Expansion of the Phenotypic Spectrum of TNRC6B-Related Neurodevelopmental Disorder in a Three-Generation Family with 22q13.1 Deletion

Jessica Archer , Sheridan O'Donnell , Melissa Buckman , Nicole Bain , Himanshu Goel *

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Article

Expansion of the Phenotypic Spectrum of TNRC6B-Related Neurodevelopmental Disorder in a Three-Generation Family with 22q13.1 Deletion

Jessica Archer [1], Sheridan O'Donnell [1], Melissa Buckman [2], Nicole Bain [3] and Himanshu Goel [1,4,*]

[1] Hunter Genetics, Waratah, NSW, Australia
[2] Tamworth Community Health Centre, Tamworth, NSW, Australia
[3] Department of Molecular Medicine, New South Wales Health Pathology, John Hunter Hospital, Newcastle NSW Australia
[4] School of Medicine and Public Health, University of Newcastle, Callaghan, NSW 2308, Australia
* Correspondence: himanshu.goel@health.nsw.gov.au; Tel.: +61-02-49853100; Fax: +61-02-49853105

Abstract

Background: *TNRC6B* encodes a core effector of the RNA-induced silencing complex and is essential for miRNA-mediated gene silencing. Pathogenic variants in *TNRC6B* have recently been associated with a neurodevelopmental disorder characterised by developmental delay, intellectual disability, and behavioural difficulties. **Methods:** We report a three-generation family with a 22q13.1 deletion encompassing *TNRC6B*. Clinical data were collected from medical records and family interviews, and the findings were compared with those of published cohorts. **Results:** Affected individuals presented with developmental delay, speech and language impairment, autism spectrum disorder, ADHD, oppositional defiant disorder, craniosynostosis, joint laxity, clinodactyly, and cardiac valve anomalies. The father and paternal grandmother had learning difficulties and neurobehavioral features, while the proband exhibited a more severe phenotype. **Conclusion:** This report expands the phenotypic spectrum of TNRC6B-related neurodevelopmental disorder, highlighting craniosynostosis, joint and connective tissue features, and cardiac involvement. Our findings also underscore variable expressivity across generations and emphasise the relevance of both copy-number and sequence variants in *TNRC6B* in patients with neurodevelopmental disorders.

Keywords: TNRC6B; neurodevelopmental disorder; intellectual disability; developmental delay; copy number variant (CNV); mRNA

1. Introduction

Precise post-transcriptional regulation of gene expression is essential for normal neurodevelopment. One of the principal mechanisms controlling mRNA stability and translation is RNA silencing, a conserved pathway that fine-tunes protein output in response to developmental and cellular signals. Disruption of this pathway has increasingly been implicated in neurodevelopmental disorders [1]. RNA silencing regulates gene expression through small RNAs, including microRNAs (miRNAs). miRNAs are transcribed as primary transcripts, processed by Drosha–DGCR8 in the nucleus and by Dicer in the cytoplasm, and then loaded onto Argonaute (AGO1–AGO4) proteins to form the RNA-induced silencing complex (RISC) [2]. Within RISC, AGO proteins mediate mRNA cleavage or translational repression [3].

TNRC6B is located on chromosome 22q13.1 and comprises 23 exons encoding a large cytoplasmic protein of approximately 1,833 amino acids (~194 kDa). It belongs to the GW182 family of scaffolding proteins (TNRC6A–C) that mediate miRNA-guided gene silencing. The N-terminal region, encoded by the early exons, is rich in glycine–tryptophan (GW) repeats, which provide docking sites for AGO proteins and form the core of the RISC. The central portion of the protein,

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encoded by the middle exons, contains a glutamine-rich region and a ubiquitin-associated (UBA) domain that contribute to localisation within cytoplasmic processing bodies (P-bodies) and facilitate interaction with downstream effector complexes. The C-terminal region, encoded by the terminal exons, harbours an RNA recognition motif (RRM) and additional GW-rich sequences that directly bind RNA and recruit the cellular machinery responsible for mRNA deadenylation, decay, or translational repression [4-7].

