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GENETICS & NEUROSCIENCE (P GEJMAN, SECTION EDITOR)

Association of *Transcription Factor 4* (*TCF4*) variants with schizophrenia and intellectual disability

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Abstract Genome wide association studies (GWAS) have revolutionized the study of complex diseases and have uncovered common genetic variants associated with an increased risk for major psychiatric disorders. A recently published schizophrenia GWAS replicated earlier findings implicating common variants in *Transcription factor 4* (TCF4) as susceptibility loci for schizophrenia. By contrast, loss of function *TCF4* mutations, although rare, cause Pitt-Hopkins syndrome (PTHS); a disorder characterized by intellectual disability (ID), developmental delay and behavioral abnormalities. *TCF4* mutations have also been described in individuals with ID and non-syndromic neurodevelopmental disorders. TCF4 is a member of the basic helix-loop-helix (bHLH) family of transcription factors that regulate gene expression at E-box-containing promoters and enhancers. Accordingly, TCF4 has an important role during brain development and can interact with a wide array of transcriptional regulators including some proneural factors. TCF4 may, therefore, participate in the transcriptional networks that regulate the maintenance and differentiation of distinct cell types during brain development. Here, we review the role of *TCF4* variants in the context of several distinct brain disorders associated with impaired cognition.

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Introduction

Family and twin studies have shown that common psychiatric disorders such as schizophrenia and autism spectrum disorder (ASD) are highly heritable. However, it is only relatively recently that genetic risk loci for these disorders have been discovered. A plethora of large-scale sequencing and genotyping projects have now started to unravel the complex genetic architecture of common brain disorders [1]. Data emerging from these studies indicate that schizophrenia, in common with many other psychiatric disorders, is a highly polygenic disease such that a large number of genomic variants of small effect size contribute to disease susceptibility [2, 3••]. In addition to the common variants that have been discovered using GWAS, rare and *de novo* mutations such as copy number variants (CNVs; sub-microscopic chromosomal deletions and insertions) and single nucleotide variants (SNVs), have been discovered at relatively high frequencies in schizophrenia and ASD [4–6]. However, and by contrast with most common disorders such as Alzheimer's Disease and ASD, few, if any, highly penetrant Mendelian variants have been found to cause schizophrenia. It would therefore seem a reasonable proposition that the genetic risk of schizophrenia involves the cumulative effects of many common variants of small effect size allied with cases of rare and/or *de novo* variants of comparatively large effect [1].

TCF4 was one of the original handful of genes to reach genome-wide significance in large-scale genetic association studies of schizophrenia [7]. Subsequently, the most recent schizophrenia GWAS of 36,989 cases and 113,075 controls discovered 128 independent associations spanning 108 different loci that surpass genome-wide significance [3••]. This

study found that three linkage disequilibrium (LD)-independent single nucleotide polymorphisms (SNPs) in or around *TCF4* exceeded the statistical threshold for genome-wide significance. Interestingly, common *TCF4* variants are also risk factors for other disorders namely Fuchs'corneal endothelial dystrophy (FECD) and primary sclerosing cholangitis (PSC). Whilst it is beyond the scope of this article to discuss these disorders in depth, readers are referred to recent publications on these topics [8–10].

In addition to schizophrenia, rare *TCF4* SNVs and CNVs that result in haploinsufficiency cause Pitt-Hopkins syndrome (PTHS). PTHS is associated with severe ID and also has behavioral features consistent with ASD [11]. Disruptive *TCF4* mutations have also been found in patients with non-syndromic developmental delay and ID [12, 13••, 14••, 15]. Collectively, these studies implicate *TCF4* variants in a range of disorders where cognitive impairment is a cardinal feature. In this article, we discuss the biology of TCF4 in the context of brain development and disease, focusing on the role of TCF4 in schizophrenia and ID.

