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Short clinical report

Autosomal insertional translocation mimicking an X-linked mode of inheritance

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ABSTRACT

Unbalanced insertional translocations are a rare cause of intellectual disability. An unbalanced insertional translocation is a rare chromosomal imbalance, which may result from a balanced insertional translocation present in a phenotypically normal parent. We report here three brothers with intellectual disability, short stature, microcephaly, craniofacial anomalies and small testes. Since their parents and their sister were all phenotypically normal, the pattern of the family suggested an X-linked mode of inheritance. Surprisingly, we identified by array comparative genomic hybridization (aCGH) and fluorescent *in situ* hybridization (FISH) in the three brothers an 8q22.3q23.2 deletion resulting from a balanced insertional translocation present in their healthy father. The deletion encompassed the *ZFPM2* gene known to be involved in gonadal development, which is consistent with the small testes and abnormal endocrine dosages in the affected brothers. The present report also illustrates that parental analyses by aCGH or qPCR methods are not sufficient when a *de novo* deletion or duplication is identified in an affected child and that FISH analysis should be performed on metaphase spreads in both parents to deliver an accurate genetic counseling.

1. Introduction

Intellectual disability (ID) represents the most frequent cause of severe handicap in children and one of the main reasons for referral in clinical genetic practices. Causes of ID are extremely heterogeneous and can result from chromosomal rearrangements, monogenic disorders, and/or environmental factors. Despite clinical examination and extensive complementary investigations, no etiology is identified in up to 50% of the patients with moderate to severe ID [1], hampering accurate genetic counseling and clinical follow-up.

Among the chromosomal rearrangements, unbalanced insertional translocations are a rare cause of ID [2,3]. An unbalanced insertional translocation may result from a balanced insertional translocation present in a phenotypically normal parent. Balanced insertional translocation is defined by the intercalation of a part of one chromosome into another non-homologous chromosome (interchromosomal insertion) or into another part of the same chromosome (intrachromosomal insertion). We report here a family with three brothers with ID, short stature, microcephaly, craniofacial anomalies and small testes and a phenotypically normal sister. Both parents were phenotypically normal suggesting an X-linked mode of inheritance. Surprisingly, we identified by array comparative genomic hybridization (aCGH) and fluorescent *in situ* hybridization (FISH) in the three brothers an 8q22.3q23.2 deletion resulting from a balanced insertional translocation present in their father.

2. Materials and methods

2.1. Clinical report

The proband (individual II-2) is a male born from healthy unrelated parents (individuals I-1 and I-2) (Fig. 1). He was referred for ID to our medical genetic department at the age of 53 years old. Walking alone was acquired between 18 and 24 months old. At 53 years old, he was able to speak isolated words but could not make sentences nor read and write. At physical examination, he presented with short stature (160 cm; −2.5 SD), microcephaly (OFC: 54 cm, −2 SD), convergent strabismus of the left eye, craniofacial dysmorphic features including a long face with a mild enophtalmia, arched eyebrows and large ears, and small testes. He had stereotyped movements. No seizures were mentioned.

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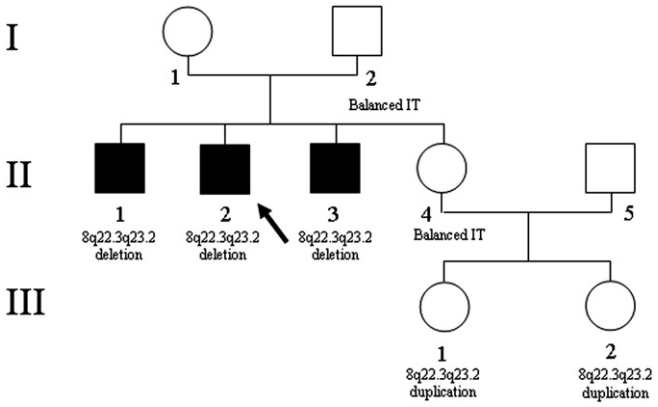

Fig. 1. Pedigree of the present family. Normal: no imbalance identified by aCGH. The arrow indicates the proband. IT: Insertional translocation.

His older brother (individual II-1) presented with the same clinical features including small and soft testes. Endocrine evaluation of pituitary gonadal axis showed elevated serum follicle stimulating hormone (FSH) (30.2 mU/ml; normal range 1–12 mU/ml) with low total testosterone (2.33 ng/ml; normal range 3–10 ng/ml) indicating gonadal dysgenesis. In addition, he had major speech disorder with stuttering. At the age of 56 years old, his weight, height and OFC were 48 kg (−2.5 SD), 162 cm (−2.2 SD) and 52.5 cm (−3.3 SD), respectively.

The youngest brother (individual II-3) physically seemed like the elders. He could walk alone at 14 months old. He could make sentences but was not able to write or read. Physical examination showed a peno-scrotal hypospadias in addition to small and soft testes. Endocrine evaluation of pituitary gonadal axis showed elevated serum follicle stimulating hormone (FSH) (34.7 mU/ml; normal range 1–12 mU/ml) with low total testosterone (1.2 ng/ml; normal range 3–10 ng/ml) indicating gonadal dysgenesis. At the age of 51 years old, his weight, height and OFC were 68 kg (+0.5 SD), 161 cm (−2.3 SD) and 53 cm (−3 SD), respectively. He was described as someone with changing mood.

