Diagnosis and clinical presentation of two individuals with a rare *TCF20* pathogenic variant

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SUMMARY

TCF20-associated neurodevelopmental disorder (TAND) is a rare and phenotypically variable genetic condition. Common features include intellectual disability, neurobehavioural concerns, postnatal tall stature and hypotonia.

Two unrelated early adolescent males were referred to genetics for assessment of developmental delay. The first male of Caucasian descent had a history of autism spectrum disorder (ASD), mitral valve prolapse and subtle craniofacial dysmorphisms. The second male of Somali descent had a history of intellectual disability, thick corpus callosum and ASD. Whole-exome sequencing revealed a pathogenic variant in *TCF20* in both individuals. Further testing revealed that the former individual's mother was mosaic for the *TCF20* pathogenic variant.

We report two individuals with *TCF20* pathogenic variants presenting with unique findings, including thick corpus callosum, family history of mosaicism and cardiac anomalies. These examples expand the TAND phenotype, describe associated dysmorphism in a minority group and highlight the importance of rare disease research.

BACKGROUND

There are currently approximately 100 individuals described with pathogenic variants in the gene *TCF20*.[1 2] This six exon gene codes for a nuclear protein TCF20, also commonly referred to as ARI, stromelysin-1 PDGF-responsive element (SPRE)-binding protein or SPBP.[2 3] TCF20 is widely expressed throughout the body,[4 5] and has increased expression within the hippocampus and cerebellum.[1] TCF20 is thought to function as a transcriptional co-regulator,[6] altering the expression of a multitude of secondary transcription factors including Sp1, Pax6, Jun and Ets,[1 6] via its ability to bind the SPRE of the stremolysin 10 matrix metalloproteinase-2 (MMP2)/MMP3.[6] Previous studies have shown that TCF20 is likely highly intolerant to loss of function variants,[2] making it a candidate gene for underlying pathology in various neurodevelopmental disorders.

Pathogenic variants in the *TCF20* gene in individuals result in 'TCF20-related disorder', also known as 'autosomal dominant developmental delay with variable intellectual impairment and behavioural abnormalities, or *TCF20*-associated neurodevelopmental disorder (TAND) (OMIM # 618430).[2] The presentation of TAND is highly variable, though certain features are more common. The majority of individuals with TAND present with mild-to-moderate intellectual disability (ID) and neurobehavioural comorbidities including autism spectrum disorder (ASD).[2 6] Physically, many patients present with proportionate overgrowth, muscular hypotonia and other neuromuscular anomalies including ataxia.[2] Subtle facial dysmorphisms are also common though highly variable and include frontal bossing, depressed nasal bridge, abnormal facial shape and deep-set eyes.[2] Other less commonly described findings include sleep disturbances, physical overgrowth, macrocephaly, digital anomalies and seizures.[2]

TCF20 is paralogous to and likely interacts with RAI1.[7] Pathogenic variants in *RAI1* cause Potocki-Lupski syndrome (PLS) via duplication/triplosensitivity and Smith-Magenis syndrome (SMS) via deletion/haploinsufficiency.[8] Like TAND, both conditions are characterised by ID, neurodevelopmental concerns and ASD.[8] Moreover, recent studies have identified *TCF20* to be the closest gene to a locus of shared genetic effects between schizophrenia and cognitive traits.[9] The associations underscore the importance of describing patients with *TCF20* pathogenic variants, and demonstrate the far-reaching effects of understanding the clinical phenotype of individuals with TAND.

We describe two additional individuals from two independent families with unique *TCF20* pathogenic variants. These patients presented with rare genotypes, phenotypes and findings on brain imaging. One of the individuals is of African descent, an ethnic background in which dysmorphisms are underreported in literature.[10–12] We hope to use these case presentations to contribute to the growing literature on TAND and associated conditions, highlight the inequities that exist in genomic research and demonstrate how rare disease research can help improve our understanding of other more common conditions.

