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Clinical report

Xp21 deletion in female patients with intellectual disability: Two new cases and a review of the literature

Solveig Heide [a,*], Alexandra Afenjar [b,c], Patrick Edery [d,e], Damien Sanlaville [d,e], Boris Keren [f], Alexandre Rouen [a], Alinoë Lavillaureix [a], Capucine Hyon [a], Diane Doummar [c], Jean-Pierre Siffroi [a], Sandra Chantot-Bastaraud [a]

[a] APHP, Hôpital Armand-Trousseau, Service de Génétique et d'Embryologie médicales, Paris, 75012, France
[b] APHP, Hôpital Armand-Trousseau, Service de Génétique Clinique, Paris, 75012, France
[c] APHP, Hôpital Armand-Trousseau, Service de Neuropédiatrie, Paris, 75012, France
[d] Hospices Civils de Lyon, Service de Génétique Clinique et Laboratoire de Cytogénétique, Lyon, 69000, France
[e] Centre de Recherche en Neurosciences de Lyon, Inserm U1028, UMR5292, UCBL, Lyon, 69000, France
[f] APHP, Groupe Hospitalier Pitié-Salpêtrière, Service de Cytogénétique, Paris, 75013, France

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ABSTRACT

Xp21 continuous gene deletion syndrome is characterized by complex glycerol kinase deficiency (*GK*), adrenal hypoplasia congenital (*NROB1*), intellectual disability and/or Duchenne muscular dystrophy (*DMD*). The clinical features depend on the size of the deletion, as well as on the number and the nature of the encompassed genes. More than 100 male patients have been reported so far, while only a few cases of symptomatic female carriers have been described. We report here detailed clinical features and X chromosome inactivation analysis in two unrelated female patients with overlapping Xp21 deletions presenting with intellectual disability and inconstant muscular symptoms.

1. Introduction

DMD gene encodes a muscular protein called dystrophin and is located in Xp21.2. Rearrangements of *DMD* gene are responsible for a spectrum of neuromuscular diseases called dystrophinopathies. Among these, Duchenne muscular dystrophy affects 1 on 3000 males and leads to the loss of walking ability occurring between 10 and 13 years. Likewise, Becker muscular dystrophy, which corresponds to the milder allelic variant of Duchenne muscular dystrophy, is characterized by a later onset of muscular symptoms and a less severe phenotype, since the ability to walk can be preserved. Duchenne and Becker muscular dystrophies are both associated with high serum rates of creatin kinase (CK). Cardiac abnormalities such as dilated cardiomyopathy or cardiac rhythm disturbance are a significant cause of death in Duchenne and Becker muscular dystrophies. Most females heterozygous for *DMD* rearrangements are asymptomatic or have mild clinical presentations [Gospe et al., 1989]. The percentage of female heterozygotes with clinical evidence of muscle weakness ranges from 2.5% to 17%. Female heterozygotes are at an increased risk for cardiomyopathy such as dilated cardiomyopathy and left ventricular dysfunction [Hoogerwaard et al., 1999].

Mutations preventing the production of any functional dystrophin tend to cause Duchenne muscular dystrophy while Becker muscular dystrophy is caused by mutations leading to an abnormal version of dystrophin that retains some function. 60–70% of dystrophinopathies are caused by deletions or duplications of the *DMD* gene which are detectible by microarrays (Del Gaudio et al., 2008).

Dystrophinopathies symptoms are in some cases associated with intellectual disability (ID), adrenal hypoplasia congenital and glycerol kinase deficiency, resulting from a deletion of the corresponding genes (respectively *IL1RAPL1*, *NR0B1* and *GK*) located nearby *DMD* gene in Xp21. More than 100 cases of male patients with an Xp21 deletion have been reported so far [Marlhens et al., 1987; Walker et al., 1992]. However, only eight cases of symptomatic female carriers from seven families have been

* Corresponding author.
E-mail address: heide.solveig@gmail.com (S. Heide).

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described [Falsaperla et al., 2003; Fries et al., 1993; Ogata et al., 2001; Shaikh et al., 2008]. We report here two female patients referred for intellectual disability and carrying an Xp21 deletion detected by CGH (Comparative Genome Hybridization) or SNP (Single Nuclear Polymorphism) microarrays.

2. Clinical reports

2.1. Patient 1

This female patient was the second child of a Caucasian non-consanguineous couple. She has one healthy older brother. The mother suffered from endometriosis, causing two previous miscarriages. The pregnancy was marked by breakthrough bleeding during the first trimester but prenatal ultrasound examinations were normal. She was born at 39 weeks of gestation with normal birth measurements. The neonatal period was uneventful. She first sat at 9 months and walked without support at 18 months. Walking was initially difficult with many falls. Expressive language was delayed. Her medical history also included hyperopia and multiple serous otitis. Neuropsychological assessment at 7 years using the Wechsler Intelligence Scale for Children (WISC) revealed low scores in total intellectual quotient (between 50 and 63). Physical examination at the age of 7 years showed a normal growth in height, weight and head circumference. She was able to write her name and to recognize alphabet letters. She had mild joint laxity. She had neither dysmorphic features nor motor deficiency. Laboratory evaluation showed normal serum level of creatin kinase. Electrocardiogram and cardiac ultrasound examinations were normal, as well as brain MRI.