A brief discussion of the molecular biology of TCF4

TCF4 is a member of the class I basic helix-loop-helix (bHLH) family of transcription factors that are widely expressed during development. The class I bHLH proteins are also known as E-proteins and are orthologous to the *Drosophila daughterless* protein [16–18]. It is generally accepted that mammals have four E-proteins. In humans, these are TCF4, Transcription factor 3 (TCF3, also known as E12/E47 or E2A) and Transcription factor 12 (TCF12, HEB). *TCF3* produces two alternatively spliced isoforms called E12 and E47 that only differ in the bHLH encoding region of their sequence [19]. Although, *TCF4* (Gene ID: 6925) is the official Human Genome Organization (HUGO) nomenclature, the literature often refers to TCF4 as E2-2, immunoglobulin transcription factor 2 (ITF2) or SL3-3 enhancer factor (SEF2). These alternative names demonstrate that many of the original studies on mammalian E-protein function concerned the immune system. Although beyond the scope of this review, it is important to remind the reader that E-proteins are important regulators of early lymphocyte development [16, 20–22].

The 450 kb *TCF4* gene is located on chromosome 18q21.1 in humans and encodes numerous protein isoforms generated via extensive alternative splicing and differential promoter usage [23•]. Although *TCF4* is a complex locus, for consistency with previously published articles we will use the reference sequence (NM_001083962.1) when describing *TCF4* gene structure and mutations. Despite these complexities, only two major TCF4 isoforms, full length TCF4, known enigmatically as TCF4-B, and the truncated TCF4 isoform TCF4-A (Fig. 1a), have been studied in detail [27, 28]. These isoforms may be functionally distinct since TCF4-A lacks both the first activation domain and nuclear localization signal found in full length TCF4-B and is transcribed from an intragenic promoter located in intron 8 [23•].

TCF4 was originally identified in functional assays to find factors that could bind to certain immunoglobulin enhancer elements [29]. Ostensibly using *in vitro* assays, it was shown that TCF4 could bind and activate gene expression at the conserved E-box (Ephrussi-box, 5'- CANNTG) containing sequences in the enhancers or promoter regions of several genes [17, 29–32]. Although TCF4 has been shown to regulate gene expression at both canonical and synthetic promoters and enhancers, surprising little is known about TCF4's genomic targets. Intriguingly, TCF4-B has also been found to be a transcriptional repressor in different cell types [33–35]. However, it has been demonstrated that this isoform can also activate transcription *in vitro*, and therefore its function is highly context-dependent [30, 36, 37].

Part of TCF4's contrasting effects on transcription may depend on its interaction with a plethora of transcriptional regulators. The domain structure of TCF4 (Fig. 1a) allows it to interact with different transcriptional regulatory proteins and to bind directly to DNA [38]. Basic amino acids at the N-terminus of the bHLH domain bind directly to DNA, whereas the remainder of the domain is required for homodimerization and heterodimerization with other HLH proteins [39–41]. TCF4 forms heterodimers with a large repertoire of HLH proteins, including class II HLH proteins that includes many proneural proteins (eg., atonal homologue 1 (ATOH1), see below). Many of the class II HLH proteins are expressed in a tissue-specific manner and function as obligate heterodimers with E-proteins [42]. By contrast, the class V HLH proteins (eg., inhibition of DNA binding 2 (ID2)) also associate with E-proteins, but since they lack a DNA-binding domain they sequester E-proteins into transcriptionally inactive heterodimers in a dominant-negative manner. In addition to the HLH family of proteins, TCF4 may also be regulated by interactions with the transcriptional co-repressor runt-related transcription factor 1 (RUNX1T1) and the E1A binding protein p300 (EP300) histone deacetylase capable of binding to TCF3 [43, 44]. TCF3 has been found to co-purify with numerous proteins in human embryonic kidney 293 T (HEK293T) and pro-B cells suggesting that E-proteins may function as part of an oligomeric protein complex [45•]. Thus, by analogy to TCF3, the activity of TCF4 in the brain is likely to be regulated through the formation of multimeric DNA-protein complexes at promoters and enhancers of a large number of target genes.

