

B3GALNT2-related disorders phenotype amplification

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ABSTRACT

Dystroglycanopathies are a group of Congenital Muscular Dystrophies (CMDs) that span a wide phenotypic spectrum, including late-onset limb-girdle muscular dystrophy, severe muscle-eye-brain disease, Walker-Warburg syndrome, and Fukuyama congenital muscular dystrophy. CMDs are distinguished by genetic

heterogeneity in addition to clinical heterogeneity. CMDs have been linked to 18 genes thus far. B3GALNT2, for example, encodes the 1,3-N-acetylgalactosaminyltransferase 2 enzyme that glycosylates dystroglycan. We found a homozygous frameshift variation in B3GALNT2 due to a mixed uniparental disomy of chromosome 1 in a 7-year-old girl with global developmental delay, significantly delayed active language development, and autistic spectrum disorder, but no indications of muscular dystrophy, using exome sequencing. In addition to this example, we present a summary of all previously reported cases, broadening the phenotypic spectrum even more.

INTRODUCTION

The Dystrophin Glycoprotein Complex (DGC) is a vast complex of glycoproteins that anchors the cytoskeleton to the extracellular matrix and is important for muscle, nerves, the heart, the eyes, and the brain's development and function. The dystroglycan gene encodes α -dystroglycans, which are components of the DGC. Posttranslationally, the encoded precursor protein is cleaved into α - and β -dystroglycans (α -DG and β -DG). Extracellular glycoprotein α -DG binds to extracellular matrix proteins like laminin, perlecan, biglycan, and neuexin, as well as transmembrane β -DG. β -DG, on the other hand, interacts with the cytoskeleton through binding to the intracellular dystrophin. In muscle vs non-muscle tissue, α -DG and β -DG are glycosylated differently. For α -DG to function as an extracellular matrix receptor, it must be correctly O-glycosylated. MDDGs, or dystroglycanopathies, are muscular dystrophies caused by abnormal glycosylation of α -DG. They cause a wide range of muscular dystrophy, from severe muscle hypoplasia with or without eye and brain defects to mild adult-onset limb-girdle muscular dystrophy. Early-onset muscular dystrophy, severe Intellectual Disability (ID) with brain malformations, and eye involvement with microphthalmia, cataract, and retinal atrophy are all symptoms of MDDG type A (MDDGA), which is similar to Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy. Muscular dystrophy is linked to ID in MDDG type B (MDDGB), although there are no ocular or structural brain abnormalities. MDDG type C (MDDGC) is a limb-girdle muscular dystrophy with a late onset. Biallelic pathogenic mutations in B3GALNT2, which encodes α -1,3-N-acetylgalactosaminyltransferase, cause MDDGA11. This transmembrane protein is found in the endoplasmic reticulum and phosphorylates O-mannosyl trisaccharide [N-acetylgalactosamine-3-N-acetylglucosamine-4-

(phosphate-6)mannose] on α -DG with O-mannose 1,4-GlcNAc transferase (POMGNT2). This last trisaccharide is required for α -DG to bind to laminin-G domains in extracellular matrix proteins in muscle and the brain with great affinity. So far, 23 patients have been identified with biallelic missense and/or truncating mutations in B3GALNT2. Though first linked to MDDGA11, a subsequent report identified patients with mild-to-moderate ID and behavioural issues that could be linked to epilepsy, but without any visible muscle or ocular involvement or abnormalities on neuroimaging. We discuss the case of a 7-year-old girl who had a homozygous frameshift mutation in B3GALNT2 and presented with isolated global developmental delay and central nervous system abnormalities, which were initially attributed to prenatal asphyxia. A mixed Uniparental Disomy (mixUPD) of chromosome 1 causes the homozygous status of the discovered B3GALNT2 variation. The ability of Whole-exome Sequencing (WES) to detect uniparental disomy is confirmed in this study (UPD). We also give a rundown of all previously described instances, emphasising that α -1,3-N acetylgalactosaminyltransferase 2 deficiency may be linked to milder abnormalities.