Karyotype analysis was normal. Single Nuclear Polymorphisms microarray analysis was performed using CytoSNP12 microarrays (Illumina, San Diego, CA, USA) and detected a 6.09 Mb deletion of the X chromosome, ranging from p21.3 to p21.1 regions with minimal extent nt: 25,878,399–31,987,991. This deletion encompassed 18 RefSeq genes as found in the UCSC Genome Browser [http://genome.ucsc.edu/, NCBI Build 37, hg19], comprising *IL1RAPL1*, *DAX1*, *GK* and the last 37 exons of *DMD* (Fig. 1). FISH analysis using the Bacterial Artificial Chromosome (BAC) clone RP11-89I17 (*DAX1*) confirmed the deletion and showed normal fluorescent signals on both X parental chromosomes, indicating that the deletion arose *de novo* in our patient. DNA analysis for X chromosome inactivation was carried out by evaluation of the methylation status of the CpG island upstream of the polymorphic CAG repeat in exon 1 of the androgen receptor gene (AR), using methylation-sensitive restriction enzyme method [Allen et al., 1992]. This analysis revealed random X chromosome inactivation (59%; 41%).

2.2. Patient 2

Patient 2 was the second child of a non-consanguineous couple. Familial history was non contributive. She was born after an uneventful pregnancy and presented with normal birth measurements. She was able to sit up around 10 months and to walk by the age of 18 months. Her language was delayed with first words at 5 years. She was not able to read or to write at the age of 11 years. Since the age of 10 years, she had muscular pains during physical exercises, initially on the feet and then extending to the legs and hands, associated with severe muscular fatigue. She had no motor deficiency. Her morphology was described as “athletic” with global muscular hypertrophy. Laboratory evaluation showed elevated serum level of creatin kinase at 579 U/l (normal <160 U/l). She had no myoglobinuria. An electromyogram showed a myogenic pattern and the muscle biopsy analysis indicated non-specific histology. Electrocardiogram and cardiac ultrasound examinations were normal. She had generalized epilepsy since the age of 16 years, with a good response to monotherapy. Her brain MRI was normal. Furthermore, she had no dysmorphic features.

Karyotype analysis was normal. Oligonucleotide array comparative genomic hybridization (a-CGH) analysis was performed using the Agilent Human Genome CGH Microarray ISCA v2, 4 × 180K (Agilent Technologies, Santa Clara, CA, USA) and detected a 2.49 Mb deletion on the X chromosome ranging from p21.3 to p21.2 regions. Deletion’s minimal extent was nt: 29,008,175–31,496,701 [NCBI Build 37, hg19]. It encompassed 11 RefSeq genes, including *IL1RAPL1*, *DAX1*, *GK* and the 22 last exons of *DMD* (Fig. 1). X chromosome inactivation analysis at the AR locus in blood and muscle cells indicated random inactivation (50%; 50% in muscle and 63%; 37% in blood).

3. Discussion

Xp21 deletion causes a well-known contiguous gene syndrome in males, named Xp21 deletion syndrome or complex glycerol kinase deficiency (GKD) [Sjarif et al., 2000; Wikiera et al., 2012]. More than 100 male patients have been reported so far. The clinical spectrum depends on the size of the deletion, as well as on the number and nature of the encompassed genes. Xp21 continuous gene syndrome comprises Duchenne muscular dystrophy (*DMD*), glycerol kinase deficiency (*GK*), and adrenal hypoplasia congenital (*DAX1*/*NR0B1*).

Only eight cases of symptomatic females carrying Xp21 deletion detected by FISH have been reported so far (Table 1) [Falsaperla et al., 2003; Fries et al., 1993; Ogata et al., 2001; Shaikh et al., 2008].

We report here two new cases of unrelated female patients carrying Xp21 microdeletions detected by microarrays. These

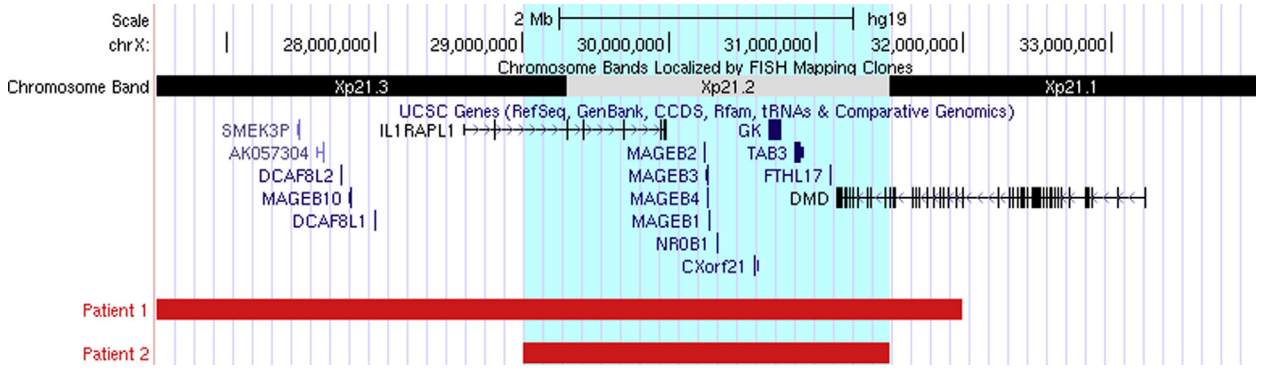

Fig. 1. Overlapping Xp21 deletions in patients 1 and 2 with encompassed genes (UCSC).