Schizophrenia Bulletin vol. 36 no. 3 pp. 443–447, 2010
doi:10.1093/schbul/sbq035
Advance Access publication on April 26, 2010

TCF4, Schizophrenia, and Pitt-Hopkins Syndrome

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Genome-wide association studies allied with the identification of rare copy number variants have provided important insights into the genetic risk factors for schizophrenia. Recently, a meta-analysis of several genome-wide association studies found, in addition to several other markers, a single nucleotide polymorphism in intron 4 of the *TCF4* gene that was associated with schizophrenia. *TCF4* encodes a basic helix-loop-helix transcription factor that interacts with other transcription factors to activate or repress gene expression. *TCF4* mutations also cause Pitt-Hopkins Syndrome, an autosomal-dominant neurodevelopmental disorder associated with severe mental retardation. Variants in the *TCF4* gene may therefore be associated with a range of neuropsychiatric phenotypes, including schizophrenia. Recessive forms of Pitt-Hopkins syndrome are caused by mutations in *NRXN1* and *CNTNAP2*. Interestingly, *NRXN1* deletions have been reported in schizophrenia, whereas *CNTNAP2* variants are associated with several neuropsychiatric phenotypes. These data suggest that *TCF4*, *NRXN1*, and *CNTNAP2* may participate in a biological pathway that is altered in patients with schizophrenia and other neuropsychiatric disorders.

Key words: schizophrenia/mental retardation/transcription factor/Pitt-Hopkins syndrome/TCF4/NRXN1/CNTNAP2

Introduction

Although a small number of genetic loci have now been strongly implicated as risk factors for schizophrenia, most of these have yet to yield novel insights into the biology of the disease. A possible exception is the implication of neurexin-1 (NRXN1) and associated proteins in disease pathogenesis through the identification of copy number variants (CNVs) associated with an approximately 5-fold increased risk of schizophrenia.[1] *NRXN1* deletions are rare even in cases (0.19%), and this raises the question of the importance of *NRXN1* for the disorder as a whole or at least a sizable proportion of it. Genome-wide association (GWA) studies have also led to the discovery of several new risk alleles for schizophrenia.[2–5] Unlike *NRXN1* deletions, these are common in the population, but the relative risks conferred are substantially lower (<1.5). For example, a synthesis of several recent GWA studies of schizophrenia with follow-up in additional samples identified a single-nucleotide polymorphism on chromosome 18q21.2 within *transcription factor 4* (*TCF4*) that was associated with an increased risk of schizophrenia at a level of support ($P = 4.1 \times 10^{-9}$) that surpasses a widely held benchmark for genome-wide significance.[5] TCF4 is a basic helix-loop-helix (bHLH) transcription factor that regulates gene expression in the immune system and in the brain during development. Haploinsufficiency of *TCF4* causes a dominant form of Pitt-Hopkins Syndrome (PTHS), a developmental disorder associated with severe mental retardation. Remarkably, autosomal recessive forms of PTHS can also be caused by deletions and missense mutations in *NRXN1* and another gene previously implicated by CNV analysis in schizophrenia and other neuropsychiatric diseases, *contactin-associated protein like-2* (*CNTNAP2*).[6] These findings potentially point to a functional link between TCF4 and both NRXN1 and CNTNAP2 and suggest that these proteins play a role in the pathogenic mechanisms of general relevance to schizophrenia and related disorders.

TCF4 and Brain Development

First, a word of caution concerning nomenclature is required. *TCF4* (Gene ID: 6925) and *TCF7L2* (Gene ID: 6934) loci are frequently confused because they share the TCF4 alias. TCF4 is the official symbol for TCF4, the protein discussed in this review, but it is also a widely used alternative name for T-cell–specific TCF4 (TCF7L2). In the present review, we have taken considerable care to include for consideration only those

data which apply to the former. TCF4 is a member of the bHLH transcription factor family homologous to the *Drosophila* protein daughterless. bHLH transcription factors can be divided into several phylogenetic groups based upon their sequence composition, expression pattern, and ability to interact with other bHLH proteins.[7]