MATERIALS AND METHODS

Exome sequencing

The ReliaPrep™ Large volume HT gDNA Isolation System from Promega was used to extract gDNA from whole blood according to the kit's instructions. After extraction, the SureSelect All Exon v6 kit (Agilent Technologies, Santa Clara, CA, USA) was used to enrich the coding exons, followed by paired-end 2150 bp sequencing on a HiSeq3000 platform. Data analysis was limited to a panel of 1109

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chosen genes related with intellectual impairment and epilepsy, and raw sequence reads were processed using an in-house built pipeline. PCR amplification and Sanger sequencing were used for confirmation and segregation investigations. Primers can be obtained upon request. PLINK software was used to detect homozygous regions on chromosome 1 since many variations were present in the homozygous condition (ROH).

RESULTS

Clinical description

After in vitro fertilisation and an uncomplicated pregnancy and delivery, the female proband is the first child born to a non-consanguineous marriage. A paternal half-sister and half-brother were born prematurely at 31 and 35 weeks of pregnancy, respectively, in the family's history. Both of their brains developed normally. The proband weighed 3110 g (p25), measured 49 cm (p25), and had a head circumference of 32.5 cm at birth (p3). Apart from limited intake, there were no neonatal issues, and the staturoponderal evolution was normal. She has a wide range of developmental delays. She crawled at the age of 18 months and was able to walk independently at the age of 27 months. She said her first words at the age of 20 months, but by the time she was four, she had only used about ten words. She picked up some basic sign language. Her passive language acquisition was improved. For a calendar age of 4 years and 3 months, her developmental age was 25 months. She also had an autistic spectrum disorder, had a high pain threshold, and had balance issues. At the age of seven years and four months, a physical examination revealed a height of 128 centimetres (p70), a weight of 27 kilogrammes (p72), a head circumference of 50 centimetres (p16), blond curly hair, upslanted palpebral fissures, light blue irises, epicanthal folds, fullness of the upper eyelids, a tubular nose with a broad nose tip, and hypoplastic al On the helical crus, she had a short auricular tag and huge ear lobes. She had nipples that were widely separated, slender hands with long fingers, and skin creases that were slightly noticeable. Physiotherapy was started after an orthopaedic evaluation revealed that the cause of frequent stumbling was retained anteversion of the hips with internal rotation of the limbs. The results of the echocardiographic examination were normal. Except for sporadic esophoria, which went away on its own, the eye examination was normal. Her hearing (at the time of the most recent evaluation, she was four years old) was normal. Increased T2 signal in the corona radiata on the left side, expanding to the lateral ventricular wall with sparing of the juxta cortical white matter, as well as bilaterally frontally, was seen on brain magnetic resonance imaging (MRI) at ages 3 years and 6 months and 6 years and 9 months. There was some ex vacuo dilation of the left lateral ventricle and shrinkage of the corpus callosum's anterior section. These results were consistent throughout time. Cerebellar hypotrophy was seen. Because of a normal prenatal history, an early diagnosis of perinatal asphyxia was ruled out. Serum amino acids, lactate, pyruvate, acylcarnitines TSH and FT4, long-chain fatty acids, phytanic and pristanic acids, and transferrin isoelectric focusing were all normal during a metabolic screening.

Molecular result

On chromosome 1, WES discovered two homozygous areas of around 12 Mb and 34 Mb, separated by a 200 Mb stretch. In B3GALNT2 (NM 152490.4), a homozygous frameshift variation was discovered within the greatest homozygous region: c.143delC; p. (Ser48LeufsTer7). This frameshift variant is found in exon 2, is not found in the gnomAD population database, and has never been reported before. The variation is most likely responsible for Nonsense-mediated Degradation (NMD). There were no substantial copy number variants discovered using genomic microarray analysis (array-CGH).