CASE PRESENTATION

Case 1

An early adolescent male (patient A) was referred to our clinic due to a constellation of ID, ASD and mitral valve prolapse (MVP). He also had chronic and refractory constipation. He was the second of three siblings, born to a woman in her 20s, of non-consanguineous European descent. He was naturally conceived and born at term via emergency caesarean section due to fetal positioning. Neonatal course was unremarkable. Birth weight was 3.4 kg and APGARs were normal. He received 1 day of phototherapy for jaundice and was noted to have mild hypothermia and plagiocephaly at birth, the latter of which was treated with a corrective helmet for 4 months in the first year of life.

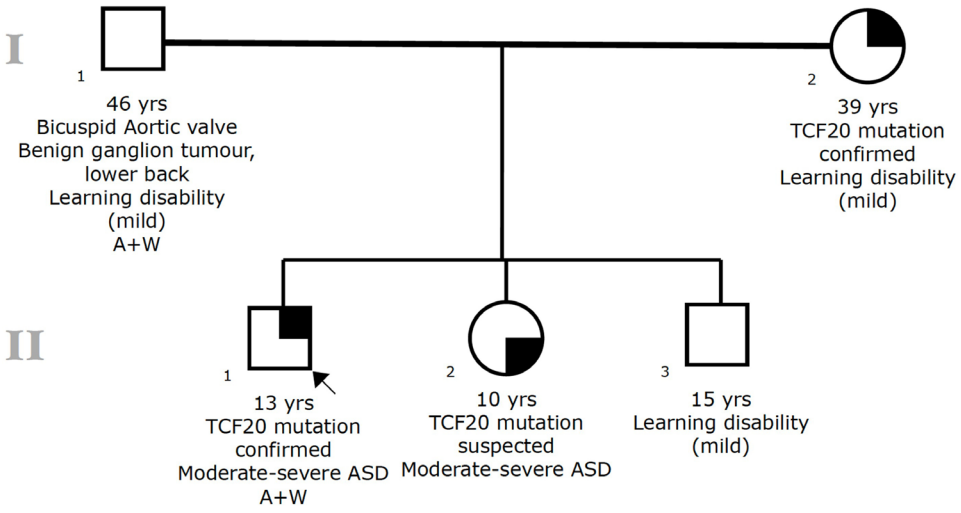

Figure 1 Pedigree. Pedigree of patient A, including ages and relevant comorbidities of family members. ASD, autism spectrum disorder.

The patient's parents noted developmental delay in all domains including gross motor, fine motor, cognition, language and social, by 1 year of age. Mild-to-moderate MVP was diagnosed incidentally at 2 years of age when the patient presented to the hospital with reactive airway disease. Psychoeducational testing at 7 years of age revealed a diagnosis of mild-to-moderate ID and ASD. He was described as being social towards adults but not peers, and demonstrated stereotypical behaviours including hand flapping, occasional rocking and a hand tic. There was no history of developmental regression.

On examination at 13 years, weight was 38.8 kg and height was 150.5 cm (17th and 15th percentile on WHO for Canadian boys 2–19 years chart, respectively), and head circumference was 51.0 cm (less than the 3rd percentile for Rollins boys chart). The patient had malar hypoplasia, deep-set eyes, narrow palpebral fissures, droopy eyelids, prominent nose with a pointed tip, short philtrum, downturned corners of the mouth and wide-spaced teeth with large central incisors. His ears were normally set and rotated with a prominent antihelix. He had upsloping of the fingernails and a short fifth finger with fetal fat pads bilaterally. Dermatological examination revealed no obvious neurocutaneous lesions.

On family history, one sibling had a mild learning disability isolated to reading, and another sibling had developmental delay and moderate-severe ASD (figure 1). The patient's mother had a vague history of learning disability in reading and writing, and had two maternal cousins with learning disabilities. She had no obvious dysmorphic features, although a formal assessment was not performed.

The following diagnostic testing prior to presentation to our clinic was unremarkable: brain MRI at age 3 years, spine MRI at age 12 years, karyotype and chromosomal microarray. Anorectal manometry at age 12 years showed a normotensive anal sphincter with no evidence of Hirschsprung's disease. He also had negative testing for both Fragile X syndrome and MECP2 duplication syndrome.

