

MR Imaging Findings in Xp21.2 Duplication Syndrome

Matthew T Whitehead^{1*}, Guy Helman², Andrea L Gropman²

1. Department of Neuroradiology, Children's National Medical Center, Washington, D.C., USA

2. Department of Neurology, Children's National Medical Center, Washington, D.C., USA

* Correspondence: Matthew T. Whitehead, MD, Department of Radiology, 111 Michigan Ave N.W., Washington, D.C. 20010, USA
(✉ Matthewthomaswhitehead@gmail.com)

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ABSTRACT

Xp21.2 duplication syndrome is a rare genetic disorder of undetermined prevalence and clinical relevance. As the use of chromosomal microarray has become first line for the work-up of childhood developmental delay, more gene deletions and duplications have been recognized. To the best of our knowledge, the imaging findings of Xp21.2 duplication syndrome have not been reported. We report a case of a 33 month-old male referred for developmental delay that was found to have an Xp21.2 duplication containing IL1RAPL1 and multiple midline brain malformations.

CASE REPORT

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Clinical History:

A 33 month-old male with global developmental delay was found to have hypotonia, spastic diplegia, and oral motor apraxia and this prompted referral for brain imaging evaluation. He first came to medical attention at age 15 months due to delayed ambulation and delayed speech (first words were at age 16 months). His family history was unremarkable, but his father was adopted. He was the term product of an uncomplicated pregnancy with careful monitoring for preeclampsia and maternal decreased end-diastolic flow velocity; he was discharged without complications. Global developmental delays were also noted at age 15 months. Parents reported that he was meeting all developmental milestones until 12 months of age and that there was never a concern by his pediatrician or day care. Early interventions in physical therapy was recommended, leading to improved ambulation. Other medical history is significant for strabismus surgery after 1 year of age and hypothyroidism at 26 months supplemented by levothyroxine.

In the context of his developmental delay, a genetic workup was pursued at 2 years of age and was remarkable for a duplication of Xp21.2 (arr Xp21.2 (29,681,183-29,818,683)x2) predicted to be possibly pathogenic and deletion at 9q21.2 (9q21.2(79,423,536-79,486,557)x1) of unclear clinical significance on oligonucleotide-SNP array. Further work-up of this child included a brain MRI at 33 months to evaluate for structural abnormalities that may be associated with spastic diplegia and speech delay.

Imaging Findings:

Brain MR was performed on a 3T magnet (General Electric, Milwaukee, WI). The following pulse sequences were prescribed: coronal Fast Spoiled Gradient-Recalled-Echo (FSPGR) T1 weighted-images (WI) reformatted into axial and sagittal planes, axial T2 fast spin echo, axial T2 Fluid Attenuated Inversion Recovery (FLAIR), axial Susceptibility Weighted Angiography (SWAN), coronal fat-saturated T2WI, and axial diffusion tensor images (DTI).

Multiple midline malformations were present on sagittal T1WI, axial T2WI, and coronal T2WI including hypothalamic union, corpus callosum dysgenesis, and hypoplasia of the fornices, anterior commissure, and inferior vermis (Figures 1-4). The pituitary gland, optic chiasm, and brainstem were normal. Coronal and axial T2WI showed failed hypothalamic separation across midline and underdevelopment of the inferior 3rd ventricle (Figures 5 and 6). Coronal T2WI through the level of the cribriform plate demonstrated absent formation of the olfactory sulci and olfactory bulbs, representing olfactory aplasia or severe hypoplasia (Figure 7). No additional structural abnormality was present. The hippocampi were normal.

Management and Follow-up:

The patient underwent evaluation and treatment by speech and physical and occupational therapy for the clinical manifestations of oral motor dyspraxia, spastic diplegia, hypotonia, and fine motor delay. Speech progressively improved from 20-40 words with inability to form sentences at 30 months to 3-4 word sentences by 3.5 years. Further mild speech progress occurred by age 5 years. Lower extremity hypertonia and ambulation improved over time with ongoing physical therapy.

On the most recent examination at 5 years of age, there was persistent oral motor hypotonia and speech dysfunction with mild dysarthria and some pauses. Full sentences were constructed. The patient could tell a story, name objects, name colors, and name body parts including the approximate location of his heart. He could answer questions and follow instructions. He could hold a pen in a mature grip and pick up small objects with a pincer grasp. However, he was unable to draw straight lines or squares or write letters.

