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Intellectual disability and epilepsy due to the K/L-mediated Xq28 duplication: Further evidence of a distinct, dosage-dependent phenotype

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Abstract

Copy number variants of the X-chromosome are a common cause of X-linked intellectual disability in males. Duplication of the Xq28 band has been known for over a decade to be the cause of the Lubs X-linked Mental Retardation Syndrome (OMIM 300620) in males and this duplication has been narrowed to a critical region containing only the genes *MECP2* and *IRAK1*. In 2009, four families with a distal duplication of Xq28 not including *MECP2* and mediated by low-copy repeats (LCRs) designated “K” and “L” were reported with intellectual disability and epilepsy. Duplication of a second more distal region has been described as the cause of the Int22h-1/Int22h-2 Mediated Xq28 Duplication Syndrome, characterized by intellectual disability, psychiatric problems, and recurrent infections. We report two additional families possessing the K/L-mediated Xq28 duplication with affected males having intellectual disability and epilepsy similar to the previously reported phenotype. To our knowledge, this is the second cohort of individuals to be reported with this duplication and therefore supports K/L-mediated Xq28 duplications as a distinct syndrome.

Keywords

GDI1; mental retardation; X chromosome duplication; Xq28 duplication; x-linked

1 | INTRODUCTION

X-chromosome copy number variants (CNVs) are a common cause of intellectual disability (ID) in males (Isrie et al., 2012). The morbidity of X-chromosome CNVs in females is not

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

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well known due to its milder phenotype. It is hypothesized that duplication of genes on the X-chromosome cause pathology by generating excessive protein expression.

The most common CNVs discovered in males with X-linked intellectual deficiency (XLID) are duplications within the Xq28 band (El-Hattab et al., 2015). The Xq28 band contains many LCR sites that predispose multiple intervals within the band to duplication (Bauters et al., 2008; del Gaudio et al., 2006). Also, at least three genes within this band (*MECP2*, *GDII*, and *RAB39B*) are critical to normal neurological development (Bianchi et al., 2009; Collins et al., 2004; Luikenhuis, Giacometti, Beard, & Jaenisch, 2004; Vanmarsenille et al., 2014). As additional data emerges, it is becoming evident that duplication along Xq28 may result in at least three distinct intellectual disability phenotypes depending on which part of this band is duplicated.

The first of these phenotypes to be described was the Lubs X-linked intellectual disability syndrome (MRXSL, OMIM 300260), characterized by infantile hypotonia, moderate to severe intellectual disability, limited, or absent speech, immune dysfunction, and distinctive facial features (brachycephaly, large ears, and midface retrusion). This syndrome was shown to be due to Xq28 duplications involving *MECP2* in the mid 2000s, based on both case reports (Meins et al., 2005; Van Esch et al., 2005) and mouse models (Collins et al., 2004; Luikenhuis et al., 2004). Over one hundred cases of *MECP2* duplication have now been reported.

In 2009, Vandewalle et al. reported eight males with X-linked intellectual disability (XLID) and variable onset epilepsy in four families carrying a duplication distal (telomeric) to that which causes MRXSL. The duplicated region is flanked by LCRs K1 and L2, which are believed to facilitate non-allelic homologous recombination events (Figure 1). The authors suggest that the gene *GDII* (GTP-Dissociation Inhibitor 1) may be responsible for the phenotype due to its role in vesicular trafficking and neurotransmission. Also, loss of function mutations have previously been associated with X-linked intellectual disability (Bienvenu et al., 1998; D'Adamo et al., 1998; Stroble-Wildermann et al., 2011), and elevated *GDII* mRNA expression is positively correlated with the severity of intellectual deficiency and likelihood of developing epilepsy (Vandewalle et al., 2009).

In 2011, El-Hattab et al. reported a third phenotype, the Int22h-1/Int22h-2 Mediated Xq28 Duplication Syndrome in four males from three families with intellectual disability and aggressive behavior. These individuals shared a duplication of Xq28 distal to both the duplication responsible for MRXSL and the duplication reported by Vandewalle. Increased expression of the gene *RAB39B* has been proposed as the most likely causative mechanism of this syndrome (Vanmarsenille et al., 2014). Twelve families have been reported with the int22h-1/int22h-2 mediated Xq28 duplication syndrome (Andersen, Baldwin, Ellingwood, Smith, & Lamb, 2014; El-Hattab et al., 2011, 2015; Isrie et al., 2012; Vanmarsenille et al., 2014).