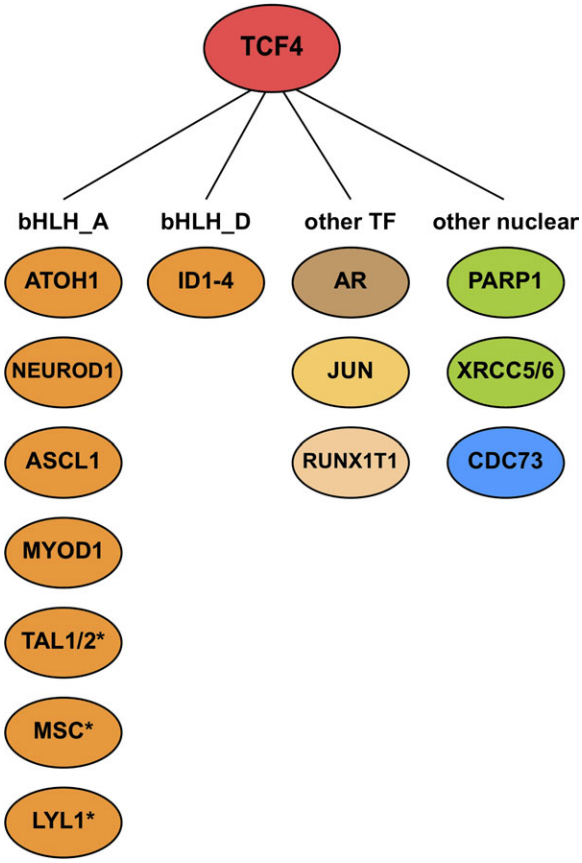

Fig. 1. The TCF4 Interactome. Although capable of homodimerization, TCF4 appears to activate or repress gene expression by forming heterodimers with other transcription factors, most notably members of the basic helix-loop-helix (bHLH) superfamily. From a functional perspective, it is necessary to consider the protein-protein interactions that constitute the TCF4 interactome alongside TCF4 itself. The BioGRID database (http://www.thebiogrid.org) was search for genes interacting with human and murine TCF4.[8] Importantly, the list of interactors was manually curated to remove genes that interact with TCF7L2. Functional clusters with group A and group D bHLH proteins are indicated. T-cell/B-cell bHLH transcription factors have been identified with an asterisk. Gene names: AR, androgen receptor; ASCL1, achaete-scute complex homolog 1, also known as HASH1 or MASH1; ATOH1, atonal homolog 1, also known as MATH1; CDC73, cell division cycle 73; ID1–4, inhibitor of DNA binding 1–4; JUN, jun oncogene; LYL1, lymphoblastic leukemia derived sequence 1; MSC, musculin; MYOD1, myogenic differentiation 1; NEUROD1, neurogenic differentiation 1; PARP, poly (ADP-ribose) polymerase 1; RUNX1T1, runt-related transcription factor 1; TAL1, T-cell acute lymphocytic leukemia 1; TAL2, T-cell acute lymphocytic leukemia 2; XRCC5, X-ray repair complementing defective repair in Chinese hamster cells 5; XRCC6, X-ray repair complementing defective repair in Chinese hamster cells 6.

Briefly, group A, which includes TCF4, and group B bHLH proteins bind core DNA sequences referred to as E (Ephrussi)-boxes defined loosely by the sequence CANNTG. Group C bHLH proteins are also known as bHLH-Per-Arnt-Sim (PAS) because in addition to the bHLH domain, they also contain a PAS domain. Group D HLH proteins lack a basic domain and are hence unable to bind DNA. Group E-proteins are related to *Drosophila hairy* and *enhancer of split* proteins and bind preferentially to N-box sequences (CACGCG or CACGAG). Finally, Group F is characterized by the presence of the Collier/Olfactory-1/Early B-Cell Factor domain that is involved both in dimerization and in DNA binding.[7]

TCF4 is 1 of 4 mammalian E-proteins, the others being E12, E47, and HeLa E-box-binding factor. Basic amino acids in the bHLH domain of this family of transcription factors bind directly to DNA, recognizing the E-box consensus sequence in the regulatory regions of many genes. Although TCF4 can form homodimers, in common with other bHLH proteins, it appears to function as a transcriptional activator or repressor only by forming heterodimers with other group A or B bHLH proteins including atonal homolog 1 (ATOH1) and achaete-scute complex homolog 1 (ASCL1) (figure 1).[9–11] These interacting proteins are often expressed in a tissue- or cell-type–specific manner. By contrast, heterodimerization of E-proteins with group D HLH proteins abrogates their transcriptional activity by sequestering them into inactive complexes that cannot bind DNA.

The majority of functional studies on TCF4 concern its role in the immune system. Here TCF4 is required for the development of lymphoid progenitors to the B- and T-cell lineages and regulates plasmacytoid dendritic cell (PDC) differentiation.[12–14] PDC cells secrete interferon in response to viral nucleic acids and form part of the innate immune response. Beyond the scope of this review, the role of TCF4 and associated transcription factors in the development of the immune system has been recently reviewed.[15]

During brain development, bHLH proteins modulate critical events in neuronal and glial progenitor cells, controlling the transition from proliferation to differentiation.[16] Although TCF4 and the other E-proteins are highly expressed in neural progenitor cells, their role in brain development has not been studied in detail. Knockouts of the genes encoding each of the 4 E-proteins have been produced. In each case, *Tcf4* included, mice that are homozygous null for any of the E-protein encoding genes die at birth, whereas heterozygous mice are viable.[14] Clearly then, *Tcf4* is required for postnatal survival. However, it appears to be dispensable, at least in mice for brain development because at the gross histological level brain morphology appears normal in *Tcf4* null animals.[9]