DISCUSSION

Etiology & Demographics:

Xp21.2 duplication is a rare chromosomal condition that has only been described in a handful of patients. The duplication at Xp21.2 contains the gene IL1RAPL1. IL1RAPL1 gene defects have previously been associated with intellectual disability [1-3]. Thus far, the clinical spectrum associated with duplication on Xp21.2 has been limited to patients with isolated gonadal dysgenesis and XY subjects with Xp21 duplications with a complex phenotype, including intellectual disability, gonadal dysgenesis, and other malformations [6-8]. The protein encoded by IL1RAPL1 is abundantly expressed in neurons, and functions to regulate synaptic activity and synaptogenesis [1, 4, 5]. The locus harboring IL1RAPL1 appears to be highly susceptible to recombination events and the majority of IL1RAPL1 causative mutations are intragenic exon deletions or pericentric inversions [9, 10]. Although identification of the underlying copy number variant has become more common as genome-wide chromosomal microarray analysis has improved and is increasingly used as a first line diagnostic test, the findings of unclear or polymorphic variants impede delivery of a clear diagnosis and characterization of disorders. As the number of

identified cases is increasing [11], there is a need to delineate the clinical features of patients in order to facilitate the diagnostic path undertaken by the clinician and patient's family. We report clinical and brain MR imaging findings in a 33 month-old male with duplication of Xp21.2.

Clinical & Imaging findings:

Clinical findings in Xp21.2 duplication include global developmental delay, hypotonia, spastic diplegia, and oral motor apraxia. These patients may or may not have gonadal dysgenesis. Multiple brain malformations were present on brain MRI, particularly affecting midline structures. Union of the medial hypothalami across midline was manifested by parenchymal tissue filling the expected area of the anterior inferior third ventricle. Corpus callosum dysgenesis was demonstrated by blunting of the rostrum, thinning of the splenium, and absence of the normal isthmus. The inferior vermis, fornices, and anterior commissure were mildly hypoplastic. Olfactory bulbs and sulci were not visible, reflecting olfactory bulb aplasia or severe hypoplasia. The remainder of the brain parenchyma was normal in volume, morphology, and signal intensity for the patient's age. The myelination pattern was age-appropriate. The bone marrow was normal in appearance.

Treatment & Prognosis:

Because of the rarity of this condition, the ultimate level of attainment of developmental skills is not certain, but there is no current evidence to suggest any regression over time.

Differential Diagnoses:

The differential diagnosis for multiple midline brain structural abnormalities is broad and includes both syndromic and nonsyndromic causes. Some of the most common syndromic causes are (in no particular order) septo-optic dysplasia, holoprosencephaly, Aicardi syndrome, Kallmann syndrome, Chiari II malformation, Dandy-Walker malformation, and Gomez-Lopez-Hernandez syndrome.

Septo-optic dysplasia is characterized by an absent septum pellucidum, optic pathway hypoplasia/dysplasia, and variable deformity and/or dysfunction of the hypothalamic-pituitary axis. In classical holoprosencephaly, portions of the telencephalon and/or diencephalon fail to separate appropriately resulting in a spectrum of manifestations generally including ventral telencephalic union, absence of the septum pellucidum, and deficiency of the falx cerebri in even the mildest forms. Aicardi syndrome is defined by the constellation of corpus callosum dysgenesis, arachnoid cysts (often midline), and chorioretinal lacunae. Kallmann syndrome is represented by the triad of delayed puberty, hypogonadotropic hypogonadism, and infertility. Anosmia is also common. Imaging in Kallmann syndrome may reveal hypoplasia or aplasia of the olfactory bulbs, pituitary abnormalities, and/or neuronal migrational abnormalities. Chiari II malformation is characterized by hindbrain herniation associated with a myelomeningocele. Supratentorial brain anomalies may coexist, including corpus callosum dysgenesis and gray matter heterotopia. Dandy-Walker malformation manifests vermian hypoplasia, enlargement of the 4th ventricle, and variable expansion of the posterior fossa.

