, Medial and Caudal Ganglionic Eminence Progenitor Cells; Anterior Entopeduncular Progenitor Cells; Mature Endothelial Cells; Endothelial Cells Eye: Mature Horizontal Cells; Dopaminergic Amacrine Cells; Dopaminergic Amacrine Cells; Mature Ganglion Cells;
DLX5^{3,4}	Homeodomain	Nervous System: Mesencephalic Neural Crest Cells; Diencephalic Neural Crest Cells; Cranial Neural Crest Cells
DLX6⁴	Homeodomain	Nervous System: Cranial Neural Crest Cells
EN2⁴	Homeodomain	Nervous System: Fetal Dopaminergic Neurons; Myelinating Oligodendrocyte Cells; Dopaminergic Progenitor Cells; Early Floor Plate Cells; Meso-diencephalic Dopaminergic Precursor Cells; Hinge Point Cells; Isthmus Cells; Neural Fold Cells;
LHX2²	Homeodomain	Nervous System: Primitive Spinal Cord; Telencephalon; Mesencephalic Basal Plate; Diencephalon; Metencephalic Alar Plate; Metencephalic Basal Plate Eye: Late Retinal Progenitor Cells; Mature Muller Glia Cells; Early Retinal Progenitor Cells; Retinal Pigmented Epithelium Progenitor Cells;
LHX6⁵	Homeodomain	Nervous System: Medial Ganglionic Eminence Progenitor Cells**Cranial Neural Crest Cells**
NKX2.2³	Homeodomain	Nervous System: Myelinating Oligodendrocyte Cells; Late MN Progenitor Cells **, V3 Neural Progenitor Cells; Astrocyte Precursor Cells; Basal Plate Cells
PITX3⁴	Homeodomain	Nervous System: Dopaminergic Neurons Eye: Anterior Lens Epithelial Cells; Lens Vesicle Cells; Lens Placode Cells
RAX³	Homeodomain	Nervous System: Hypothalamus; Pituitary Gland; Thalamus; Pons Eye: Late Retinal Progenitor Cells; Mature Rod Cells; Muller Glia Precursor Cells; Early Retinal Progenitor Cells;
SHOX⁴	Homeodomain	No differential expression during embryo stages
SIX3³	Homeodomain	Nervous System: Anterior Neural Ridge Cells; Zona Limitans Intrathalamica Cells; Neural Fold Cells; Cranial Neural Plate Cells; Intraembryonic Neural Ectoderm Cells;
PAX6^{3,4}	Homeodomain; Paired box	Nervous System: Lateral and Caudal Ganglionic Eminence Progenitor Cells; d3, d4 and d5 Neural Progenitor Cells; Mature Endothelial Cells; Endothelial Cells; Neocortical Radial Glia Cells; Early MN Progenitor Cells; VA1 and VA2 Fibrous Astrocyte Cells;

POU3F1 ³	Homeodomain; POU	No differential expression during embryo stages
POU3F2 ⁵	Homeodomain; POU	Nervous System: Pro-myelinating Schwann Cells**; Immature Schwann Cells
POU3F3 ²	Homeodomain; POU	Nervous System: Hypothalamus; Thalamus; Striatum; Medulla Oblongata; Cerebral Cortex; Midbrain tegmentum; Mesencephalic Ventricular Zone; Telencephalon; Diencephalic Ventricular Zone; Diencephalon; Metencephalic Alar Plate; Cerebellar Ventricular Zone Metencephalic Basal Plate
POU5F1 ³	Homeodomain; POU	No differential expression during embryo stages
HSF1 ³	HSF	No differential expression during embryo stages
MEF2C ⁶	MADS box	Nervous System: Telencephalon; Metencephalic Alar Plate; Metencephalic Basal Plate
MECP2 ²	Methyl-CpG DNA-binding, AT-hook	No differential expression during embryo stages
NR2F2 ²	Nuclear receptor	No differential expression during embryo stages
RARB ⁴	Nuclear receptor	No differential expression during embryo stages
RORyt ⁴	Nuclear receptor	Immune System: Double Positive Thymocytes
PAX5 ⁴	Paired box	Nervous System: Metencephalic Alar Plate; Metencephalic Basal Plate Immune System: Small Pre B-Cells; Pro B-Cells; Large Pre B-Cells; Immature B-Cells
NF-Kb ^{3,4}	Rel	Nervous System: Medulla Oblongata; Metencephalic Basal Plate
STAT1 ⁵	STAT	Nervous System: Cerebral Cortex Immune System: T Helper Cells; T-Cytotoxic Cells
STAT3 ^{3,4}	STAT	No differential expression during embryo stages
T-bet ⁴	T-box	Eye: GABAergic Amacrine Cells
TBR1 ^{3,4}	T-box	Nervous System: Hypothalamus; Thalamus Cerebral Cortex; Telencephalon; Diencephalon; Metencephalic Alar Plate