The clinical significance of *TNRC6B* has only recently been established. A *de novo* frameshift and a *de novo* nonsense variant in *TNRC6B* were first noted in the Deciphering Developmental Disorders (DDD) study of whole exome sequencing for more than 2500 simplex families with a child with an autism spectrum disorder [8]. Granadillo et al. (2020) described 17 individuals (12 males, 5 females) with heterozygous *TNRC6B* variants, including 7 nonsense, 5 frameshift, 2 splice-site, 2 intragenic deletions, and 1 missense variant. All individuals demonstrated developmental and neurobehavioral abnormalities, with high frequencies of speech delay (94%), autism or autistic traits (76%), ADHD (65%), hypotonia (59%), and variable skeletal and cardiovascular anomalies [9].

Most prior studies focused on single-nucleotide variants, whereas copy-number variants (CNVs) affecting *TNRC6B* remain underrepresented. Here, we describe a three-generation family with a 22q13.1 deletion encompassing only *TNRC6B*. Affected members demonstrated neurodevelopmental and behavioural features consistent with prior reports, along with previously under-recognised phenotypes, including craniosynostosis, joint laxity, clinodactyly, and cardiac valve anomalies. This study, therefore, expands the phenotypic spectrum of TNRC6B-related disorders and highlights variable intergenerational expression.

2. Methods

2.1. Genetic Testing

Chromosomal microarray analysis (CMA) was performed on the proband using Illumina SNP 850k v1.4 and data was analysed using BlueFuse Multi v4.5. Variants are reported using Genome Reference Assembly GRCh38(hg38). A 22q13.1 deletion (chr22:40233976–40489019, GRCh38) encompassing *TNRC6B* (exon 2-23) was identified. No other gene was included in the deleted region. Segregation studies were performed in available family members via CMA.

2.2. Clinical Assessment

Clinical phenotyping included review of medical records, developmental assessments, and structured interviews with parents. Data collected encompassed growth parameters, developmental milestones, behavioural profiles, congenital anomalies, and imaging studies (brain MRI, echocardiogram). Standardised developmental scales, including Bayley Scales of Infant Development and Wechsler assessments, were incorporated when available.

2.3. Literature Review

A targeted literature search was performed in PubMed using "*TNRC6B*," "neurodevelopmental disorder," "intellectual disability," and "RNA-induced silencing complex." Phenotypic comparisons were made between published cases and the present family.

2.4. Ethical Considerations

Informed consent for genetic testing and publication of clinical data was obtained from the proband's parents. This study was approved by Hunter New England Research Office Ethics Manager; Reference: 20260116-001.

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3. Case Report

3.1. Proband (IV-3)

The proband was first reviewed at 7 months of age for global developmental delay and failure to thrive. She is the youngest of three sisters. She was born at 39 weeks after an unremarkable pregnancy via an elective Caesarean section. Her Apgar scores were 6 at 1 minute, 7 at 5 minutes and 6 at 10 minutes, respectively. She required 21 hours of respiratory support. She was treated for congenital pneumonia with 5 days of penicillin. Her birth weight was 2736 gm (5-10th percentile; 1.55 standard deviations below the mean for gestation), length was 45 cm and her head circumference was 33 cm. She was re-admitted at 6 weeks of age for failure to thrive in the context of loose stools and frequent vomiting, subsequently managed with a proton pump inhibitor and feed thickener. Ultrasounds of her head and abdomen, including liver and kidneys, were normal. She did not have any other imaging.

At 7 months of age, she was not sitting independently and was not crawling or babbling. At 13 months old, she was crawling, standing and cruising along furniture, waving, clapping and using a pincer grip. However, she only had two inconsistent words, did not produce varied vocalisations and primarily growled. She demonstrated head-banging behaviour, which was thought to be a form of sensory stimulation. She has a diagnosis of global developmental delay. At 16 months of age, her weight was at the 7th percentile and her head circumference was at the 9th percentile. She looked like her father. She had mild upslanting palpebral fissures. Her SNP microarray showed a deletion of 0.25Mb in the chromosome 22q13.1 region.

3.2. Sister (IV-2)

The proband's 3-year-old sister is being investigated for neurodevelopmental concerns. Her early developmental milestones were achieved within acceptable limits; however, her early education teachers noted an inability to socialise with other children. At 3 years of age, she had just started combining words into 3-word sentences and was toilet-trained during the day. She has self-harming behaviours.