The role of TCF4 in development

As mentioned above, class I bHLH proteins such as TCF4 interact with a multitude of other HLH transcription factors to

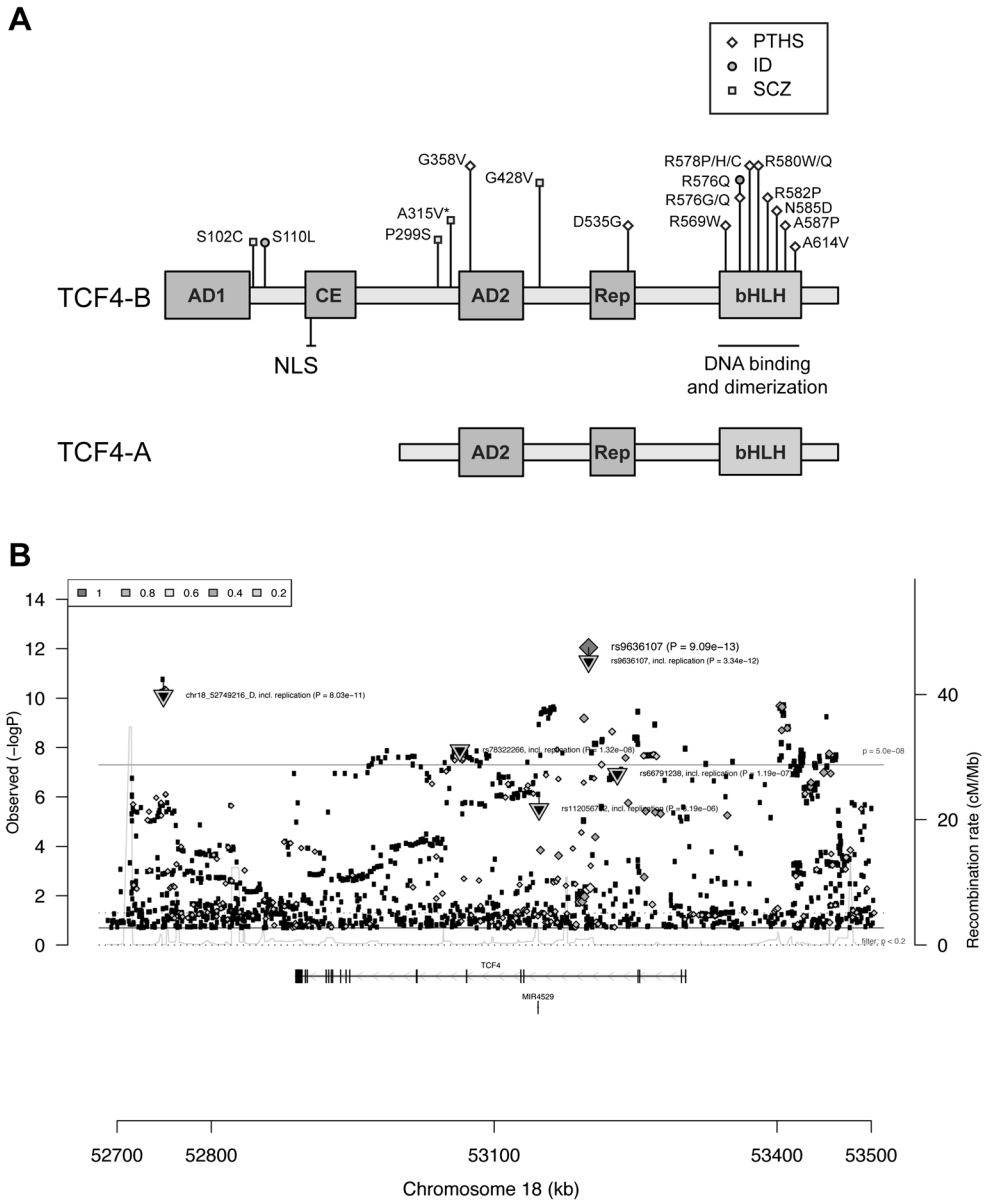

Fig. 1 The *TCF4* gene and genetics. TCF4 isoforms and missense mutations (**a**). Schematic showing the domain organization of the major TCF4 isoforms and the location of putative or actual functional mutations associated with PTHS, schizophrenia and ID. Missense mutations were collated from the literature, notably Whalen *et al*. [24], Marangi *et al*. [25] and the Leiden Open Variation Database (http://chromium.liacs.nl/LOVD2/home.php?select_db=TCF4). Schizophrenia-associated *TCF4* mutations were described by Hu *et al*. [26], whereas the ID-associated S110L and R576Q mutations were reported by Rauch *et al*. [13••] and de Ligt *et al*. [14••], respectively. *Mutation was also observed in the control sample, albeit at a lower frequency [26]. Abbreviations: Activation domain 1 (AD1; 1-100); CE repressor domain (CE; 160-179); nuclear localization signal (NLS; 157-176); activation domain 2 (AD2; 340-400); Rep repressor domain (Rep; 511-540); basic helix loop helix domain (bHLH; composed of the basic domain (566-583); helix-loop-helix domain (583-622); and domain C (622-646)). Note the diagram is not drawn to scale. Schizophrenia-associated SNPs at the *TCF4* locus (**b**). Plots of schizophrenia-associated SNPs in and around the *TCF4* gene were visualized using the Ricopili tool (http://www.broadinstitute.org/mpg/ricopili/). Data were derived from the recently published schizophrenia GWAS conducted by the Psychiatric Genetics Consortium (PGC2) [3••]. The three-linkage disequilibrium (LD)-independent genome-wide significant SNPs (rs9636107, chr18_52749216_D and rs78322266) are displayed above the horizontal line ($P=5.0\times10^{-8}$). SNPs labeled with different colors represent genetically independent loci ($r^2>0.1$), as indicated. Note that by convention the positive DNA strand is shown. Accordingly, *TCF4* is represented in the 3'-5' orientation

regulate a range of developmental processes [42, 46]. Although relatively little is known about the role of TCF4 in neurodevelopment, many of the proteins that form heterodimers with TCF4, such as the proneural bHLH genes, are required for neurogenesis [42, 47]. Proneural bHLH transcription factors such as achaete-scute complex homolog 1(ASCL1), ATOH1 and neurogenin 2 (NEUROG2) are defined as being both necessary and sufficient to specify