The effects of duplications distal to *MECP2* on female carriers are less well studied, but are expected to produce milder phenotypes that correlate with the patient's X inactivation pattern. In all reports of int22h-1/int22h-2 and K/L mediated Xq28 duplications, it is noted

that at least some of the female carriers reported a history of learning disability or mood disorder (Andersen et al., 2014; El-Hattab et al., 2011, 2015; Vandewalle et al., 2009; Vanmarsenille et al., 2014).

In this report, we discuss two families with the K/L-mediated duplication, review the literature of distal Xq28 duplications, and compare these emerging phenotypes to the more clearly characterized *MECP2* duplication syndrome.

2 | MATERIALS AND METHODS

2.1 | Array-CGH analysis

Array-CGH analysis was performed at Children's National Medical Center Molecular Diagnostics Laboratory. Total genomic DNA isolated from peripheral leukocytes was analyzed for copy number changes and areas of homozygosity by Affymetrix CytoScanHD or CytoScanDx SNP-based chromosomal microarray. The CytoscanHD array has 2.7 million probes (2 million copy number probes and 700,000 SNP genotyping probes). The array was read by the GeneChip® System 3000Dx and analyzed by Chromosome Analysis Suite (ChAS) software using the human genome build GRCh37/hg19 (Figure S2).

2.2 | Fine mapping

The duplication interval observed in our families coincides with that previously described in four families with intellectual disability and a recurrent but variable copy-number gain of Xq28 (supplementary Table S1). The break points of the duplicated segments map to low copy repeats (K1, K2, L1, L2) on the X chromosome (supplementary Table S2). A visualization of these CNVs was constructed using the UCSC Genome Browser (<http://genome.ucsc.edu>) and is available as supplementary Figure S1 (Kent et al., 2002). Low copy repeats are defined as genomic duplications greater than 1000 bp in length that share greater than 90% identity. Mispairing and subsequent non-allelic homologous recombination of these LCRs during meiosis has been proposed as a mechanism for recurrent segmental duplications of the Xq28 locus (Vandewalle et al., 2009). This mechanism is consistent with the observation that the duplication breakpoints are similar across families, but the absolute value of the copy number gain is variable (Figure S3).

2.3 | X-chromosome inactivation analysis

Peripheral blood was sent to the Greenwood Genetic Center Molecular Diagnostic Laboratory for X-chromosome inactivation analysis and was performed according to their protocols. Testing is reported to be based on PCR analysis of polymorphic CAG repeats within the androgen receptor gene.

3 | CLINICAL REPORTS

3.1 | Family 1

Patient 1 (Figures 2a and 2c) was the full-term child of nonconsanguineous African American parents. Prenatal history was remarkable for intrauterine growth restriction and abnormal brain imaging. Prenatal brain MRI at 31 weeks revealed a small cerebellar vermis,

borderline low cerebral and cerebellar volume for age, small subependymal cystic lesions adjacent to the lateral ventricular frontal horns, and normal appearance of the corpus callosum and septum pellucidum. His birth weight was 2.7 kg (7.5th centile) and birth length was 50.8 cm (68th centile). He has had multiple admissions for failure to thrive, respiratory illnesses, and seizures. Onset of seizures was at 14 months in the setting of febrile illness. Seizures are well controlled with levetiracetam and oxcarbazepine. An EEG at 18 months showed general background slowing with posterior basic rhythm less than expected for age and increased beta activity. An ophthalmologic evaluation revealed left esotropia. Developmental assessment at 24 months indicated he was functioning at the 9–10-month range across all skills. At his last genetics evaluation (28 months-old) he was sitting up but was unable to stand and had a vocabulary of 3–5 words. On physical exam, he has down-slanting palpebral fissures and epicanthal folds. At his first exam at 1-month-old he was noted to have normal tone but later developed progressive hypertonia, especially of the lower extremities and right hand. At 28 months, growth parameters included weight of 11.85 kg (25th centile), length 78 cm (<2nd centile), and OFC was 46 cm (<2nd centile). SNP microarray showed a complex duplication-quadruplication-triplication-duplication rearrangement within the K/L mediated region of Xq28 (hg19 153,560,741–153,868,484). Twenty-two genes are included within this region with *GDII* contained within the quadruplicated region (hg19 153,622,203–153,722,204). All reported individuals from family one carry this copy number variant.

