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ORIGINAL ARTICLE

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# De novo variants in *TCF7L2* are associated with a syndromic neurodevelopmental disorder

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## Abstract

*TCF7L2* encodes transcription factor 7-like 2 (OMIM 602228), a key mediator of the evolutionary conserved canonical Wnt signaling pathway. Although several

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large-scale sequencing studies have implicated *TCF7L2* in intellectual disability and autism, both the genetic mechanism and clinical phenotype have remained incompletely characterized. We present here a comprehensive genetic and phenotypic description of 11 individuals who have been identified to carry de novo variants in *TCF7L2*, both truncating and missense. Missense variation is clustered in or near a high mobility group box domain, involving this region in these variants' pathogenicity. All affected individuals present with developmental delays in childhood, but most ultimately achieved normal intelligence or had only mild intellectual disability. Myopia was present in approximately half of the individuals, and some individuals also possessed dysmorphic craniofacial features, orthopedic abnormalities, or neuropsychiatric comorbidities including autism and attention-deficit/hyperactivity disorder (ADHD). We thus present an initial clinical and genotypic spectrum associated with variation in *TCF7L2*, which will be important in informing both medical management and future research.

**KEYWORDS**
autism, intellectual disability, myopia, neurodevelopmental disorder, *TCF7L2*

## 1 | INTRODUCTION

*TCF7L2* encodes a high mobility group (HMG) box-containing transcription factor and is located on chromosome 10q25.2-q25.3. Although it was initially identified and referred to as *TCF4* (Castrop et al., 1992; Clevers, 2006), it should not be confused with the currently designated *TCF4* (ITF2/SEF2-1B/SEF2/E2-2, MIM 602272), which is located on Chromosome 18 and associated with Pitt–Hopkins syndrome. *TCF7L2* mediates canonical Wnt signaling. Signaling by secreted Wnt proteins through this pathway leads to release of the protein beta-catenin (CTNNB1) from a repressive degradation complex in the cytoplasm, allowing it to accumulate and translocate to the nucleus, where it acts with DNA-binding factors including TCF7L2 to turn on Wnt-responsive target genes. TCF7L2 thus acts with beta-catenin as an on/off switch for transcriptional regulation. Through mostly genome-wide association studies, *TCF7L2* has been involved in a variety of human disease, including Type 2 diabetes mellitus, colon cancer, and schizophrenia (Alkelai et al., 2012; Folsom et al., 2008; Grant et al., 2006). *TCF7L2* is also known to be critical in central nervous system development (Chodelkova et al., 2018; Lee et al., 2017; Nagalski et al., 2013). It has been directly involved in processes as diverse as neurogenesis and thalamic development to mediating the effects of neuropsychiatric pharmacological agents including lithium and nicotine (Chodelkova et al., 2018; Duncan et al., 2019; Lee et al., 2017; Misztal et al., 2017; Nagalski et al., 2013). Large-scale sequencing studies have also identified a handful of isolated patients with de novo variants in *TCF7L2* in association with neurodevelopmental disorders, but clinical details are lacking (Iossifov et al., 2014; De Rubeis et al., 2014; Lelieveld et al., 2016; Jeremy F McRae et al., 2017 (Deciphering Developmental Disorders [DDD] Study), 2017; Guo et al., 2018; Liu et al., 2018; Satterstrom et al., 2020; Wang et al., 2020).

*TCF7L2* encodes multiple alternatively spliced transcripts, and alternative splicing has been demonstrated to play an important role in the function and specificity of the transcriptional repertoire of TCF7L2 in a variety of tissues and contexts, including the brain (Nagalski et al., 2013; Prokunina-Olsson et al., 2009; Weise et al., 2009). *TCF7L2* is significantly intolerant to loss-of-function (LOF) variation, with significantly fewer observed LOF variants as compared to predicted, as indicated in the probability of being loss-of-function intolerant (pLI) score of 0.99–1 reported in the gnomAD and ExAC databases. There is also a region of missense constraint encompassing the HMG box domain indicating additional intolerance to missense variation (Samocha et al., 2017).