Table 2: Enriched pathways associated with the set of transcription factors described as altered in Section 2 – Genetic-associated neurodevelopmental disorders. All TFs described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The table is an adaptation of the complete map (Supplementary Figure 1). ¹Rett Syndrome; ²Pitt Hopkins Syndrome; ³SOX-associated disorders (Lamb-Shaffer Syndrome; Waardenburg–Hirschprung disease, campomelic dysplasia and Coffin-Siris Syndrome); ⁴Williams Syndrome; ⁵Dravet Syndrome.

Gene Transcription
Alteration in MECP2 binding processes to methylated DNA¹; Regulation of MECP2 transcription and its activity on TF and pathways associated with GABAergic signaling¹; FOXO-mediated transcription of cell cycle genes¹ Regulation of transcription mediated by RUNX1 AND 3 genes³ Regulation of the transcription pathway associated with the YAP1 TF⁴; Regulation of transcription associated with the development of Treg lymphocytes⁴.
Cell Cycle ⁵
Cyclin D signaling⁵; Regulation of DNA duplication processes⁵; Regulation of G1 and G2 states and cellular differentiation processes⁵.
WNT/ β -catenin Pathway ²
Developmental Biology Pathways ³
Activation of HOX genes during differentiation³ Schwann cell myelination³
NOTCH 3/4 signaling pathway ⁴
Myogenesis ⁴

Table 3: Enriched pathways associated with the set of transcription factors described as altered in Section 3 – Environmental factors and TFs in Psychiatric Disorders. All TF described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The table is an adaptation of the complete map (Supplementary Figure 2). The superscript numbers indicate overlaps of enriched pathways observed in this section with: ¹Genetic disorders; ² Autism Spectrum Disorder, and ³Schizophrenia.

Gene Transcription
Regulation of RNA polymerases I and II ^{1,2,3} ; Regulation of siRNA and miRNA biogenesis; Regulation of transcription associated with RUNX 1 and 3 genes ^{1,2,3} .
Cell Signaling
Autophagy; Establishment of senescence-associated secretory phenotype; Estrogen signaling; Leptin signaling ^{2,3} ; NF-kb signaling ² ; NTRK signaling; Response to hypoxia; β-catenin deactivation ^{2,3} ; Notch signaling
Development
Activation of HOX genes ^{1,2} ; Adipocyte differentiation; Cell proliferation ^{2,3} ; Granulopoiesis ³ ; Maintenance of differentiation especially in the rhombencephalon ² ; Myogenesis ³ ; Regulation of myelination in Schwann cells ¹ ; Stem cell differentiation ^{2,3} .
Immune System

Control of inflammasome production²;
Interferon Signaling^{2,3};
Interleukin signaling (IL1², IL4², IL6^{2,3}, IL9^{2,3}, IL12^{2,3}, IL13^{2,3}, IL15^{2,3}, IL17², IL21², IL23^{2,3}, IL27^{2,3},
IL35^{2,3})
MAPK activation²;
Regulation of pathways associated with Toll-like 2, 3, 4, 5, 7, 8, 9 and 10 receptors.