She also has the same chromosome 22q13.1 deletion of 0.25Mb. She was born at 39 weeks after a normal pregnancy via elective Caesarean section. Her APGAR scores were normal. Her birth parameters were within normal limits. She has had episodes of recurrent vomiting followed by floppiness.

3.3. Sister (IV-1)

The proband's 4-year-old sister has consistently achieved normal developmental milestones. She does not have the 22q13.1 deletion.

3.4. Father (III-2)

The proband's 28-year-old father experienced neurodevelopmental challenges and he struggled academically compared to his unaffected brother (III-1). He obtained a full-scale IQ of 75 on WPSSI-R testing when he was 5 years of age, and a full- scale IQ of 83 on the WISC-III at 7 years of age. He had childhood diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD), with ongoing behavioural dysregulation into adolescence. He underwent assessment for autism spectrum disorder (ASD) but was found not to meet criteria. He was born at 38 weeks of gestation with a birth weight of 2300g (2 standard deviations below the mean for gestation). He required a 5 day admission for nasogastric tube feeding support due to a poorly developed suck. Additional features included thin blonde hair, joint laxity, and mitral valve prolapse. He had a broad nose, a small, narrow chin and prominent ears. CMA confirmed the same 22q13.1 deletion.

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3.5. Paternal Grandmother (II-2)

She is 52 years old and required surgery for craniosynostosis during childhood. She has strabismus, middle ear infections, conductive hearing loss, hiatus hernia and inguinal hernia. She had learning difficulties and required additional educational support. She did not complete secondary schooling. She first began using 2-word combinations at 4 years of age. She was given a diagnosis of dyslexia in Grade 3. She exhibited clinodactyly and mild joint laxity. Genetic testing confirmed the 22q13.1 deletion. Her husband (II-1) was unaffected.

II-2 reported a family history of an uncle who attended a special school, with particular difficulty with literacy skills. He is deceased and has no descendants. (Figures 1 and 2)

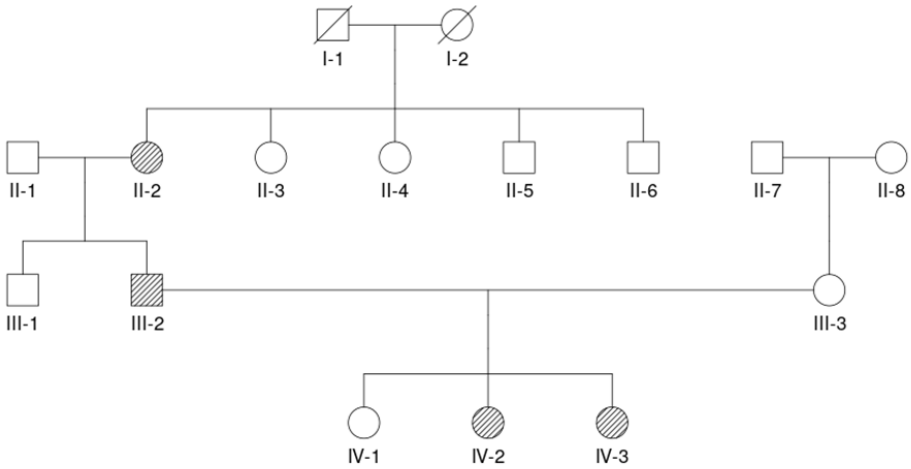

Figure 1. Family pedigree. III-1 has not undergone genetic review or testing but is reported by family not to be affected.