We describe here the genotypic and clinical phenotypic spectrum of 11 individuals with de novo, heterozygous variants in *TCF7L2* presenting with a neurodevelopmental disorder.

## 2 | MATERIALS AND METHODS

Patients were ascertained from GeneMatcher through the Matchmaker Exchange Network between May 2019 and December 2020 (Philippakis et al., 2015; Sobreira et al., 2015). *TCF7L2* variants were detected on exome sequencing in 10 individuals, and on a trio autism/intellectual disability gene panel at a commercial lab in one individual. No additional plausible candidate gene variants were identified (Supplementary Table 1). One additional patient was excluded from the cohort because the phenotype was confounded by perinatal hypoxic–ischemic injury; the data for this individual (S1) are included in Supplementary Table 1. Institutional review board approval was obtained.

## 3 | RESULTS

The reported variants in *TCF7L2* in our cohort are annotated on the coding sequence and protein structure in Figure 1. We found a marked pattern of clustering of the variants, with all missense variants located in or immediately adjacent to the PFAM predicted HMG box domain. Two residues, Tyr423 and Asn381, are each affected by two different missense variants (Figure 1). All of the missense variants occur at highly conserved locations, and none are found in the gnomAD database v2.1.1. All truncating variants occurred greater than 55 nucleotides upstream of the last exon–exon junction and are predicted to be subject to nonsense-mediated decay. The two splice variants we report are predicted by splice prediction tools (MaxEnt, NNSPLICE,SSF) with high likelihood to affect splicing.

Individuals with truncating variants and missense variants in our cohort present with largely indistinguishable phenotypes, although sample size is too small to make definitive conclusions regarding this (see Table 1 and Supplementary Table 1). All individuals present with developmental delays, including delayed speech and motor milestones. Intellectual abilities range from average cognitive functioning to mild/moderate intellectual disability. Variability in speech language abilities is notable regardless of intellectual functioning; abilities range from individuals who are completely non-verbal to individuals with hypophonia, dysphasia, and dysarthria. Autism and/or social communication deficits are frequently observed, and comorbid attention-deficit/hyperactivity disorder (ADHD) and executive functioning challenges are also seen. One individual has a history of glioma status post resection and focal motor seizures; this individual was also found to have a heterozygous TP53 variant of uncertain significance, and is being managed as Li–Fraumeni syndrome. Myopia is seen in 6 of 11 individuals, and is very severe in two patients. Dysmorphic features are present in several individuals, but variable (see Supplementary Table 1). Dermatologic findings include hypertrichosis ($n = 2$), mildly hyperextensible skin ($n = 1$), hyperpigmented plaque ($n = 1$), and angiomas ($n = 1$). Orthopedic findings include abnormal thorax morphology ($n = 2$), short distal phalanges ($n = 1$), talipes equinovarus ($n = 1$), scoliolis ($n = 1$), and abnormal foot morphology ($n = 2$).

We also reviewed previous reports of variation in *TCF7L2* to evaluate whether phenotypes were consistent with this cohort (Supplemental Table 2); however, our assessment of previous reports was limited due to lack of validation, absent clinical descriptions, and varied methodological approaches. Thus, these limitations preclude definitive interpretation of previously reported variants.

## 4 | DISCUSSION

We present a series of 11 patients with de novo, heterozygous variants in *TCF7L2* manifesting with neurodevelopmental abnormalities. All individuals had initial developmental delays, and intellectual and verbal abilities ultimately demonstrate significant heterogeneity. Some individuals have average cognitive functioning and fluent speech, while others are nonverbal. Other phenotypic features variably included autism spectrum disorder, social communication disorder, ADHD, speech–language impairment, dysmorphic features, myopia, hypertrichosis, and orthopedic abnormalities.