Although little is known about the role of TCF4 in the brain, it is useful to consider the roles of the 2 proneural

genes, ATOH1 (the mammalian orthologue of the *Drosophila atonal* gene, also known as *MATH1*) and ASCL1, that have been shown to form functional heterodimers with TCF4 in this review. The proneural genes, of which there are less than 10 in mammals, are key transcriptional regulators of neurogenesis that specify all the different neurons in the mammalian nervous system.[16] During brain development in the mouse, *Atoh1* is essential for the establishment of a neural progenitor population in the rhombic lip and external granule layer that gives rise to multiple hindbrain structures.[17] Although *Tcf4* is widely expressed, *Atoh1* interacts with *Tcf4* to form neurons specifically in the pontine nucleus, a region in the ventral pons that conveys information between the motor cortex and cerebellum.[9] In spite of no obvious neurodevelopmental abnormality in *Tcf4* null mice, *Tcf4* is required for the differentiation of subsets of neurons in the developing brain. TCF4 also interacts with ASCL1 in SH-SY5Y neuroblastoma cells to form a heterodimer that drives transcription of E-box–containing reporter genes (figure 1).[10] The formation of heterodimers between TCF4 and different proneural genes provides a mechanism to regulate gene expression in specific subsets of neuronal precursors. Temporal and spatial regulation of neurogenesis by TCF4 and other E-proteins can also be achieved by repressing the transcriptional activity in a dominant-negative manner.[18] Again in a neuronal cell culture model, the transcriptional activity of TCF4 is attenuated through the formation of heterodimers with the class D bHLH protein ID2 (figure 1).[19]

Surprisingly, little is known about the genes regulated by TCF4 in the central nervous system. The rat tyrosine hydroxylase enhancer has been shown to have an E-box–binding site for Tcf4.[20] That study also showed that TCF4 could act as a transactivator but only when co-expressed with the homeobox transcription factor CUX/CDP2 (CCAAT displacement protein-2). Interestingly, microarray detection of Atoh1-regulated genes in the developing cerebellum found that Atoh1 targets are E-box–regulated genes that cluster into a few functional categories that include transcriptional regulation, cell proliferation, and signal transduction.[21] By comparison with Atoh1, the identification of genes regulated by TCF4 not only in the developing brain but also in adult brain is likely to be pivotal to understanding the role of TCF4 in schizophrenia.

Pitt-Hopkins Syndrome

Genetic studies of other common disorders such as type II diabetes have shown that genes carrying common risk alleles frequently contain rare, more highly penetrant variants that can be associated with more severe phenotypes.[22] For example, loss of function mutations in *WFS1* cause autosomal dominant Wolfram Syndrome whose symptoms include early-onset non-autoimmune diabetes, optic atrophy, and deafness.[22] By contrast, common variants in *WFS1* confer risk of type II diabetes.[22,23]

Heterozygous deletions of the *TCF4* gene cause PTHS (OMIM: 610954); a neurodevelopmental disorder characterized by severe mental retardation, microcephaly, epilepsy, poor motor development, and breathing abnormalities.[24] In these families, the disease is inherited in a dominant manner and is the result of haploinsufficiency of *TCF4*.[25–27] In addition to chromosomal deletions, *TCF4* nonsense and missense mutations also cause dominant forms of PTHS. In comparison to forms of PTHS caused by deletions or nonsense mutations, *TCF4* missense mutations are associated with an increased incidence of seizures, suggesting subtle differences in the disease mechanisms by class of mutation.[28] Importantly, most *TCF4* missense mutations are located within the basic region of the bHLH domain and have been shown to abrogate transcriptional activity in cells co-expressing ASCL1.[26,29] Heterodimerization of TCF4 with other bHLH transcription factors such as ATOH1 and ASCL1 may explain one of the cardinal features of PTHS; a respiratory abnormality associated with hyperventilation and apnea. Mice lacking either *Atoh1* or *Ascl1* die shortly after birth due to an apparent inability to initiate respiration.[17,30] In these mice and patients with PTHS, the functional dependence of heterodimer formation between the products of these proneural genes and TCF4 may result in a shared deficit in formation or activity of subpopulations of neurons that control breathing.