Concomitant cerebral malformations are often found, especially corpus callosum dysgenesis. Gomez-Lopez-Hernandez syndrome is a clinical condition characterized by rhombencephalosynapsis, parieto-occipital alopecia, and trigeminal anesthesia. Brain imaging shows variable union of the cerebellar hemispheres and vermian absence, trigeminal hypoplasia, and aqueductal stenosis that may be complicated by hydrocephalus.

Although underlying chromosomal abnormalities may be common in patients with multiple midline brain abnormalities, the specific genetic defects are not yet known in many cases. We recently described a patient with a deletion involving the long arm of the X chromosome (Xq21 deletion) who had multiple midline anomalies similar to our patient including corpus callosum dysgenesis, forniceal hypoplasia, hypothalamic malformations, and vermian hypoplasia [12]. We suggest that the finding of hypothalamic union and absent olfactory bulbs may be suggestive of Xp21.2 duplication although this must be examined in more patients as they are identified. As chromosomal microarray becomes more universally employed in the workup of developmental delay, we anticipate that many more chromosomal defects associated with brain malformations will be exposed.

TEACHING POINT

Xp21.2 duplication is a rare syndrome with a complex phenotype that manifests with intellectual disability and gonadal dysgenesis among other abnormalities. The Xp21.2 gene contains IL1RAPL1 that encodes neuronal proteins that function to regulate synaptogenesis. Consequently, multiple associated midline brain malformations may be found in Xp21.2 duplication syndrome including hypothalamic union, olfactory hypoplasia, corpus callosum dysgenesis, and hypoplasia of the vermis, brainstem, and anterior commissure.

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FIGURES

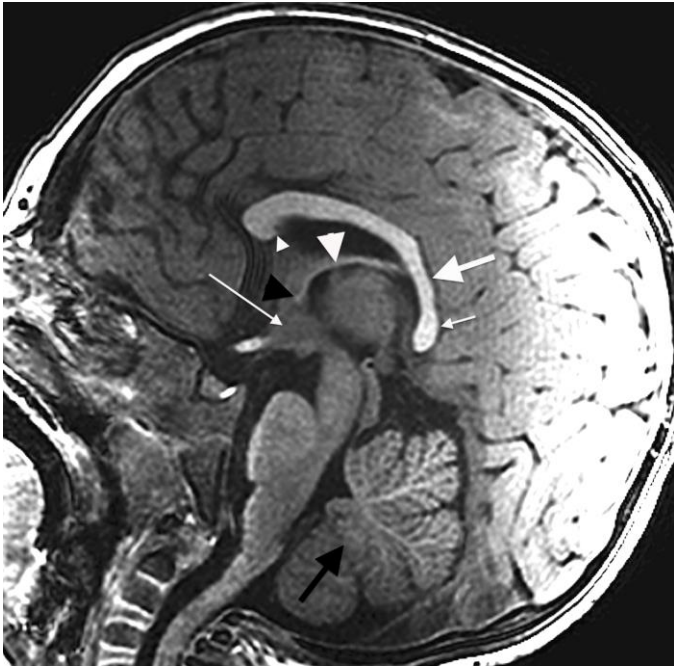


Figure 1: 33-month-old male with Xp21.2 duplication. FINDINGS: Sagittal T1WI demonstrates abnormal midline tissue occupying the anterior inferior 3rd ventricle, representing failed hypothalamic separation (long thin white arrow). The corpus callosum is mildly dysgenetic, with truncation of the rostrum (small white arrowhead), generalized thinning of the splenium (short thin white arrow), and absence of the typical isthmus (thick white arrow). Hypoplasia of the inferior vermis (black arrow), anterior commissure (black arrowhead), and fornices (large white arrowhead) is also present. TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Sagittal midline T1 Fast Spoiled Gradient Echo (FSPGR) image (TR/TE/IT = 11/2/500).