neuronal subtypes via activation of a differentiation program and by promoting cell cycle exit in uncommitted neural progenitors [42, 47, 48]. Thus, proneural genes can negatively regulate the proliferation and migration of neural progenitors in a context-specific manner through interactions with their cognate E-proteins [42].

While the majority of neurodevelopment studies have focused on proneural genes, ubiquitous expression of the E-proteins and their ability to form active heterodimers with the class II bHLH proteins strongly suggest that E-proteins are involved in the neurodevelopment program. Many of the activities of the proneural factors were delineated by loss-of-function studies in mice and through genome-wide profiling of their transcription targets [48, 49•]. Studies on mouse mutants have shown that homozygous *Atoh1* (*Atoh1*$^{-/-}$) and *Ascl1* (*Ascl1*$^{-/-}$)-deficient mice both die in the early postnatal period with feeding and respiratory defects [50, 51]. Similarly, homozygous *Tcf4* knockout (*Tcf4*$^{-/-}$) mice die within 24 h of birth [20, 52]. *Tcf4*$^{-/-}$ mice have no gross anatomical defects, although detailed analysis of their hindbrain has shown that these mice have disrupted pontine nucleus development [52]. Loss of *Tcf4* causes a reduction in the number of neurons forming the pontine nucleus and an accumulation of ectopic neurons that fail to migrate to their correct location. Importantly, these deficits are highly specific to *Tcf4*, as the development of this hindbrain nucleus in other E-protein knockout mice (*Tcf3*$^{-/-}$ and *Tcf12*$^{-/-}$) was found to be normal [52]. The development of the pontine nucleus is also dependent on expression of the proneural gene *Atoh1* that forms functional heterodimers with *Tcf4* [52]. Interestingly, *Atoh1*$^{+/-}$/*Tcf4*$^{+/-}$ mutant mice also display defects in pontine nucleus development whereas *Tcf4*$^{+/-}$ mice have no abnormalities in this region [52]. Thus, the abundance of specific *Tcf4* heterodimers is likely to be important for the development of specific neuronal subpopulations in the brain.