Case 2

An early adolescent male (patient B) was referred to genetics for history of ID, ASD, corpus callosum abnormality on MRI and concern for seizures. He was the eldest of four healthy siblings born to non-consanguineous parents of Somali descent. He was born via spontaneous vaginal delivery at term to a primigravida woman in her 20s from a planned pregnancy. The pregnancy and prenatal ultrasounds were unremarkable. Birth weight was approximately 3 kg. There were no neonatal concerns.

The patient spoke his first words around 7–8 months. He was initially able to speak full sentences but began to regress developmentally at 7 years of age with poverty of speech and social isolation. Aggressive tendencies for self-harm began around 8 years of age when the patient began repeatedly hitting his head against the wall. The details of his ultimate ASD diagnosis were not clear at the time of presentation. Of note, this period coincided with when the patient and his family moved to Ethiopia as refugees. Further detailed developmental history was not available as the patient's father, and primary collateral historian, was not living with the patient for a large portion of his childhood. The patient and his family eventually moved to Canada when he was 8 years of age. There were no illnesses or major medical issues around that time. The concern for seizures came from a vague history from his parents of staring episodes and fluttering eyes followed by a period of confusion.

At assessment at 14 years, the patient did not consistently know body parts or colours, and he could count to 10. He was able to read children's picture books and was unable to write his name legibly. He was unable to do basic addition. He was able to run, walk, go upstairs and ride a bicycle, but did walk with a somewhat unsteady gait. In terms of fine motor skills, he was able to dress himself, and feed himself with a spoon and his hands. He had a pincer grasp but was not able to reliably write letters or draw shapes. He was only able to stay at school for 3 hours due to behavioural concerns.

Physical examination at 13 years was again significant for subtle phenotypical findings. His weight was 51.3 kg, and his height was 172 cm (73rd and 98th percentile on the WHO for Canadian boys 2–19 years chart, respectively). His head circumference was 56.5 cm (90th percentile on the Rollins boys chart). He had slightly upslanted palpebral fissures, broad depressed nasal bridge and broad tip consistent with his ethnicity. He also had hooded eyelids, a prominent maxilla and mandible, full lips, and well-developed widely spaced teeth. His ears were normally set and rotated with a prominent pointed helix. He had a broad forehead and deep palmar creases.

A brain MRI at age 11 years old showed that the corpus callosum had an abnormal appearance with overall thickening and slightly lobulated contour, likely reflecting underlying

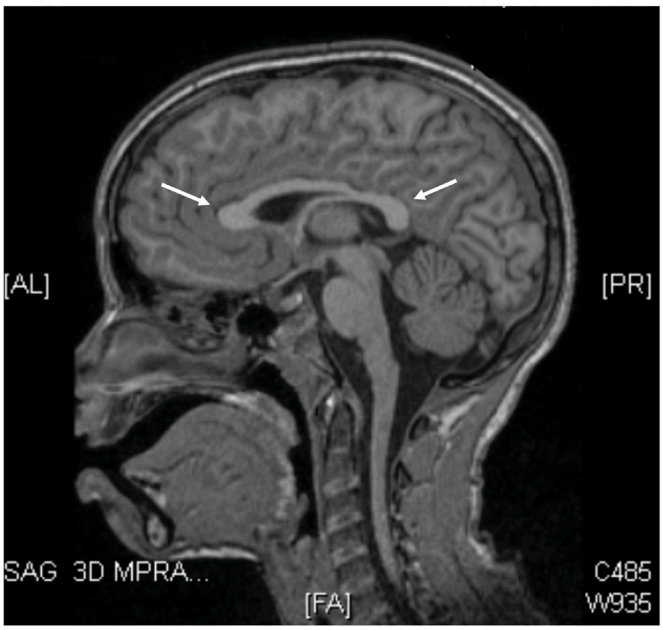

Figure 2 Neuroimaging findings. Brain MRI of patient B, at 11 years of age, showing abnormally appearing corpus callosum with overall thickening and slightly lobulated contour (arrows) on MP-RAGE T1-weighted sagittal plane.

abnormalities in the organisation of the white matter (figure 2). An electroencephalogram at age 11 years was unremarkable. Previous chromosomal microarray demonstrated a normal male karyotype, and Fragile X syndrome testing was normal.