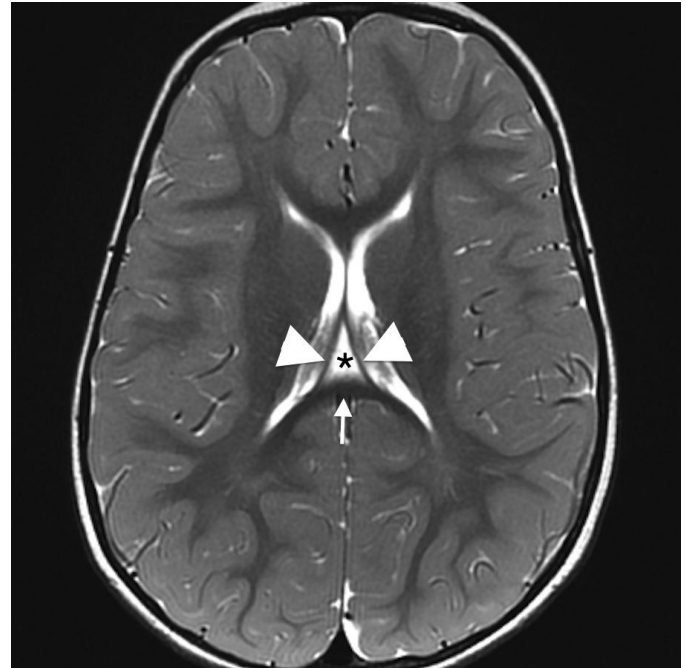


Figure 2: 33-month-old male with Xp21.2 duplication. FINDINGS: Axial T2WI demonstrates thinning of the callosal splenium (arrow) and hypoplasia of the fornices (arrowheads). A small cavum vergae is also noted (*). TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Axial fast-spin-echo (FSE) T2WI (TR/TE = 3334/104).

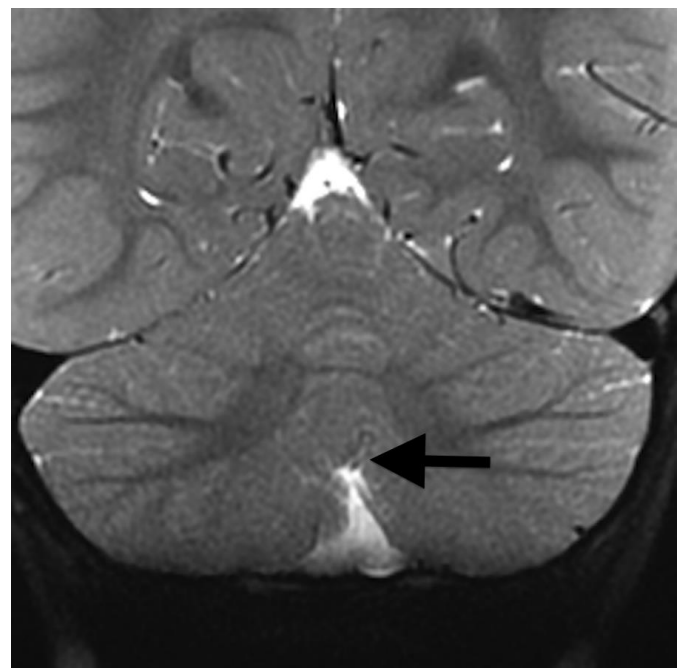


Figure 3 (right): 33-month-old male with Xp21.2 duplication. FINDINGS: Coronal T2WI demonstrates inferior vermian hypoplasia (arrow). TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Coronal T2-weighted image (TR/TE = 2000/80).