TCF4 is also an important regulator of epithelial-mesenchymal transition (EMT). EMT is a complex developmental process in which epithelial cells lose apicobasal polarity and acquire a migratory and invasive phenotype [53]. EMT is regulated by a network of transcription factors that orchestrate a differentiation program converging on the repression of epithelial cell markers such as E-cadherin (*CDH1*) [54]. Several of the prototypical EMT inducers such as the SNAIL and zinc finger E-box binding homeobox (ZEB) family of transcription factors bind to E-boxes in the promoter regions of certain genes (eg., *CDH1*) to repress their expression [55].

Interestingly, ectopic over-expression of TCF4 potently induces EMT in epithelial cells [28]. Epithelial cells over-expressing either TCF4-A or TCF4-B acquire a motile and invasive phenotype associated with wholesale changes in gene expression, including repression of *CDH1* [28]. Whilst EMT has been extensively studied in peripheral tissues and in cancer, the role of EMT in the brain is more opaque [56]. Knockdown of TCF4 in SH-SY5Y neuroblastoma cells affects cell survival, EMT and neuronal differentiation [57•, 58]. In this study, Forrest and colleagues found that EMT inducers such as SNAIL were down-regulated in TCF4-depleted cells, contrasting with induction of these factors in epithelial cells over-expressing TCF4. Furthermore, during brain development, the SNAIL superfamily proteins, Scratch1 and Scratch2, are expressed under the control of bHLH proneural genes such as *Ascl1* in neuronal precursors, as their fate is determined [59, 60•]. Scratch1/2 induce delamination and radial migration of neural precursors during neocortical development in mice concomitant with the repression of *Cdh1* [60•]. Taken together, these studies suggest that TCF4, via direct or indirect interactions with other transcription factors, may participate in an EMT-like process during brain development.

Pitt-Hopkins Syndrome and intellectual disability

In 1978, David Pitt and Ian Hopkins described two unrelated patients with severe ID, dysmorphic facial features and intermittent over-breathing [61]. While this clinical description succinctly encapsulated the salient features of PTHS, it was almost three decades later when the genetic defect responsible for the syndrome was found to be haploinsufficiency of *TCF4* [62, 63]. Following the identification of the gene, in excess of 120 molecularly confirmed cases of PTHS have been reported. In addition to the clinical features described by Pitt and Hopkins, developmental delay, stereotyped movements, absent speech and epilepsy are frequently found in PTHS patients [24, 64]. Brain abnormalities such as agenesis or hypoplasia of the corpus callosum, decreased hippocampal volume and enlarged ventricles have been detected by magnetic resonance imaging (MRI) in approximately half of the cases examined [24]. It is also evident that many PTHS patients have a cluster of developmental, behavioral and cognitive traits consistent with autism spectrum disorder (ASD) [11]. In a study of ten individuals from the Netherlands and Belgium, van Balkom and colleagues found that, in addition to ID, PTHS patients had severe impairments in social interactions, communication and language and had stereotyped motor behaviors [11]. Although these are recognized clinical features of the syndrome, autism-like behaviors are not necessarily attributable to the degree of cognitive impairment in PTHS. Conversely, many individuals with ASD have normal or superior intelligence suggesting that some shared behavioral traits in PTHS and ASD may be unrelated to IQ. It is also important to note that (at the time of this writing) *TCF4* mutations have yet to be found in ASD cohorts.