Both patients were referred to our clinic for overall assessment and consideration of whole-exome sequencing (WES) due to a strong suspicion for a genetic condition underlying their presentations.

INVESTIGATIONS

WES trio was performed on both patients using peripheral blood for patients A and B, as well as peripheral blood from their biological parents to optimise results. We clarified with patient A's parents that full sequencing would occur in patient A only, and additional samples from biological parents would be used for variant classification only. WES was chosen as the most appropriate test for patient A over a targeted ID/ASD gene panel as he presented with multiple other phenotypical features, including MVP and microcephaly.

For patient B, approval from the Ministry of Health was initially granted to complete an ID panel trio at Fulgent Genetics as he primarily presented with neurodevelopmental features. When the results of the panel were inconclusive, we reflexed to perform WES for the patient.

DIFFERENTIAL DIAGNOSIS

Given the varying phenotypical findings in both patients along with non-specific developmental delay and features of ASD, the differential diagnosis was broad from a genetics perspective. It included in utero exposures, chromosomal aberrancies, trinucleotide repeat disorders such as Fragile X syndrome and single-gene disorders. Given the normal pregnancy histories, chromosomal microarray and Fragile X syndrome testing, the group of disorders still necessitating further work-up included single-gene disorders. As the facial features and clinical phenotype were not consistent with a common, well-delineated, single-gene disorder, WES was determined as the most cost-effective and comprehensive test for determining a diagnosis.

WES confirmed heterozygous pathogenic variants in *TCF20* for both patients. Specifically, patient A's WES returned positive for a heterozygous *TCF20* pathogenic variant (c.558G>A, p.W1861X, figure 3A). This nonsense variant is predicted to result in protein truncation or nonsense-mediated decay, both ultimately leading to loss of function of TCF20. Testing of patient A's mother revealed that she was mosaic for this pathogenic variant. The variant was identified as present in 6.98% of 129 sequencing reads in the mother, indicating that it was under-represented in comparison with the reference allele in the specimen tested. The level of mosaicism was noted to be potentially different in other tissues. We were unable to predict the proportion of the two different cell populations in other organs of the patient's mother. His father was negative for this pathogenic variant in *TCF20*.

Patient B's WES results also revealed a de novo heterozygous, likely pathogenic variant in *TCF20* (c.1261A>T, p.Thr421Ser, figure 3B). This missense variant is predicted to result in a single amino acid substitution of threonine to serine at codon 421 in exon 2 of the *TCF20* gene. Neither of patient B's parents harboured the *TCF20* variant, confirming the de novo event. Additionally, the ID gene panel revealed five inherited variants of uncertain clinical significance in four different genes (one variant in *DDX3X, MAOA* and *MET,* respectively; two variants in trans in *EPG5*). All variants were inherited from an unaffected parent.

Both patients were ultimately diagnosed with TAND following review of their genetic results.

OUTCOME AND FOLLOW-UP

Genetic counselling was provided to both patients and their caregivers. The autosomal dominant inheritance pattern of TAND was discussed, specifically that should either patient A or patient B have children in the future, they would have a 50% chance to pass on the pathogenic variant in each pregnancy. We recommended that each patient be re-referred for genetic counselling to discuss family planning implications and reproductive options when appropriate.

For patient A, specific counselling was provided regarding the maternal mosaicism for the *TCF20* variant. It is suspected that the mosaicism may be contributing to his mother's learning difficulties, but this cannot be determined with certainty. Furthermore, as we could not determine the level of mosaicism in her gonads, she was counselled as having an up to 50% chance of having another child with TAND in any future pregnancy. Given one of patient A's siblings also has developmental delay and moderate ASD, TAND was suspected and genetic testing was initiated; results are currently pending. Testing for the other sibling, who has an isolated mild learning disability but no ASD, was deferred until they wish, such as for family planning, as it would not impact their current medical management.

Conversely, we discussed the implications of future pregnancies for the biological parents of patient B. The *TCF20* variant appears to have arisen de novo in patient B, and we discussed that there is a possibility for germline mosaicism in either parent but that this would be unlikely; we estimated the chance for patient B's parents to have another child with the *TCF20* variant is up to 1%.[13 14] A letter to help the family advocate for support and school resources for patient B in light of the new diagnosis was provided.