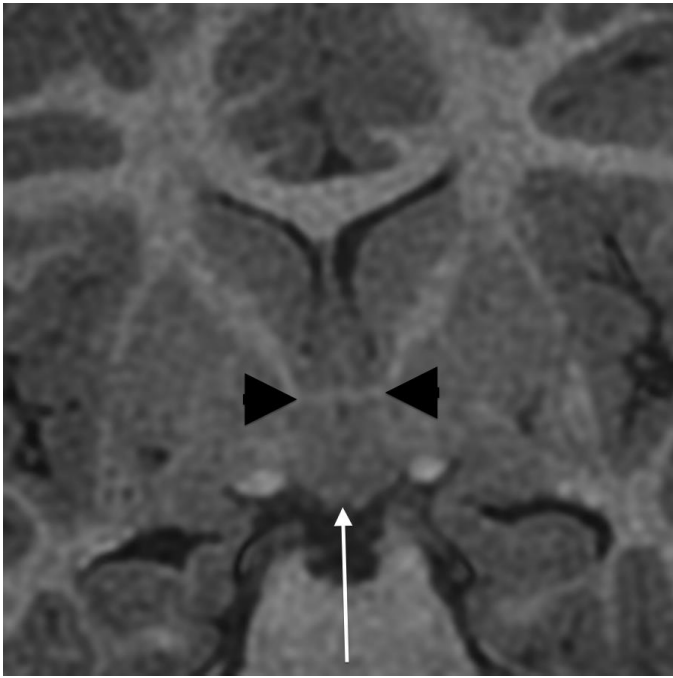


Figure 4: 33-month-old male with Xp21.2 duplication. FINDINGS: Coronal T1WI demonstrates abnormal midline tissue occupying the anterior inferior 3rd ventricle, representing failed hypothalamic separation (arrow). The anterior commissure is hypoplastic (black arrowheads). TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Sagittal midline T1 Fast Spoiled Gradient Echo (FSPGR) image (TR/TE/IT = 11/2/500).

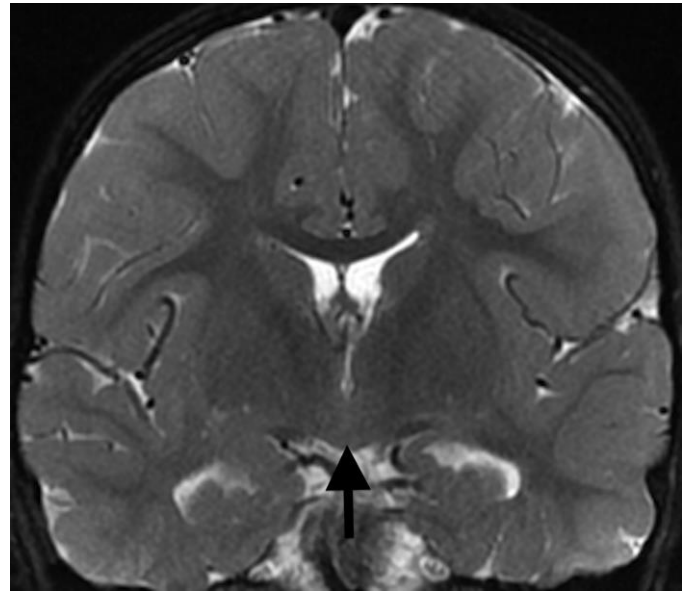


Figure 6: 33-month-old male with Xp21.2 duplication. FINDINGS: Coronal T2WI demonstrates midline parenchyma contiguous with the medial hypothalamic occupying the expected region of the anterior inferior 3rd ventricle, representing failed hypothalamic separation (arrow). TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Coronal T2-weighted image (TR/TE = 2000/80).

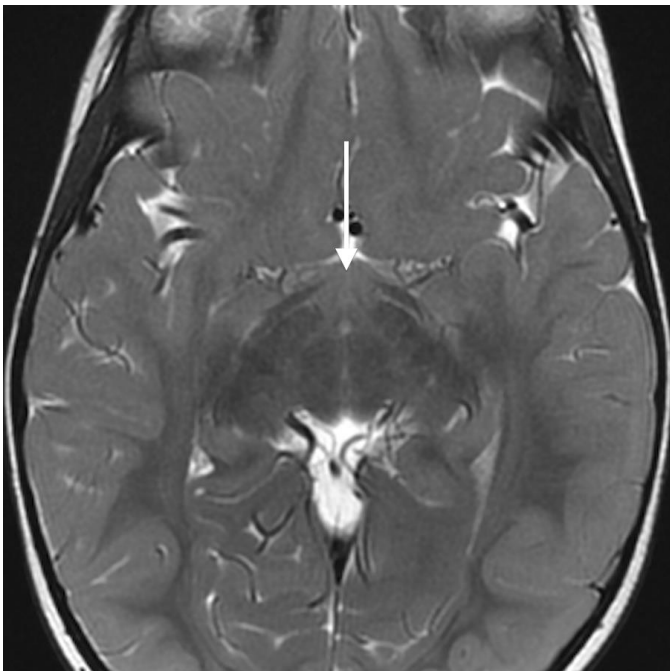


Figure 5: 33-month-old male with Xp21.2 duplication. FINDINGS: Axial T2WI demonstrates midline parenchyma contiguous with the medial hypothalamic occupying the expected region of the anterior inferior 3rd ventricle, representing failed hypothalamic separation (arrow). TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Axial fast-spin-echo (FSE) T2WI (TR/TE = 3334/104).