In addition to *TCF4*, autosomal recessive forms of PTHS have recently been found to be caused by mutations in *NRXN1* and *CNTNAP2* (Caspr2).[6] Neurexins are synaptic cell adhesion molecules found on axon terminals that together with their cognate neuroligins connect the pre- and postsynaptic membranes of synapses.[31] Three neurexin genes exist in humans, each one encodes 2 major isoforms (in the case of *NRXN1*, NRXN1α, and NRXN1β) that are transcribed from different promoters. There is now strong evidence that deletions of *NRXN1*, or parts of that gene, increase risk of schizophrenia, implicating one or both of the major NRXN1 isoforms in the etiology of that disorder.[1]

The second autosomal recessive PTHS gene *CNTNAP2* has been implicated in the genetic etiology of several diseases, again including schizophrenia (table 1). Truncating mutations in *CNTNAP2* cause autosomal recessive cortical dysplasia-focal epilepsy (CDFE). CDFE is a rare congenital epilepsy syndrome with neuropsychiatric comorbidities that include mental retardation, autism, and attention-deficit hyperactivity disorder.[35] By contrast, heterozygous genomic deletions of *CNTNAP2* have been described in patients with mental retardation, epilepsy, and schizophrenia.[33] The expression of CNTNAP2 is regulated in part by FOXP2; a forkhead transcription factor that has an important role in the neurobiology of speech and language acquisition.[36] CNTNAP2 is also a member of the

Table 1. Pitt-Hopkins Syndrome (PTHS) Genes and Their Association with Schizophrenia and Other Neuropsychiatric and Neurological Diseases

	Inheritance	Locus	Mutations	Genome-Wide Association Studies	CNV
TCF4	AD	18q21.1	PTHS	SZ[5]	—
NRXN1	AR	2p16.3	(i) PTHS (ii) ASD	—	SZ[1] ASD[32]
CNTNAP2	AR	7q35	(i) PTHS (ii) CDFE (iii) ASD	—	SZ[33] ASD[34] Epilepsy[33]

Note: This table summarizes the association of the 3 PTHS genes with different neuropsychiatric disorders. References are indicated in superscripts. AD, autosomal dominant; AR, autosomal recessive; ASD, autism spectrum disorder; CDFE, cortical dysplasia-focal epilepsy syndrome; SZ, schizophrenia.

neurexin superfamily and is encoded by one of the largest genes in the human genome spanning in excess of 2 Mb. CNTNAP2 and its ligand contactin form a receptor signaling complex that mediates neuron-glial interactions and neuronal migration in the developing cortex and regulates the clustering of Kv1 channels at nodes of Ranvier.[37] Histological examination of mice lacking *CNTNAP2* revealed no gross abnormalities in the brain of homozygous animals contrasting with the defect in cortical lamination found in patients with CDFE.[35,38]

In a recent report, a small proportion of patients diagnosed with Angelman Syndrome, a neurodevelopmental disorder affecting the epigenetic regulation of the ubiquitin ligase UBE3A, were in fact found to have *TCF4* mutations.[39] The phenotypic similarities shared by these disorders include mental retardation and motor dysfunction. This study suggests that *TCF4* mutations may be found in other mental retardation syndromes including Rett Syndrome that have a similar spectrum of phenotypes.

Conclusions

There is increasing evidence that schizophrenia results from a combination of rare mutations of relatively large effect and common variants that confer low risk. For example, common variants in *TCF4* and rare CNVs in *NRXN1* and, though the evidence is weaker, also *CNTNAP2* are associated with schizophrenia. It can be argued that rare, highly penetrant variants are useful for defining biological pathways whose disruption can lead to schizophrenia, but their presence in only a limited number of cases means that further evidence is required to determine their relevance to schizophrenia more generally. The observation that rare mutations in *TCF4*, *NRXN1*, and *CNTNAP2* can result in similar neurodevelopmental phenotypes suggests a functional link between the proteins they encode. The implication of a common variant in *TCF4* in schizophrenia is therefore evident that the functions of NRXN1 and CNTNAP2 might also be of general importance in this disorder. In doing so, it demonstrates the utility of seeking both common and rare variants in complex genetic disorders.

The identification of biological pathways that may be altered in schizophrenia is a fundamental aim in deciphering the complex genetic factors that contribute to disease susceptibility. Several of the CNVs associated with schizophrenia and other neuropsychiatric disorders are found in genes that encode synaptic and neurodevelopmental genes.[40] Moreover, some of the CNVs associated with schizophrenia are also found in patients with mental retardation, autism spectrum disorder, or bipolar disorder, suggesting that these may represent a continuum of overlapping phenotypes that range in severity of neurodevelopmental insult and age of onset.[41,42] In common with many other GWA candidates in complex diseases, schizophrenia-associated mutations or alterations in gene expression have yet to be described for *TCF4*. Alterations in transcript levels, alternative splicing, or alternative promoters may generate subtle functional variants of TCF4 that could be altered in schizophrenia. While it is tempting to speculate that the expression of *NRXN1* and *CNTNAP2* may be regulated by *TCF4*, more work is required to further delineate the genetic role of TCF4 in schizophrenia.

Funding

Wellcome Trust (WT088866); Medical Research Council.

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