Patient 2 (Figure 2b) is the 11-year-old maternal half-sister of patient 1 who has a history of behavioral problems, ADHD, depression, and anxiety. Her development was significant for mild delay of motor milestones with ability to walk at 2 years old. Speech development was reportedly normal. Fine motor development was delayed. She is described as being “less coordinated” than other children and was unable to tie her shoes until she was nine years old. She began to have severe tantrums at around the age of two. She continued to have explosive and unpredictable outbursts of anger and has been repeatedly disciplined for fighting at school. She receives cognitive behavioral therapy and this has been effective in controlling her symptoms. She is at grade level with an individualized education program (IEP). Her modifications are aimed at dealing with difficulties in following either verbal or written directions. She has the most difficulty with mathematics and writing. Physical exam did not reveal any dysmorphic features. Head circumference was 51 cm (10th centile), height was 137.2 cm (10th centile), and weight was 32.8 kg (10–25th centile). X-inactivation for this patient showed skewing (90:10).

Patient 3 (Figure 2c) is the mother of patients 1 and 2. She has a history of learning disability and post-traumatic stress disorder (PTSD). She did not have any behavior problems in childhood but recalls that she was very quiet and rarely got into trouble. She has difficulty with reading comprehension which began in fifth grade, but does well with writing and mathematics. She was able to graduate high school at age twenty and has maintained employment. Her symptoms of PTSD have responded well to therapy with trazodone and bupropion. Prior to a triggering event she never had any negative emotional symptoms such as anxiety or depression. Her physical exam did not reveal any dysmorphic features. Her head circumference was 49.8 cm (<3rd centile). X-inactivation showed random X-inactivation (38:62).

3.2 | Family 2

Patient 4 (Figure 3a) is the male child of non-consanguineous Hispanic parents. Full-term birth weight was 4.0 kg (90th centile) and birth length was 46 cm (2nd centile). He had global developmental delay and was reported to walk at 2 years old and speak at age 3. He was described as a very shy child who spoke little. Poor memory and language skills were noted at an early age. His receptive language skills are much better than expressive. He can perform most activities of daily living independently but requires some assistance. He is currently employed part-time at a grocery store. Staring spells with jerking was noted at age 4 years. A brain MRI revealed a small pons and small posterior fossa structures, bilateral peri-atrial white matter volume loss without gliosis and a microcephalic appearance. An overnight EEG was normal at age 15 years. He does not require anti-epileptic medication. On his most recent exam (at 19 years old) weight was 82.7 kg (75–90th centile), height was 160.6 cm (below 3rd centile), and head circumference was 56.5 cm (75th centile). He had brachycephaly and an abnormal palmar crease unilaterally. SNP microarray showed a duplication-triplication-duplication within the K/L-mediated region at Xq28 with *GDI1* included within the triplicated region. All individuals from family 2 carry this copy number variation.

Patient 5 (Figure 3b) is a female maternal half sibling of Patient 4. Trisomy 21 was also diagnosed prenatally. Full-term birth weight was 3.6 kg (75th centile), length was 44 cm (< 2nd centile). Development was delayed but consistent with established milestones for children with Down syndrome. Health issues included surgical PDA ligation, hypothyroidism, and obstructive sleep apnea. EEG was performed at 8 months of age and was normal. On her most recent exam at 9 years of age, she was noted to have the facial stigmata of Down syndrome, her head circumference was 50.2 cm (10th centile), height was 118.7 cm (25th centile), and weight was 28 kg (50th centile). All parameters were plotted on the Down syndrome specific growth charts.

Patient 6 is the mother of patients 4 and 5. She is 37 years old, currently healthy and a home maker. She had no behavioral or developmental issues as a child. She is bilingual, has completed an associate's degree and maintained employment for many years. She reports that she has only dealt with depression and anxiety during circumstances of extreme stress and has never experienced these symptoms otherwise.

Patient 7 is the male child of healthy non-consanguineous Hispanic parents. He is the maternal first cousin to patients 5 and 6. Full-term birth weight was 4.3 kg (90th centile) and length was 54 cm (98th centile). Gross motor and speech development were reported to be normal, but fine motor skills are delayed. Beginning at approximately age 2 years he developed temper tantrums, threats of self-violence, and violent behavior towards others. He is in special education classes and is felt to be two grade levels behind. He presented to our clinic at age 8 years old, with a known maternal family history of an Xq28 duplication. Exam was significant for brachycephaly, synophrys, bilateral epicanthal folds, a broad chest with inverted nipples, and an abnormal palmar crease unilaterally. The feet were remarkable for pes planus as well as bilateral cutaneous syndactyly between toes 2 and 3. Head circumference was 51.5 cm (25th centile), height was 126.4 cm (50th centile) and weight was 32.4 kg (95th centile).