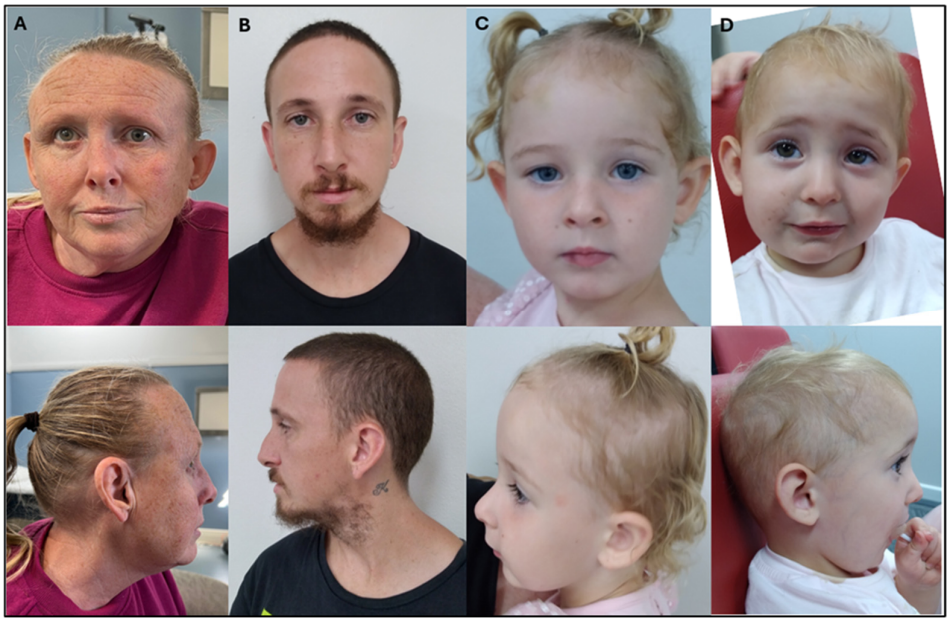

Figure 2. Clinical photography of the paternal grandmother (II-2; A), father (III-2; B), proband's sister (IV-2; C) proband (IV-3; D).

 doi:10.20944/preprints202603.0365.v1

4. Discussion

TNRC6B haploinsufficiency causes a distinct neurodevelopmental disorder characterised by developmental delay, intellectual disability (ID), speech impairment, ASD and ADHD. The present family demonstrates multigenerational segregation of a 22q13.1 deletion including *TNRC6B*, with variable phenotypic expressivity, intergenerational phenotypic differences, and under-recognised systemic features.

While core neurodevelopmental features were consistent, additional findings, including craniosynostosis, joint laxity, clinodactyly, and cardiac valve anomalies, expand the known spectrum. The proband presented with developmental delay, speech impairment, and sleep disturbances, while the father and paternal grandmother exhibited learning difficulties and behavioural dysregulation (ADHD, ODD), reflecting variable severity across generations [7]. Behavioural phenotypes, particularly ASD, ADHD, and oppositional behaviours, are prominent in both published cases and the current family. Dysregulated miRNA networks have been implicated in ASD pathogenesis, targeting genes involved in synaptic function, metabolism, and immune response [10]. Although TNRC6B-associated syndromes generally present with mild dysmorphic features, our family illustrates expanded systemic involvement. Notably, cardiac involvement was evident in the father (floppy heart valve) and has been reported in previous cohorts as aortic root dilation in two patients [9]. While relatively uncommon, these findings suggest that *TNRC6B* may influence vascular or valvular development, potentially through miRNA-mediated regulation of developmental genes. These observations warrant longitudinal cardiovascular monitoring in affected individuals. Exome sequencing of 362 probands with non-syndromic tetralogy of Fallot (TOF) and their parents within the Paediatric Cardiac Genomics Consortium (PCGC) showed one individual with a *de novo* heterozygous c.2482C>T variant (p.Gln828*)[11]. TNRC6B-associated ID, ADHD, and autism share similarities with other RNA-induced silencing complex (RISC) disorders. Disease-causing variants in *AGO1* and *AGO2* have also been linked to ID and autism, while expansions of intronic TTTCA and TTTTA repeats in *TNRC6A* are implicated in benign familial myoclonic epilepsy [12-15].

Our family's CNV (22q13.1 deletion) further underscores that haploinsufficiency, whether by CNV or sequence variant, produces overlapping phenotypes. Granadillo et al. (2020) described 17 individuals with heterozygous *TNRC6B* variants. All individuals demonstrated developmental and neurobehavioral abnormalities, with high frequencies of speech delay (94%), autism or autistic traits (76%), ADHD (65%), hypotonia (59%), and variable skeletal and cardiovascular anomalies [9]. Genotype–phenotype analysis suggested that N-terminal variants affecting the Argonaute-binding domain were associated with macrocephaly, whereas C-terminal variants affecting the silencing domain were linked to microcephaly. However, no strong correlations were observed with specific neurodevelopmental symptoms. Notably, 23% of pathogenic variants were inherited, emphasising the importance of genetic counselling and highlighting variable expression among carriers. Speech delay was the most prevalent developmental challenge, while autism and ADHD were frequently observed neurobehavioral traits. Loss-of-function variants in *TNRC6B;* c.2040G>A, p.(Trp680*) and c.830_836del, p.(Asn277Metfs*3) were reported in patients with developmental language disorder, like childhood apraxia of speech (CAS) [16],[17]. Functional studies have also demonstrated that synonymous variants, such as c.3141G>A, can disrupt RNA splicing, highlighting the diverse molecular mechanisms by which *TNRC6B* variants can contribute to disease [18]. A 31-year-old woman with epilepsy with onset during infancy, ASD without ID had a *de novo* pathogenic variant in the *TNRC6B*: c.2189del, p.(Gln730Argfs*62) [19].