In this cohort, all missense variants occurred in or directly adjacent to the HMG box domain. The HMG box domain is an evolutionary conserved region that mediates interactions with DNA. This region is highly missense constrained. Interestingly, we also identify one splice variant that occurs at the start of an exon immediately following an alternatively spliced exon that is absent in both the canonical and the highest brain expressed isoforms (c.553-1G>A, Gnomad

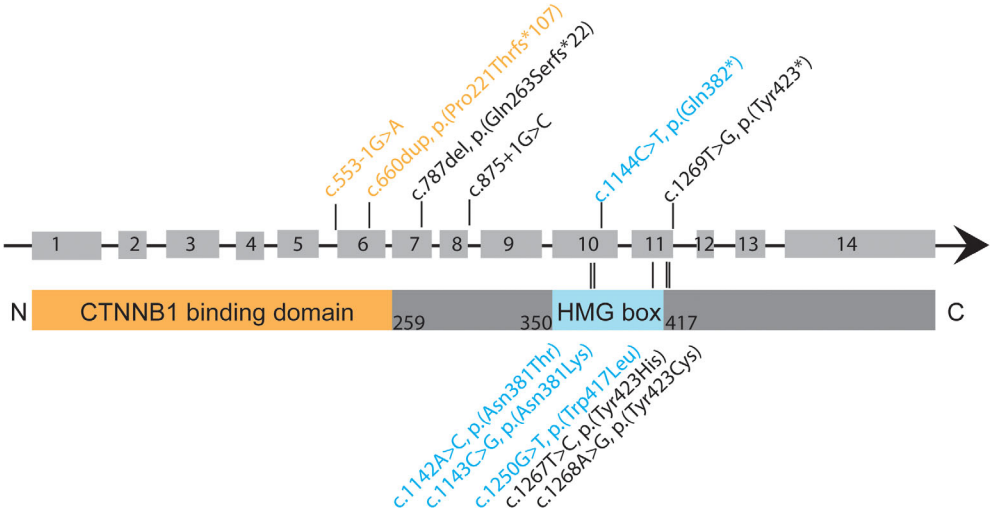


**FIGURE 1** Annotation of loss of function and missense variation in *TCF7L2*. Top bar indicates exon structure of NM_001146274.1. Second bar represents protein structure with PFAM amino acid ranges overlaid, that is, the CTNNB1-binding domain (orange) spanning amino acids 1–259, and the HMG box domain (light blue) spanning 350–417. Predicted splicing and loss-of-function variants are annotated above the figure and missense variants are annotated below [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Clinical features of affected patients

| | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Variant information* | | | | | | | | | | | | |
| Coding variant (c.) (NM_001146274.1) | c.553-1G>A | c.1269T>G | c.787del | c.1144C>T | c.660dup | c.875 +1G>C | c.1143C>G | c.1142A>C | c.1250G>T | c.1267T>C | c.1268A>G | |
| Amino acid variant | | p.(Tyr423*) | p.(Gln263Serfs*22) | p.(Gln382*) | p.(Pro221Thrfs*107) | | p.(Asn381Lys) | p.(Asn381Thr) | p.(Trp417Leu) | p.(Tyr423His) | p.(Tyr423Cys) | |
| Inheritance | De novo | De novo | De novo | De novo | De novo | De novo | De novo | De novo | De novo | De novo | De novo | |
| *Demographics* | | | | | | | | | | | | |
| Sex | Male | Male | Female | Female | Female | Male | Male | Male | Male | Male | Male | |
| Age at evaluation | 12 year | 11 year | 18 year | 8 year 7 months | 5 year 7 months | 11 year | 4 year | 17 year 10 months | 3 year 9 months | 5 year 7 months | 7 year 6 months | |
| *Development* | | | | | | | | | | | | |
| Motor delay? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No | Yes | $n = 8/11$ |
| Age at walking | 16 months | 24 months | 18 months | 12-13 months | 15 months | 14 months | 14 months | 15 months | 18 months | 14 months | 24 months | |
| Speech delay? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | $n = 11/11$ |
| Age at first words | 24 months | Delayed | 7 years | 4 years | Unknown | Unknown | 2.5 years | Unknown | 18 months | Unknown | Not verbal | |
| Verbal at evaluation? | Yes | Minimally | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | $n = 8/11$ |
| Intellectual disability? | No | Yes | Yes | No | No | No | No | Yes | No | Yes | Yes | |
| *Behavioral features* | | | | | | | | | | | | |
| Autism? | No | Yes | Yes | Yes | No | No | No | No | No | No | Yes | $n = 4/11$ |
| ADHD? | Yes | Yes | No | Yes | No | Yes | No | No | No | No | No | $n = 4/11$ |
| Sleep disturbances ? | No | Yes | Yes | No | Yes | No | Yes | No | No | No | No | $n = 4/11$ |
| *Neurologic features* | | | | | | | | | | | | |
| Tone abnormalities? | No | Yes | No | No | No | No | No | Yes | No | No | Yes | $n = 3/11$ |
| *Other clinical features* | | | | | | | | | | | | |
| Dysmorphic features? | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | $n = 8/11$ |
| Ophthalmology findings? | Yes | No | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | $n = 7/11$ |
| Dermatology findings? | No | Yes | No | Yes | Yes | No | Yes | No | No | No | Yes | $n = 5/11$ |
| Orthopedic findings? | No | No | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | $n = 6/11$ |