PTHS can be caused by mutations ranging from whole gene deletions (CNVs) to missense mutations (SNVs)

affecting only a single amino acid (Table 1). Although epilepsy may be more common in PTHS patients with missense mutations, the disease phenotype seems remarkably similar across the mutational spectrum [24, 64–66]. Almost of all the *TCF4* mutations that cause PTHS are predicted to disrupt transcripts encoding TCF4-A and TCF4-B. However, pathogenic truncating mutations in exons 7 and 8 upstream of the TCF4-A promoter have been described in at least three patients, suggesting involvement of both major TCF4 isoforms in PTHS [24]. All mutations that cause PTHS are thought to result in haploinsufficiency of TCF4, consistent with the disorder being inherited in an autosomal dominant manner [62, 63, 67]. The majority of PTHS-associated missense mutations appear to attenuate transcriptional activity in reporter- based assays of gene function and also may impair heterodimer formation with other bHLH transcription factors [36, 37, 63, 68].

In addition to classical PTHS, milder phenotypes may arise through balanced translocations, CNVs or SNVs that only disrupt part of the *TCF4* gene. For example, Kalscheuer and colleagues described a *de novo* balanced translocation in a female patient with moderate ID and minor facial abnormalities [69]. The translocation in this individual was between *TCF4* and *CHD6* on chromosome 20 and was proximal to *TCF4* exon 4, thereby only disrupting transcripts encoding the major TCF4-B isoforms. Although *CHD6* mutations may contribute to the milder phenotype, it is tempting to speculate that the implied preservation of TCF4-A transcripts may attenuate disease severity in this patient. Furthermore, a *de novo* truncating mutation in *TCF4* exon 7 (R157X), again only affecting TCF4-B isoforms, was found in another patient with non-syndromic ID [70]. Although the same mutation has been described in a PTHS patient, these studies demonstrate the variable phenotypes associated with *TCF4* mutations [65, 70].

Table 1 Spectrum of *TCF4* mutations that cause PTHS

Mutation type	Number of patients (%)
Deletions (CNV)	
Whole gene deletion	23 (20)
Intragenic deletion	10 (9)
Point mutation (SNV)	
Frameshift	34 (29)
Nonsense	18 (16)
Splice site	7 (6)
Missense	24 (21)
Total	116 (100)

The number of patients with each mutation type and its corresponding percentage is presented in Table 1. The table was modified from data published by Whalen *et al.* and Marangi *et al.* [24, 25]

TCF4 mutations have also been found in patients with ID and other neurodevelopmental disorders. Talkowski *et al.* described twins with a neurodevelopment disorder that had a balanced chromosome translocations involving intron 15 of *TCF4* and chromosome 3q13.32 [12]. This translocation is in a more distal part of *TCF4* and is predicted to disrupt the transcripts encoding both TCF4-A and TCF4-B. Importantly, *TCF4* transcripts were decreased by approximately 50 % in lymphoblastoid cell lines derived from each of these individuals, demonstrating that the translocation affected *TCF4* expression resulting in haploinsufficiency.

Whole exome sequencing is a robust and reliable method for mutation detection in rare genetic disorders [71]. *TCF4* mutations have been found by whole exome sequencing in patients primarily presenting with ID [13••, 14••, 15]. Although *TCF4* mutations represent relatively rare events, each study identified at least one *TCF4* mutation in their respective cohorts. Interestingly, de Ligt *et al.* found an R576Q mutation previously described in PTHS (Fig. 1a) [14••, 36]. By contrast, Rauch and colleagues reported a novel mutation, S110L, towards the N-terminus of TCF4-B that only affects the longer TCF4 isoforms (Fig. 1a) [13••]. Redin *et al.* used a targeted approach to sequence 217 genes in a cohort of 106 patients with ID of unknown etiology that had been previously screened for CNVs [15]. Three patients were found to have truncating *TCF4* mutations, two of which had phenotypes inconsistent with PTHS [15]. Whether these rare *TCF4* variants in patients with ID and other neurodevelopmental disorders are undiagnosed PTHS cases remains to be determined.