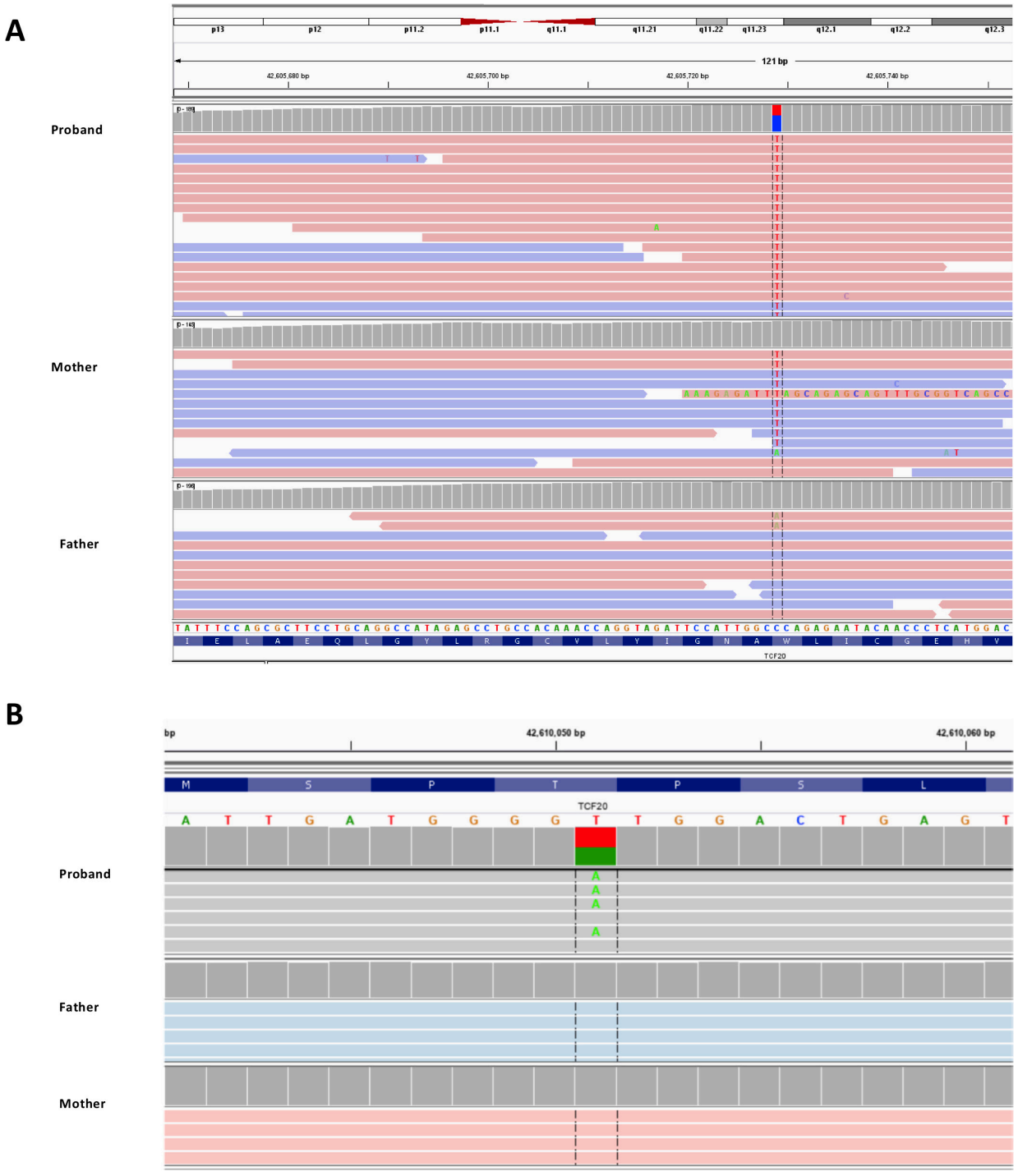

Figure 3 *TCF20* genetic testing findings. (A) In patient A, a missense variant (c558G>A, p.W1861X) in the *TCF20* gene was detected in the proband (upper panel) as well as in mosaic form in the proband's mother. Read alignments are sorted by change in base first. Figure supplied by GeneDx Laboratory. (B) In patient B, a missense variant (NM-005650.3:c.1261A>T, pThr421Ser) in the *TCF20* gene was detected in the proband (upper panel) and absent in either parent (middle and lower panel) in a trio whole-exome sequencing, consistent with de novo occurrence. Figure and legend supplied by Fulgent laboratory (B).