v2.1.1). Although speculative, it is thus possible that in addition to LoF as a possible mechanism of pathogenicity, this variant may lead to inappropriate exon retention.

No clear phenotypic differences were observed between individuals in this cohort with truncating and missense variants. For example, the five individuals with missense variants demonstrated a wide range of cognitive functioning similar to the individuals with truncating variants. Across the different forms of variation, individuals also shared findings like myopia and hypertrichosis. We hypothesize that the missense variation clustering at the HMG domain may interfere with appropriate DNA binding and interaction, contributing to a similar LoF effect as the truncating variants.

Given the genomic wide association study findings of intronic variants associated with diabetes risk, it is also interesting that there are no reported endocrine abnormalities, including diabetes mellitus, in any of the patients presented here, although it is important to note that this cohort reflects a predominately pediatric population and thus may not yet manifest certain findings.

*TCF7L2* has been implicated in oligodendrocyte development and it has recently been posited that expression in this cellular subtype may represent an underappreciated mechanism of pathogenicity in neurodevelopmental disorders (Polioudakis et al., 2019; Ye et al., 2009; Zhao et al., 2016). Interestingly, recent work on Pitt–Hopkins syndrome, caused by mutations in *TCF4*, as well as idiopathic autism, has recently implicated oligodendrocyte pathology in autism (Phan et al., 2020). Further work will be needed to identify more definitively the cellular subtypes and neuronal circuitry responsible for mediating the effects of variation in *TCF7L2*, as well as functional interrogation of the described variation.

In conclusion, we present 11 patients with de novo, heterozygous variants in *TCF7L2* presenting with a distinct neurodevelopmental disorder associated with initial developmental delay, speech–language difficulties, and variable risk for intellectual disability, autism, ADHD, myopia, and orthopedic abnormalities. All reported missense variants occurred in or adjacent to the HMG box domain. The phenotypes of individuals with missense and truncating variants were indistinguishable. Based on this, we hypothesize that the molecular mechanism for this disorder is haploinsufficiency, although further work to confirm this is required on a research basis.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Caroline Dias contributed to drafting and revision of the manuscript. Lance H. Rodan contributed to conception and design of the study, acquisition of clinical data, and revision of the manuscript. Rolph Pfundt, Tjitske Kleefstra, Janneke Shuurs-Hoeijmakers, Elles M. J. Boon, Johanna M. van Hagen, Petra Zwijnenburg, Marjan M. Weiss, Boris Keren, Cyril Mignot, Arnaud Isapof, Karin Weiss, Tova Hershkovitz, Maria Iascone, Silvia Maitz, René G. Feichtinger, Dieter Kotzot, Johannes A. Mayr, Tawfeg Ben-Omran, Laila Mahmoud, Lynn S. Pais, Christopher A. Walsh, Vandana Shashi, Jennifer A. Sullivan, Nicholas Stong, Francois Lecoquierre, Anne-Marie Guerrot, and Aude Charollais contributed to the acquisition of clinical data and revision of the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

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