Novel copy number variations (CNVs) are considered as an important reason for numerous neurodevelopmental disorders including intellectual disability (ID). CNVs are operationally defined as genomic deletions or amplifications greater than 1 kb in size. Typically, CNVs involve regions containing several to dozens of genes, often with multiple candidates in the smallest region of overlap (SRO) between similar cases. Thus, the likely candidate genes within the SRO can be proposed as the main drivers of the phenotype. To date, four males with an Xp11.22 deletion reported in three families have been described to cause a new chromosomal X-linked syndrome. Four males were described from three families with ID, developmental delay, hypotonia, joint hypermobility, and relative macrocephaly. They all carried small, overlapping Xp11.22 deletions. To date, the described smallest region of overlapping deletion at this locus spanned ~430 kb and included four genes (CENPVL1, CENPVL2, MAGED1, and GSPT2), which are proposed as the main drivers of the phenotype. We describe a male patient who matches the phenotype and contributes to defining a narrow phenocritical region at Xp11.22. We propose that GSPT2 loss-of-function might be the probable cause of the phenotypic features seen in these patients.
He had a delay in acquiring developmental milestones; he sat at the age of seven months, walked at 18 months, was able to go upstairs using alternate feet at the age of three years, and ran at four years old. At the age of five, he was able to hold a pencil, scribble, draw a circle, and copy letters. At the age of five, he had only 20 words, could not join two words, and understood simple commands only. He was able to identify two colors and count from one to three. He was toilet trained at the age of three and a half years.

Detailed psychoeducational assessment was completed at the age of five and a half years using the Stanford–Binet Intelligence Scale Fifth Edition (SB5). The test scores were as follows: full-scale IQ 56 (mildly impaired or delayed), nonverbal IQ 66 (mildly impaired or delayed), and verbal IQ 47 (moderately impaired or delayed).

Growth parameters determined at five years old were as follows: height 104.5 cm (tenth percentile), weight 14.7 kg (third percentile), and head circumference 51.5 cm (fiftieth percentile). Facial features included a prominent forehead and bilateral low set ears with overfolded helices. His skeletal examination showed joint hypermobility. Otherwise, his general and neurological exams were normal. At the age of five years and six months, his brain magnetic resonance imaging was reported as normal.

The DNA sample was sent to Sistemas Genómicos, Spain. The chromosomal microarray was completed using 4x180 CGH+SNP Microarray Kit (SurePrint G3 Human, Agilent Technologies). The array's results were analyzed with Agilent "CytoGenomics v. 4.0.3.12 software, and the Aberration Detection Method 2 (ADM-2: 6.0) algorithm was used to identify chromosomal aberrations. The chromosomal microarray showed a 334 kb deletion at Xp11.22 [Figure 1] with genomic coordinates.

| Table 1: Summary of the phenotype of patients reported with Xp11.22 deletion syndrome. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Current patient |
| Xp11.22 deletion minimum (hg19) | chrX:50,847,688–51,773,705 | chrX:51,079,343–51,912,188 | chrX:51,357,052–52,838,176 | chrX:51,442,546–51,776,830 |
| Xp11.22 deletion maximum (hg19) | chrX:50,789,912–51,786,912 | chrX:51,079,341–51,990,483 | ND | ND | ND |
| Age, years | 3 years 8 months | 7 years 9 months | 6 | 4 | 5 |
| Gender | Male | Male | Male | Male |
| Intellectual disability/developmental delay | + | + | + | + |
| Hypotonia | + | + | + | ND | + |
| Joint hypermobility | + | + | + | + |
| Relative macrocephaly | + | + | + | + |
| Other growth problems | None | Failure to thrive | Failure to thrive, short stature | Short stature | Failure to thrive, short stature |
| Other medical problems | Congenital muscular torticollis, laryngomalacia, right-sided cryptorchidism, right-sided inguinal hernia, gastroesophageal reflux disease, food allergies. | Gastroesophageal reflux disease. | Hypermetropia, intermittent exotropia, arthralgias. | Exotropia, amblyopia. | Cleft palate. |
| Other physical exam findings | Small testes, hypoplastic scrotum, medial malleolar displacement, sandal gap. | Pes planus, medial malleolar displacement. | Epicanthal folds, capillary nevus, pes planus. | Prominent forehead, bilateral low set ears with overfolded helices. |

ND: not determined.
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His inheritance from his asymptomatic mother.

**DISCUSSION**

Recently, Grau and colleagues reported four males with Xp11.22 deletions associated with a distinct deletion syndrome. Our patient shares the same phenotype as these four males but with a 334 kb deletion that corresponds to the minimal region of overlap reported in Table 1. This region encompasses two protein-coding genes: MAGED1 and GSPT2.

Both the MAGED1 and GSPT2 genes are ubiquitously expressed in the brain, and are conserved among vertebrates; however, the GSPT2 gene exhibits greater evolutionary conservation. Based on silico statistical methods such as the Exome Aggregation Consortium pLi score and the Residual Variation Intolerance Score, both genes exhibit intolerance to loss-of-function (LOF) mutations within the normal adult population. However, at least for the GSPT2 gene, there are no LOF single nucleotide variants (SNVs) in the gnomAD database or copy number deletions in the Database of Genomic Variants (DGV; http://dgv.tcag.ca/dgv/

**Table 2:** Comparison between GSPT2 and MAGED1 by interrogating genomic databases.

| Databases                                | GSPT2 | MAGED1 |
|------------------------------------------|-------|--------|
| Brain expression (GTEX)                  | ++    | +++    |
| Conservation (phyloP100wayAll)           | +++   | +      |
| RVIS (genic intolerance)                 | -0.07 (48.12%) | -0.54 (20.54%) |
| ExAC pLi                                 | 0.90  | 0.98   |
| DGV deletions encompass the gene         | Absent| Y/e (rs5906, esv2664331, esv3573968, esv3558875) |
| GnomAD high impact mutations (males)     | Absent| Five LOF variants |
| ClinVar SNV                              | One pathogenic and two VUS | Absent |

RVIS: Residual Variation Intolerance Score; ExAC: Exome Aggregation Consortium; DGV: Database of Genomic Variants; LOF: loss of function; SNV: single nucleotide variant; VUS: variant of uncertain significance.
In contrast, four different copy number deletions encompassing the MAGED1 gene have been reported in the DGV database, and five healthy adult males with high impact LOF mutations have been reported in gnomAD [Table 2]. Of note, these SNVs affect all three known transcripts of this gene.

GSPT2 consist of one exon and encodes one known transcript. It encodes for peptide chain release factor 3b (eRF3b), one of the classic translation factor GTPase family. It is involved in the final step of protein synthesis where translation ends in response to the termination codons (UAA, UAG, and UGA). While GSPT1, which encodes for eRF3a, is expressed in every tissue. GSPT2 is highly expressed in the brain among other tissues in humans and mice. The effects of GSPT2 deficiency on central nervous system function have not been demonstrated in humans or studied in mice yet.

CONCLUSION

In summary, the phenotype of our patient is consistent with those previously reported cases of deletions involving MAGED1 and GSPT2. Interrogation of different public genomic databases indicates that GSPT2 is likely to be indispensable for brain function. Further understanding of the molecular function of this gene and its effect when knocked out in mouse and human cell lines is required.

Disclosure

The authors declared no conflicts of interest.

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