Patient 8 is the mother of patient 7 and the sister of patient 6. She is known to have a history of learning disability and psychiatric disease, but she declined further interview.

4 | DISCUSSION

The importance of copy number variation of genes on the X-chromosome has been well established to be physiologically relevant in both males and females. For males, two distinct duplication syndromes of the Xq28 band have already been defined: the *MECP2* duplication syndrome and the int22h-1/int22h-2 mediated duplication syndrome. A third syndrome was suggested by Vandewalle et al. (2009) based on a cohort of patients with a duplication confined to a region that is intermediate to the others, and at its greatest length spans between LCRs K1 and L2.

We have reported eight individuals from two families that are confirmed to harbor a duplication of Xq28 between LCRs K1 and L2 that is the same duplication reported by Vandewalle and colleagues. Combining our patient data with that of the Vandewalle cohort demonstrates correlation between the severity of symptoms in affected males and the copy number of the segment containing *GDI1* (Table 1). This provides additional evidence that this is a recurrent duplication syndrome producing a unique dosage-dependent phenotype.

A comparison of the phenotypic features of all three conditions is presented in Table 2. Distal Xq28 duplications as a whole differ from *MECP2* duplications in that they are not as likely to produce severe intellectual disability, absence of speech, gastrointestinal complications, or lead to severe immunologic dysfunction. Only one male patient with the K/L-mediated duplication has been so far reported with a phenotype severe enough to be confused with *MECP2* duplication. No patients with int22-h1/int22h-2 mediated duplications have been reported to have severe intellectual disability or be non-verbal.

The primary phenotypic distinction between the K/L-mediated duplication and the int22h-1/int22h-2 mediated duplication appear to be predisposition to infection, epilepsy, and spasticity. None of the patients with K/L-mediated duplication have so far been reported to exhibit any predisposition to infection. Conversely, epilepsy is possible and appears to be likely in individuals with sufficient increases in gene dosage from K/L-mediated duplication but so far has not been reported in int22h-1/int22h-2 mediated duplication. Finally, spasticity may be frequent in individuals with K/L-mediated duplication similar to *MECP2* duplication while this is not reported in int22h-1/int22h-2 mediated duplication. Our index patient (patient 1) experienced a neurological progression similar to that seen in *MECP2* duplication with congenital hypotonia that progressed to spasticity.

Female carriers of both distal Xq28 duplications are sometimes reported to have learning disability and predisposition to psychiatric illness, but have not so far been reported to have intellectual disability or epilepsy. This contrasts with *MECP2* duplication syndrome where symptomatic females may have epilepsy and ID (Bijlsma et al., 2012; Fieremans et al., 2014; Novara et al., 2014; Shimada et al., 2013).

It should also be noted that cases of combined duplications (duplication encompassing *MECP2* and *GDI1*, or *MECP2*, *GDI1*, and *RAB39B*) are regularly reported (Bartsch et al.,

2010; Lugtenberg et al., 2009; Yamamoto et al., 2014). In all reported cases the phenotype is indistinguishable from the *MECP2* duplication syndrome. For this reason, *MECP2* duplication could be considered a dominant phenotype in relation to the distal duplication syndromes. However, since both of the distal regions contain genes that are believed to have dosage sensitive effects on the brain it is likely that individuals possessing duplication of these additional genes will develop at the more severe end of the phenotypic spectrum of *MECP2* duplications. Some studies have commented specifically on genotype-phenotype correlations: Yamamoto and colleagues noted that patients with terminal duplications of Xq28 were more severely affected than children with interstitial duplications that included only the *MECP2* region, but saw only differences in brain MRI when comparing patients with duplications including *GDI1* (Yamamoto et al., 2014). In a report by Lugtenberg and colleagues it is noted that their most severely affected family had a duplication including *GDI1* (Lugtenberg et al., 2009). An individual with a duplication that encompasses *GDI1* and *RAB39B* but not *MECP2* has not yet been reported.

Several mild variations in facial and bodily features were reported in each of the patients characterized by Vandewalle. Comparing our physical exams (6 of our 8 patients had physical exams) with those from the Vandewalle report, we recognize three distinct phenotypic features that appear to be consistent: microcephaly (present in 4/10 or 40% of patients), 2–3 toe syndactyly (4/14 or 29%) and indications of abnormal neurological function, mostly affecting the lower extremities (4/14 or 29%).