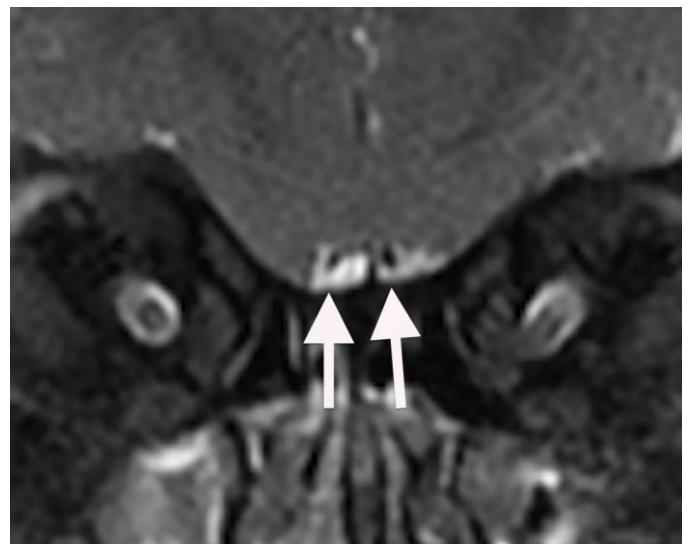


Figure 7: 33-month-old male with Xp21.2 duplication. FINDINGS: Coronal T2WI at the level of the cribriform plate shows absent olfactory bulbs and sulci (arrows). Small linear hypointense structures along the cribriform subarachnoid space represents a normal blood vessel. TECHNIQUE: 3T MR (General Electric, Milwaukee, WI). Coronal T2-weighted image (TR/TE = 2000/80).

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|----------------------------|---|
| Etiology | Congenital. Xp21.2 duplication. |
| Incidence | Unknown but rare (less than 10 reported cases) |
| Gender ratio | Unknown. |
| Age Predilection | Congenital. |
| Risk Factors | Unknown. |
| Treatment | Supportive therapy |
| Prognosis | Unclear. Likely related to additional concurrent developmental abnormalities |
| Findings on Imaging | Hypothalamic union, corpus callosum dysgenesis, aplastic olfactory bulbs and sulci, and hypoplasia of the fornices, anterior commissure, and inferior vermis. |

Table 1: Summary table for Xp21.2 duplication.

| | CC | fornix | hypothalami | vermis | olfactory | SP | OP | Pit |
|---------------------------|-----|--------|-----------------|--------|-----------|----|-----|-----|
| Xp21.2 duplication | + | + | + (union) | + | + | - | - | - |
| Xq21 deletion | + | + | + (diverticula) | + | - | - | - | - |
| SOD | - | - | - | - | +/- | + | + | + |
| HPE | + | +/- | + | - | + | + | +/- | +/- |
| Aicardi | + | - | - | - | - | - | + | - |
| Kallmann | +/- | - | +/- | - | + | - | - | +/- |
| Chiari II | +/- | - | - | + | - | - | - | - |
| DWM | + | +/- | - | + | - | - | - | - |
| GLH | +/- | - | - | + | - | - | - | - |

Table 2: Differential diagnosis table for Xp21.2 duplication.

Differential diagnosis (1st column) and anatomic abnormalities (columns 2-9) for Xp21.2 duplication. SOD = septo-optic dysplasia, HPE = holoprosencephaly, DWM = Dandy-Walker malformation, GLH = Gomez-Lopez-Hernandez syndrome, CC = corpus callosum, SP = septum pellucidum, Pit = pituitary, OP = optic pathway, + = abnormal formation, +/- = may be abnormal, - = not typically involved.

ABBREVIATIONS

MRI = magnetic resonance imaging

KEYWORDS

Xq21.2 duplication; hypothalamus; corpus callosum; fornix; vermis; olfactory

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