Follow-up is planned for both patients in 2 years' time, as new information about TAND may be available for reassessment. Currently, supportive treatment is the mainstay treatment option for patients with TAND.

DISCUSSION

TAND is a rare genetic condition caused by heterozygous pathogenic variant in the *TCF20* gene. The description of this condition is limited; common presenting symptoms include congenital hypotonia, motor delay, ID, ASD, moderate-to-severe language disorder, variable dysmorphic facial features and additional neuropsychiatric findings.[1 2] We present two unrelated individuals with unique *TCF20* pathogenic variants to add to the growing body of literature for this condition. Our patients presented with some features consistent with those previously described with TAND, including ID, ASD and mild

Table 1 Clinical and phenotypical summary of our patients and previously published patients with variants in *TCF20**

Clinical features	Schneeweiss *et al*, 2022 (n=2)	Levy *et al*[15] (n=7)	Torti *et al*[1] (n=27)	Vetrini *et al*[2] (n=32)†	DDD[16] (n=7)	Shäfgen *et al*[17] (n=2)	Lelieveld *et al*[18] (n=4)	Babbs *et al*[5] (n=4)	Total (n=85)	Total %
DD/ID	2/2	5/6	27/27	24/32	7/7	2/2	4/4	3/4	74/84	88
ASD/autistic features	2/2	1/4	18/26	15/32	2/7	1/2	NR	4/4	43/77	56
Attention disorder/hyperactivity	0/2	1/3	18/27	10/32	2/7	NR	NR	NR	31/71	44
Other neurobehavioural diagnosis or concerns	0/2	2/3	23/27	7/32	NR	2/2	1/4	NR	35/70	50
Hypotonia	0/2	1/3	17/27	21/32	NR	2/2	1/4	NR	42/70	60
Seizures	1/2	1/5	3/26	8/32	NR	1/2	0/4	NR	14/71	20
Other neurological presentations	0/2	NR	22/27	12/32	NR	1/2	NR	NR	35/63	56
Normal brain MRI	1/2	2/3	16/21	NR	0/2	2/2	NR	NR	21/30	70
Dysmorphic craniofacial features	2/2	4/5	18/27	25/32	NR	0/2	3/4	NR	52/72	72
Other minor malformations	1/2	NR	10/27	11/32	NR	0/2	0/4	NR	22/67	33
Gastrointestinal	1/2	NR	15/27	NR	NR	NR	1/4	NR	17/33	52
Skeletal	1/2	3/5	14/27	NR	NR	0/2	0/4	NR	18/40	33
Ophthalmological	0/2	5/5	14/27	NR	2/7	NR	0/4	NR	21/45	47
Dermatological	0/2	NR	7/27	NR	NR	NR	NR	NR	07/29	24
Cardiovascular	1/2	NR	4/27	NR	NR	NR	0/4	NR	05/33	15
Genitourinary	0/2	0/3	2/27	NR	NR	NR	0/4	NR	02/36	06
Immunological	0/2	NR	2/27	NR	NR	NR	NR	NR	02/29	07
Overgrowth	1/2	NR	2/22	9/32	NR	2/2	0/4	NR	14/62	23
Macrocephaly	0/2	NR	2/27	8/32	2/7	2/2	0/4	NR	14/74	19
Craniosynostosis	0/2	NR	0/27	NR	NR	NR	NR	2/4	02/33	06

*Adapted from Torti *et al*.[1] This article was published in *Genetics in Medicine*, 21, Torti *et al,* Copyright Elsevier (2019).[1]
†Five patients from the original McRae *et al*. DDD cohort was included in the Vetrini *et al* cohort. Moreover, two additional patients in this cohort were included in the meta-analysis from previous studies. The clinical phenotype of two subjects was determined to come from a combination of *TCF20* variants and additional contributions in variants detected in *SLC6A1* and *ZBTB18*.
ASD, autism spectrum disorder; DDD, Deciphering Developmental Disorders; DD/ID, developmental delay/intellectual disability; NR, not reported.

craniofacial abnormalities. Patient B also specifically presented with overgrowth. Both patients presented with features previously described as rare or isolated, including familial mosaicism (patient A), thick corpus callosum (patient B) and cardiac anomalies (patient A).