Microcephaly, while still present only in a minority of the patients, is the most consistent phenotypic feature. Lugtenberg and colleagues commented that microcephaly seemed to be more common in patients with *MECP2* duplications of sufficient length to include *GDI1*; they reported this based on two of their own patients and six patients from previous studies with five out of the eight patients (62%) having microcephaly (del Gaudio et al., 2006; Lugtenberg et al., 2006, 2009; Smyk et al., 2008; Van Esch et al., 2005).

The issue of peripheral neurological dysfunction remains unclear; Patient 1 from our cohort has been diagnosed with spasticity that is global but affects the lower extremities more severely. In the cases presented by Vandewalle and colleagues there are exam findings suggestive neurological dysfunction primarily affecting the lower extremities but specific diagnoses are not stated (Vandewalle et al., 2009). One case reports “brisk DTR and inability to walk on heels,” another “lower extremity clonus and positive Babinski,” and a third reports “stiff gait.” Neurological exams are not specifically addressed in the rest of the cases and none of the other patients in our cohort have been examined by a neurologist. Therefore, it is likely that this is an area that warrants further investigation.

We do not find any specific facial features that are extremely common among individuals with K/L-mediated duplication. However, changes in the size of the forehead (broad or tall) and the peri-orbital structures such as deep-set eyes (2 patients), upslanting or down-slanting palpebral fissures (2 patients), epicanthal folds (2 patients), medial eyebrow flare (1 patient), and hypotelorism (1 patient) were the most consistently reported physical features. In this respect, K/L-mediated duplication bears some similarity to the int22h-1/int22h-2 mediated duplication syndrome in which tall forehead, upper eyelid fullness, wide nasal bridge and

thick vermillion of the lower lip are the most frequently reported features. These features have little similarity to *MECP2* duplication which is typically characterized by large ears, midface retrusion, and a depressed nasal bridge.

Female patients with K/L-mediated duplications are not overtly dysmorphic. The only notable dysmorphism discovered was that patient 3 is microcephalic. Coincident with this is the fact that her X-inactivation pattern is random which indicates that she is most likely affected by this duplication (Lugtenberg et al., 2006). Her daughter, patient 2, has learning disabilities, psychiatric disease, a normal head circumference, and an X-inactivation pattern at the borderline of random.

Learning disability or psychiatric disease has been reported in 10 out of 16 female carriers of int22h-1/int22h-2-mediated Xq28 duplication (62%), with one individual having declined interview (Andersen et al., 2014; El-Hattab et al., 2011, 2015; Vanmarsenille et al., 2014). Of all reported females with K/L-mediated Xq28 duplications, 3/10 (33%) have a report of psychiatric disease or learning disability, excluding our patient who also has Down syndrome (Vandewalle et al., 2009).

Brain MRI findings appear to be as common in this duplication syndrome (5 out of 10 reported males) as they are in the other Xq28 duplication syndromes and cerebellar anomalies appear to be common at high copy numbers.

In previous brain imaging reviews of individuals with *MECP2* duplications it has been found that there may be higher rates of corpus callosum defects in individuals with duplications that extended to LCR L1 (thus including the segment that is duplicated in our cohort) (El Chehadeh et al., 2016; Honda et al., 2012; Yamamoto et al., 2014). Brain imaging data was available for seven out of ten affected males so far reported; only one of which had a report of corpus callosum defect (20%). However, it is certainly possible that the predisposition to corpus callosum defects is a cumulative effect of the duplicated regions, and not a specific feature of duplications between K1 and L2.

Testing algorithms for both males and females with intellectual disability are already an established protocol (Miller et al., 2010). New information that may be of clinical use in counseling families is the implication of copy number on the prognosis for developmental milestones and likelihood for having brain anomalies and epilepsy.

In males harboring more than three copies of this region, families should be counseled that their risk for moderate to severe intellectual disability, brain anomalies, and epilepsy may be higher than individuals with fewer copies.

If no problems arise, it is reasonable to allow female patients to follow-up as needed with a reminder of a potential predisposition to psychiatric illness later in life and the ramifications on future reproduction.