Accepted Article

Table 4: Enriched pathways associated with the set of transcription factors described as altered in Section 4.1 - Autism Spectrum Disorder (ASD) and TFs.

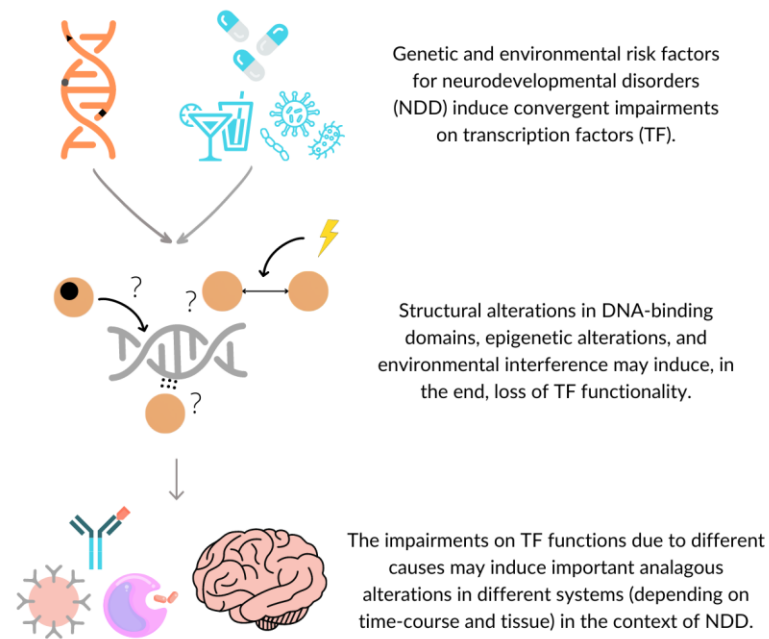
The TFs described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The figure is an adaptation of the complete map (Supplementary Figure 3).

Gene Transcription
Epigenetic regulation of genetic transcription; Regulation of pathways associated with nuclear receptors; Regulation of RNA polymerases I and II; Regulation of transcription associated with MECP2; Regulation of transcription associated with RUNX 1, 2 and 3 TF and their impact on the WNT pathway.
Cell Signaling
Leptin signaling; NF- κ b signaling; PDGF signaling; Tyrosine kinase receptor signaling; WNT / beta catenin signaling.
Development
Activation of HOX genes; Cell proliferation; Maintenance of differentiation especially in the rhombencephalon; Stem cell differentiation.
Immune System
Activation of chemokine production; Control of inflammasome production; Detection of pathogenic DNA and signal transduction; GM-CSF signaling; Interferon signaling; Interleukin signaling (IL1, IL3, IL4, IL5, IL6, IL9, IL12, IL13, IL15, IL17, IL21, IL23, IL27, IL35); MAPK activation.
Protein Metabolism
Activation of chaperones. Incretin signaling; Synthesis of peptide hormones.

Table 5: Enriched pathways associated with the set of transcription factors described as altered in Section 4.2 – Schizophrenia and TFs. The TFs described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The Table is an adaptation of the complete map (Supplementary Figure 4).

Gene Transcription
Epigenetic regulation of gene transcription; Regulation of RNA polymerases I and II; Regulation of transcription associated with MECP2; Regulation of transcription associated with RUNX 1, 2 and 3 genes.
Cell Signaling
Leptin signaling; PDGF Signaling; SCF/KIT Signaling; Tyrosine kinase receptor signaling; WNT/ β -catenin signaling; WNT-independent β -catenin pathways; β -catenin degradation complex.
Development
Cell proliferation; Granulopoiesis; Myogenesis; NODAL signaling; Stem cell differentiation.
Immune System
Growth hormone signaling; Interferon alpha, beta and gamma signaling; Interleukin signaling (IL2, IL4, IL6, IL9, IL12, IL13, IL15, IL20, IL23, IL27, IL35).

Graphical Abstract



Accepted