We hope to use these two cases to bring attention to the identification of features rarely described in the literature (table 1).[15–18] Patient A's mother is mosaic for the *TCF20* pathogenic variant; to our knowledge, Babbs *et al* reported one pair of siblings suspected to have a family history positive for mosaicism related to TAND,[5] and Torti *et al* reported two other families suspected to be mosaic in gonadal cells[1] (table 2). The sibling pair reported by Babbs *et al* also presented with autism and mild ID.[5] Additional cases of non-mosaic patients with a positive family history of *TCF20* mutations have been described in a number of studies. Specifically, Vetrini *et al* identified 31 unrelated families with *TCF20* pathogenic variants, including one family with a set of affected monozygotic twins and four affected heterozygous parents, but no history of mosaicism.[2] Vetrini *et al* found that parent carriers typically present with a milder phenotype, including mild dysmorphic facial features (eg, prominent forehead) and mild ID. Though inherited pathogenic variants have been described, TAND is commonly understood to be a condition that arises through de novo mutations. However, there is clearly a growing subset of patients with a positive family history. Parental testing of individuals with TAND with special attention paid to capturing any low-level mosaicism is paramount to providing accurate genetic counselling and recurrence risks.

Patient B presented with abnormalities on brain MRI including thickening of the corpus callosum. Previous studies have estimated that the majority of patients present with a normal brain MRI, and only two previous individuals have been noted to have thickening of the corpus callosum.[1] Three other patients studied by Torti *et al* were found to have other abnormal findings on MRI including mild prominence of the atria and occipital horns and non-specific gliosis. Thus far, cerebellar hypoplasia is the only brain malformation that has been reported previously.[19] The emerging pattern of the corpus callosum findings raises the suspicion for a meaningful association of these characteristics in TAND. The overall small sample size of patients with diagnosed TAND prevents statistical investigation for the likelihood of true

Table 2 Review of reported familial cases of TAND

Cohort	Number of cases	Type of pathogenic variant	Variant information
Schneeweiss *et al*, 2022 (patients A and B)	Familial=1 Confirmed mosaic=1	Nonsense	c558G>A; p.W1861X
Torti *et al*[1]	Familial=5 Confirmed mosaic=0	N/A	c.2224 C>T; p.Arg742Ter c.2224 C>T; p.Arg742Ter c.3803_3804delGA; p.Arg1268ThrfsTer9 c.3803_3804delGA; p.Arg1268ThrfsTer9 c.3803_3804delGA; p.Arg1268ThrfsTer9
Vetrini *et al*[2]	Familial=5 Confirmed mosaic=0	Frameshift Nonsense Frameshift Frameshift Frameshift	c.310_313dupCCAC; p.Gln106Profs*30 c.2260C>T; p.Gln754* c.2685delG; p.Arg896Glyfs*9 c.5732delC; p.Pro1911Argfs*17 c.5732delC; p.Pro1911Argfs*17
Babbs *et al*[5]	Familial=4 Confirmed mosaic=0	N/A	Inversion break intron 1 Inversion break intron 1 c.4670C>T; p.P1557L c.4670C>T; p.P1557L

N/A, not applicable.TAND, *TCF20*-associated neurodevelopmental disorder;

association or delineation of a clear pattern. However, as future reports emerge of patients with this condition, a methodical investigation may be possible. Thus, we encourage clinicians to continue to describe their patients with rare conditions in detail so we may advance our understanding of TAND and other rare genetic diseases.