PTHS-like (PTHSL) phenotypes have also been described in patients with neurexin 1 (*NRXN1*) and contactin-associated protein-like 2 (*CNTNAP2*) mutations. Zweier and colleagues found CNVs and SNVs in four patients with autosomal recessive disorders and phenotypes resembling PTHS (severe ID, ASD-like behavior, epilepsy and breathing anomalies) [72]. *NRXN1* and *CNTNAP2* both encode neuronal cell adhesion molecules. Heterozygous *NRXN1* and *CNTNAP2* variants have been found in a range of neuropsychiatric and neurodevelopmental disorders, including ASD and schizophrenia, often in association with mild ID [73]. However, the spectrum of disease associated with heterozygous *NRXN1* and *CNTNAP2* mutations has recently been shown to include patients with severe ID [74]. Following the identification of *NRXN1* and *CNTNAP2* mutations in PTHSL, Forrest and colleagues demonstrated that TCF4 could regulate transcription at the *NRXN1* and *CNTNAP2* promoters in heterologous cells [37]. These data suggest that a shared genetic mechanism, albeit with reduced penetrance and phenotypic variability, may converge upon the activities of *TCF4*, *NRXN1* and *CNTNAP2*. Genetic variation in each of these genes may therefore alter neurodevelopmental processes causing differing severities of ID.

Common and rare *TCF4* variants in schizophrenia

TCF4 can now be considered one of the most robustly replicated schizophrenia susceptibility genes described to date [3••, 7, 75]. At least three independent *TCF4* SNPs (Fig. 1b) exceed the statistical threshold for genome wide significance in schizophrenia [3••]. Furthermore, targeted re-sequencing of *TCF4* in a relatively small number of schizophrenia patients has uncovered a number of non-synonymous SNVs that were statistically under-represented in controls [26]. Intriguingly, all of the rare *TCF4* variants discovered by Hu and colleagues were located in the proximal region of the *TCF4* gene, often affecting only the TCF4-B isoform, and did not overlap with the mutations that cause PTHS (see Fig. 1a) [26].

In addition to *TCF4*, other ID genes with Mendelian variants were also found to exceed genome-wide significance in recent GWAS [3••]. These include: the myocyte enhancer factor 2C (*MEF2C*); the special AT-rich sequence-binding protein 2 (*SATB2*); and a locus on chromosome 22 that encompasses *EP300* [3••]. Interestingly, haploinsufficiency of *MEF2C* has been described in patients with severe ID, absent speech and motor dysfunction clinically overlapping the PTHS phenotype [76, 77]. *MEF2C* is also differentially expressed in TCF4-depleted cells suggesting that both transcription factors may participate in similar pathways in certain cells types [57•]. It is also noteworthy that rare heterozygous mutations in *EP300* cause Rubenstein-Taybi syndrome, a disorder associated with ID, distinctive facial features and microcephaly [78]. As mentioned above, EP300 directly regulates TCF4 activity through competitive interactions with the activation domains of TCF4. Similarly, haploinsufficiency of *SATB2* causes a syndromic form of ID with cleft palate and facial dysmorphism [79].

TCF4 variants have also been found to impact some schizophrenia endophenotypes and cognition [80]. Paradoxically, schizophrenia patients carrying the risk allele of rs9960767, the original *TCF4* SNP to exceed genome-wide significance [7], were less impaired in verbal declarative memory tests compared to patients homozygous for the non-risk allele [81]. However, using a different study design, Wirgenes and colleagues found that the risk alleles of several *TCF4* SNPs influenced verbal learning and a range of other endophenotypes in schizophrenia patients compared to controls [82]. Importantly, this study also found that *TCF4* expression in blood was increased in patients with psychoses (schizophrenia, bipolar disorder and other psychoses) compared to controls [82]. Whilst this is a potentially interesting finding, the authors of this study acknowledged that they could not exclude the effects of anti-psychotic medication on *TCF4* expression in patients compared to controls [82].