In our report, female carriers frequently give a history of learning disability or mental health concerns. We hypothesize that the prevalence of Xq28 duplications in females with a diagnosis of learning disability may be comparable to the prevalence of these duplications in

males with intellectual disability. Also, it should be noted that the one patient so far reported with only two copies of *GDI1*-containing segment also had very mild symptoms at the age of two. It is then also possible that this duplication could also go unrecognized in a male with only mild symptoms. Accordingly, we would like to conclude with the suggestion that members of the pediatric, developmental pediatric, child psychiatry, and genetics disciplines should begin to consider whether routine screening with cytogenetic microarray of children with a diagnosis of learning disability alone would be prudent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Diagram of K and L LCRs and position relative to other known Xq28 duplication syndromes. Genes that are between these LCRs are indicated below the diagram

FIGURE 2. Family 1. (a) Patient 1 (8-months-old). (b) Patient 2. (c) Patient 3 and Patient 1 (24-months-old). [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3.
Family 2. (a) Patient 4. (b) Patient 5. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Comparison of male patients in order of copy number repeats of the segment containing *GDI1*

	Vandewalle F4 II.1	Vandewalle FIV.2	Vandewalle F1 III.10 ^a	Vandewalle F1 III.19	Vandewalle F3II.2	Patient 4	Patient 7	Patient 1	Vandewalle F2 II.1	Vandewalle F2 II.2 ^a
Copy # (GDI1)	2	3	3	3	3	3	3	4	5	5
Age	2 years	6 years	37 years	Adult	7 years	18 years	8 years	17 months	3.5 years	19 months
Dev delay	Mild motor speech	Mild motor speech	Delayed—otherwise unspecified	Unreported	Mild speech	Mild motor	Mild speech	Moderate limited speech & motor	Severe two words no ambulation	Severe crawling only
ID	ND	IQ 50	“Moderate” (Functional)	“Moderate” (Employed)	IQ 58	“Mild” (Employed)	“Mild”	ND	Severe	Severe
Behavior	ND	No problems	Shy/quiet	Shy/friendly	ND	Shy/limid	Hyperactive aggressive	No issues	ND	ND
Epilepsy	-	-	-	-	-	-	-	+	+	-
OFC (Centile)	48 cm (25th)	51cm (50th)	59 cm (>97th)	56 cm (75th)	49.5 cm (<3rd)	56.5 cm (75th)	51.5 cm (25th)	46 cm (< 3rd)	46 cm (<3rd)	41cm (< 3rd)
Brain imaging	Normal HUS	Enlarged fourth ventricle	ND	ND	Ventricular dilation	Hypoplastic pons	ND	Mild vermian hypoplasia	Dandy-Walker malformation	Dandy-Walker malformation
	Normal Head CT				Large asymmetric cisterna magna	Small posterior fossa structures		Borderline low cerebral and cerebellar volume	Cerebellar hypoplasia	Agenesis of cerebellar vermis
					Peri-atrial white matter volume loss			Subependymal cystic lesions ^b	Agenesis of the corpus callosum	Hypoplasia of the corpus calosum

HUS, Head ultrasound; ID, Intellectual disability; ND, No data.

^aIt is not explicitly stated that the copy number variation was confirmed in this patient.

^bPatient 1 only had a prenatal MRI.

TABLE 2

Comparison of male phenotypes with different Xq28 duplications

	MECP2/IRAK	K/L (GDII)	Int22h-1/int22h-2 (RAB39B)
Intellectual disability	Typically severe (94–99%), with mild cases occasionally reported—speech severely limited, usually absent (70–88%)	Mild to severe, dependent on gene dosage—speech affected but not absent	Mild to moderate—speech affected but not absent
Behavior disturbances	Consistent with severe ID—hand stereotypies, teeth grinding, etc.	Common (40%)—shyness most commonly reported	Common (64%)—aggression most commonly reported
Epilepsy	43–54%	Some risk, dependent on gene dosage	Not reported
Spasticity	59–64%	At least some risk	Not reported
Immune dysfunction or recurrent infections	Recurrent severe respiratory infections (72–78%)	No apparent predisposition	Frequent sino-pulmonary infections (71%) atopic disease (43%)
Gastrointestinal problems	Majority, many require gastrostomy	Not reported—PO feeding maintained	Not reported—PO feeding maintained
Symptoms of female carriers	Unaffected to severe cognitive impairment	Learning problems with predisposition for psychiatric illness; Possibly unaffected	Learning problems with predisposition for psychiatric illness; Possibly unaffected

Andersen et al. (2014); Bijlsma et al. (2012); El-Hattab et al. (2011); El-Hattab et al. (2015); Lim, Downs, Wong, Ellaway, and Leonard (2016); Ramocki, Tavayev, and Peters (2010); Van Esch (2011); Vandewalle et al. (2009); Vanmarsenille et al. (2014).