Our case report presents the second published case of MVP in a patient with TAND,[1] as seen in patient A, and the first case of MVP in a child. It is currently unclear if this finding is related to the patient's TAND diagnosis or not. Only a handful of other individuals have presented with cardiac anomalies. One individual with mild prominence of the atria was included in the cohort studied by Babbs *et al*,[5] and at least 4 of 27 patients studied by Torti *et al* were found to have various cardiovascular issues including MVP, bundle branch block, Wolf-Parkinson-White and borderline hypertension.[1] Again, the small sample size of patients with TAND limits our ability to determine if this is a true association with TAND over a coincidental finding in our patient. However, it is noteworthy that patient A's MVP was only identified incidentally, on an admission related to reactive airway disease. The circumstances of this discovery lead us to question if other patients with TAND also have cardiac abnormalities that are simply asymptomatic in childhood and early adulthood, and therefore no investigations are performed. An echocardiogram should be considered for patients with TAND to identify any significant cardiac lesions and look for an emerging pattern among patients with TAND.

Patient B is of Somali background, identifying as Black and African-Canadian. Framing the relationship between genetic variation and ethnic/racial background is difficult, and one of the most complicated debates of the genomic era.[20 21] Globally, most genomic research occurs in populations of European ancestry, and descriptions of dysmorphisms in non-white individuals are lacking.[10–12 20 22–24] We hope to use this case to highlight these inequalities in research and education and to add to the scientific literature on under-reported ethnic backgrounds. Increased literature of rare disorders in different ethnicities could facilitate earlier recognition and diagnosis of genetic conditions in these respective groups.

Learning points

- In cases of intellectual disability and autism spectrum disorders of unknown aetiology, whole-exome sequencing is emerging as the next step for diagnosis.
- Pathogenic variants in *TCF20* have been linked with intellectual disability, autism spectrum disorder and proportionate overgrowth; however, mosaicism, corpus callosum thickening (as seen on MRI) and cardiac anomalies, though previously rarely reported, have been identified in one additional individual, respectively, and may represent true associations.
- There are no current guidelines regarding the treatment of *TCF20*-associated neurodevelopmental disorder, aside from supportive measures.
- Most literature describes dysmorphic features in Caucasian patients as that is the cohort in which most of the scientific research is conducted; it is important to research and publish genotypes and phenotypes in other ethnic backgrounds to facilitate faster diagnosis in those groups.
- Description of rare diseases is important and may help increase our understanding of other disease processes.

It is increasingly understood that 'rare diseases' are not as rare as once believed; while each individual rare disease itself affects less than 5 out of every 10 000 people, over 900 rare diseases have been described in total. When combined, rare diseases affect 1 in 16 people.[25] In Canada specifically, about 1 of 12 adults is affected by a rare disorder, and 25% of children with a rare disease will not live to see their 10th birthday.[26] Describing the presentations of these rare diseases is crucial to directly providing affected individuals and their caregivers a possible clinical course and prognosis. Moreover, rare disease research has been shown to improve the understanding of related common diseases.[27] TCF20 interacts with RAI1, pathogenic variants in which are known to cause PLS or SMS; each condition has a prevalence of at least 1 in 25 000 people.[8] *TCF20* is also a Simons Searchlight gene of interest.[28] Simons Searchlight is an initiative of the Simons Foundation Autism Research Initiative that aims to better understand genetic neurodevelopmental conditions, specifically those associated with ASD, which has an estimated worldwide prevalence of 1 in every 160 children.[24] Finally, TCF20 has been implicated in other neuropsychiatric disorders including schizophrenia.[9] Descriptions of those with *TCF20* pathogenic variants will directly help patients and caregivers affected by TAND, and may contribute to understanding of a plethora of neuropsychiatric health conditions that collectively affect thousands.

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Contributors MRS is an MD candidate who collected the data on the patients' presentation, and drafted the initial case report summarising the presentation and findings. MRS also liaised with patients to gather more information on their presentation and treatment outcomes. MRS was also responsible for gaining parental/patient consent and perspectives in writing the case reports. BD was the genetic counsellor involved in the care of the patients in question and RE was the medical geneticist. Both BD and RE were involved clinically in diagnosing the patients' conditions and providing treatment/counselling after a diagnosis was confirmed. Both BD and RE oversaw MRS in her role of drafting the initial report and working with patients/parents to understand their perspectives and obtain consent. Both BD and RE revised the draft paper into the final manuscript.

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