Other schizophrenia endophenotypes that can be assessed using psychological and neurophysiological paradigms are also influenced by common *TCF4* polymorphisms. Sensory gating filters redundant or unnecessary information during cognitive tasks [83]. Sensory gating-abnormalities are an early sign of schizophrenia and are manifest by a decreased ability to inhibit responses to insignificant stimuli impacting attentional function [84]. Quednow and colleagues found that the schizophrenia risk allele of rs9960767 in the *TCF4* gene was associated with significantly decreased prepulse inhibition (PPI) of the acoustic startle response in both patients and healthy controls [84]. These data are of particular interest since transgenic mice over-expressing *Tcf4* were found to have sensorimotor-gating impairments and deficits in fear conditioning [85]. *Tcf4* transgenic mice also showed dysregulated circadian expression of transcripts encoding other bHLH transcription factors in the hippocampus [85]. Thus, subtle alterations in *Tcf4* expression may interfere with cognitive functions and circadian processes in mice and possibly humans.

Auditory sensory gating is also another measure of sensory gating function. The P50 wave, typically recorded by electroencephalography (EEG), occurs 50 ms after an auditory stimulus such as a single click. Normal subjects commonly show suppressed amplitude of the P50 wave after hearing the second acoustic stimulus. By contrast, schizophrenia patients often fail to show a reduced response to the second stimulus [86]. In healthy volunteers, carriers of the schizophrenia risk alleles at four *TCF4* SNPs showed reduced auditory sensory gating as measured by P50 suppression [87••]. Although there was moderate linkage disequilibrium between most of these SNPs, this study replicated earlier findings showing the *TCF4* genotype may affect neuropsychological functions that are abnormal in schizophrenia. Furthermore, this study also examined the genetic influence of the *TCF4* genotype on smoking behavior related to P50 suppression in the same cohort [87••]. Intriguingly, the authors of this study found that heavy smokers had a more pronounced deficit in P50 wave suppression compared to non-smokers or light smokers, while smoking behavior was not influenced by *TCF4* genotype [87••]. These data are particularly interesting since smoking prevalence is much higher in schizophrenia patients compared to the general population and is likely to be related to the increased mortality rate associated with the disorder. In summary, these studies demonstrate the *TCF4* genotype may interact with other genetic or environmental factors to affect neuropsychological and cognitive functions that are abnormal in schizophrenia.

Conclusion

The association of rare and common *TCF4* variants across a range of neuropsychiatric and neurodevelopmental diagnoses provides compelling evidence that *TCF4* is required for normal brain development. Experiments on *Tcf4* mutant mice

(considered a model of PTHS), have shown that *TCF4* has an important neurodevelopmental role that is distinct from other E-proteins. It is also clear that haploinsufficiency of *TCF4* resulting from loss of function mutations or deletions of one *TCF4* allele causes PTHS and probably other forms of ID. However, how *TCF4* variants increase the risk for schizophrenia is less clear. Given the acute dosage sensitivity of *TCF4*, subtle alterations in *TCF4* expression may have wide-ranging effects on neuronal function. Transcription factors implicitly regulate gene expression in *trans*- by binding to *cis*-regulatory elements in promoters and enhancers of target genes, thereby allowing them to sample *cis*-acting variants such as functional SNPs in regulatory regions of genes. Thus, the key to understanding the role of *TCF4* in the developing and adult brain may reside in the identity of TCF4's genomic targets. Integrating this data with neurophysiological studies of model organisms, patient cohorts and genetic epidemiological samples will greatly advance our knowledge of PTHS, ID and schizophrenia, possibly paving the way for new avenues to treat these disorders. What is clear is that *TCF4* is only one of a handful of genes that sits at the nexus between rare and common disorders that have cognitive dysfunction as their unifying feature.

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Compliance with Ethics Guidelines

Conflict of Interest All authors have no conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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