B3GALNT2 (NM 152490.4) deletion variant c.143delC (Hg38). Bottom: this mutation was found to be homozygous in the proband, heterozygous in the mother, and absent in the father in a segregation analysis. SNP-array verified loss of heterozygosity (LOH) in two places on chromosome 1, which was discovered by ES; array-CGH ruled out a deletion. The biggest LOH region (q32.2-q44) contains B3GALNT2. The variation is present in the mother in a heterozygous condition but not in the father. Paternity was established, and array-CGH ruled out a paternal loss on chromosome 1. As a result, the vast interspace of heterozygous variations between the two homozygous regions suggested mixed UPD, which was supported by SNP-array analysis, which determined the homozygous regions' sizes to be 12 Mb and 34 Mb, respectively, on chromosome 1 at p36.32-p36.21 and q32.2-q44. Individuals 1-15 have MGGDA-like symptoms, but individuals 16-23 have mild-to-moderate ID with no severe eye, muscle, or brain involvement. All of them have intellectual disabilities and motor delays of varying degrees of severity. All present with significant active language delay, with absent speech or speech confined to single words or sign language, with the exception of those for whom no information on language development is known. Epilepsy affects almost half of all probands, but it has little bearing on the severity of the ID. In 10 of the 18 people tested, hypotonia was found. Additional neurological symptoms, such as ataxia, spasticity, and balance issues, are present in 10% of the patients (10/13). Optic nerve hypoplasia, microphthalmia, cataract, esotropia, and blindness are all symptoms of ocular involvement, which occurs in ten percent of patients. Patients without ocular involvement appear to have superior speech and motor development. B3GALNT2 missense and truncating variants have been discovered. Missense variations are enriched in exons 6, 7, 8, and 10, while truncating variants are found across the gene. Exons 8 and 10 are responsible for encoding a portion of the galactosyltransferase domain. This domain contains four pathogenic missense variations, including the recurrent p.(Asp327Asn) variant. Individuals P18-P22, who are all homozygous for p.(Asp327Asn), have intellectual disability, motor delay, and epilepsy but no notable muscular problems, in contrast to patients P9, who do have muscular problems and are compound heterozygous for this variant as well as the p.(Glu65Ter)(in P9) or the p.(Pro474del) variant (in P13 and P15).

DISCUSSION

A homozygous truncating variation in B3GALNT2 caused by a mixed uniparental disomy of chromosome 1 resulted in a 7-year-old girl with global developmental delay, significantly delayed active language development, and autistic spectrum disorder. Exome sequencing revealed two homozygous sections separated by a huge heterozygous region, which could be explained by recombination and trisomic rescue during meiosis I or II. This demonstrates that ES data can be used to discover uniparental disomy, which is a potentially important but often missed cause of Mendelian disease. Our example further shows that the phenotypic spectrum caused by B3GALNT2 pathogenic mutations might manifest as a milder illness phenotype with isolated ID and no involvement of the eyes or main muscles. White matter anomalies, with or without cerebellar hypoplasia, may be seen in those on the mild end of the spectrum, but no significant brain deformities. Bi-allelic loss-of-function mutations have been linked to a severe phenotype of WWS. Nonetheless, the findings suggest that truncating mutations that cause nonsense-mediated degradation can cause disease on both ends of the spectrum. Indeed, a homozygous frameshift mutation p.(Ser48LeufsTer7) can present with isolated ID in our situation.

Furthermore, WWS has been linked to a nonsense variant at codon 475, which is located in the transcript's last exon, and is thus predicted to avoid nonsense-mediated decay while retaining the functional domain. As a result, neither the position nor the type of mutation can entirely explain the severity of the symptoms. To date, homozygosity for p.(Asp327Asn) has been linked to a milder phenotype; however, all patients are from the same family, and additional phenotypic modifiers could have been present. In patients with mild illness, no glycosylation staining of α -dystroglycan has been conducted to yet.

CONCLUSION

This research indicates that B3GALNT2 pathogenic mutations can cause a milder disease with isolated intellectual disability than previously thought. For B3GALNT2-related dystroglycanopathy, no clear genotype-phenotype relationships have been discovered. We also show that ES is an excellent tool for detecting uniparental disomy.