Mild dysmorphic features were noted previously, though no consistent facial pattern emerged. Two unrelated Chinese patients had *de novo TNRC6B* variants, c.335C>T (p.Pro112Leu) and c.1632delC (p.Leu546fs*63). The clinical features of the patients were DD/ID, delayed speech, ADHD, behavioural abnormalities, short stature, low body weight, café-au-lait spots, metabolic abnormalities, and facial dysmorphism, including coarse facial features, sparse hair, frontal bossing, hypertelorism, amblyopia, strabismus, and downslanting palpebral fissures [20].

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Marked intrafamilial variability is evident in TNRC6B-associated neurodevelopmental disorder, with phenotypes ranging from isolated learning difficulties and behavioural traits to global developmental delay and structural anomalies. Several non–mutually exclusive mechanisms may underlie this heterogeneity. Allelic heterogeneity and variant position are critical determinants: premature termination codons (PTCs) located upstream of the final exon–exon junction are predicted to trigger nonsense-mediated decay (NMD), resulting in haploinsufficiency. In contrast, truncating variants in the terminal exon may escape NMD and produce partially functional proteins, depending on preservation of key domains such as the AGO-binding GW repeats or the C-terminal RRM and silencing regions. In addition, although typically inefficient, basal stop-codon readthrough could theoretically permit low-level synthesis of full-length protein from certain PTC alleles, potentially modifying residual TNRC6B activity and contributing to phenotypic variability [21].

Beyond allele-specific effects, TNRC6B functions as a dosage-sensitive scaffold within the RNA-induced silencing complex (RISC), and modest differences in residual protein levels may disproportionately affect miRNA-regulated neurodevelopmental gene networks. Variable buffering by paralogues (TNRC6A and TNRC6C), together with genetic modifiers within the miRNA pathway, likely further shapes the clinical spectrum observed in TNRC6B-related disorder.

5. Conclusions

This three-generation family confirms *TNRC6B* haploinsufficiency as a cause of neurodevelopmental disorder and expands the phenotypic spectrum to include craniosynostosis, connective tissue features, and cardiac anomalies. Variable expressivity across generations emphasises the need for careful genetic counselling. Recognition of both copy-number and sequence variants in *TNRC6B* is essential for accurate diagnosis, prognostication, and management of affected individuals. Further studies are warranted to clarify genotype–phenotype correlations and elucidate mechanisms underlying variable expression.

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Abbreviations

The following abbreviations are used in this manuscript:

RNA	Ribonucleic acid
miRNA	Micro- Ribonucleic acid
ADHD	Attention Deficit Hyperactivity Disorder
CNV	Copy number variant
RISC	RNA-induced silencing complex
AGO	Argonaute
mRNA	Messenger Ribonucleic acid
GW	glycine–tryptophan
UBA	ubiquitin-associated
RRM	RNA recognition motif
DDD	Deciphering Developmental Disorders
CMA	Chromosomal microarray
MRI	Magnetic Resonance Imaging
SNP	Single Nucleotide Polymorphism
APGAR	Appearance, Pulse, Grimace, Activity, Respiration

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IQ	Intelligence Quotient
WPSSI-R	Wechsler Preschool and Primary Scale of Intelligence—Revised
WISC-III	Wechsler Intelligence Scale for Children—Third Edition
ASD	autism spectrum disorder
ODD	Oppositional Defiant Disorder
ID	Intellectual disability
TOF	tetralogy of Fallot
PCGC	Paediatric Cardiac Genomics Consortium
PTCs	premature termination codons
NMD	nonsense-mediated decay

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