The fourth and last infant of the couple (individual II-4) was a healthy woman who attended higher education. At 46 years old, she had two phenotypically normal daughters (individuals III-1 and III-2). Her older daughter (individual III-1) attended a regular school and is working as a nurse's aide. She lives as husband and wife. At 29 years old, she was 175 cm tall (+2 SD) and had normal intelligence and no dysmorphic features. Her younger sister (individual III-2) also had a normal phenotype. She attended higher education and is working as a special needs worker. She also lives as husband and wife.

3. Cytogenetic and molecular tests

Informed consent for genetic analyses was obtained from all individuals according to local ethical guidelines. Karyotyping based on R-banding Thymidine Buder Giemsa (RTBG) was performed using standard methods on metaphase spreads from peripheral blood of the patients. Genomic DNA was extracted from peripheral blood using standard protocols. Mutation screening in the *FRAXA*, *FRAXE*, *ARX*, *PQBP1* genes was performed in patient II-1 and in the *JARID1C* gene in patient II-2. Array CGH experiments were performed using Agilent Human Genome CGH 180K oligonucleotide arrays (Agilent, Santa Clara, CA; www.agilent.com) with the ISCA design (www.iscaconsortium.org) following the protocols provided by Agilent. The arrays were analyzed with the Agilent scanner and the Feature Extraction software (v. 9.1.3). Graphical overview was obtained using the CGH analytics software (v.3.5.14). Fluorescence *in situ* hybridization (FISH) was performed in individuals I-1, I-2, II-1, II-2, II-3, II-4 and III-1 with two different probes located in the 8q deleted region (RP11-188I06 and RP11-695B04 probes), the RP11-797C19 probe in the 8p subtelomeric region and the CTB-62I11 probe in the 6p subtelomeric region used as control probes (http://bacpac.chori.org/home.htm).

4. Results

The pedigree of the family led us to hypothesize an X-linked mode of inheritance (Fig. 1). Mutation screening in several genes responsible for X-linked mental retardation was normal in patient II-1 (*FRAXA*, *FRAXE*, *ARX*, *PQBP1*) and in patient II-2 (*JARID1C*). Surprisingly, an aCGH analysis showed normal results on the X chromosome but revealed a 9 Mb deletion in the 8q22.3q23.2 region (arr 8q22.3q23.2(103,043,561x2,103,059,472–112,124,080x1,112,148,713x2) (coordinates based on hg18 build) (Fig. 2). Array CGH analyses showed normal results in both parents (individuals I-1 and I-2).

FISH analyses using the RP11-188I06 and RP11-797C19 probes confirmed the 8q deletion in the proband and showed that the other two affected brothers also carried the same deletion (Fig. 3A). At this stage, we hypothesized that the recurrence of this chromosomal imbalance in the three brothers could be due to a gonadal mosaicism of the deletion in one of the parents. However, FISH analyses in the parents of the proband showed a balanced insertional translocation in the father, for whom the 8q22.3q23.2 region was inserted in the long arm of chromosome 6 (Fig. 3B). Subsequently, this balanced insertional translocation was also identified in the phenotypically normal sister of the proband (individual II-4). The daughters of individual II-4 (individuals III-1 and III-2) were phenotypically normal but both carried a duplication of the 8q22.3q23.2 region (Fig. 3C).

5. Discussion

Balanced insertional translocations are chromosomal rearrangements that require at least three breaks in the chromosomes involved and thus qualify as complex chromosomal rearrangements (CCR). The frequency of unbalanced insertional translocation is estimated to be between 1/1400 and 1/500 in patients referred for ID and/or congenital anomalies carrying apparently *de novo* copy-number variant (CNV) [2–4]. When only autosomes are implicated in the rearrangement, both sexes may be affected and patients may present with ID and/or malformations. In the present report, three brothers presented with ID while their sister and their parents were normal suggesting an X-linked mode of inheritance. Surprisingly, no anomaly on the X chromosome was present but an unbalanced autosomal insertional translocation was identified in the three affected brothers. FISH analysis showed that the genomic imbalance was inherited from the phenotypically normal father who carried a balanced insertional translocation.

In this family, carrying the 8q22.3q23.2 deletion led to an abnormal phenotype while individuals with the reciprocal 8q22.3q23.2 duplication were normal. This is consistent with the fact that deletions are usually responsible for a more severe phenotype than duplications. Large duplications may even be observed in phenotypically normal individuals, as here for the two women carrying the 8q22q23.2 duplication. Balikova et al. [5] previously reported a phenotypically normal individual with a 10qter duplication encompassing 7.8 Mb and involving 78 genes. Similarly, Spreiz et al. [6] described a woman carrying an 11.3 Mb duplication with an almost unremarkable phenotype. Several explanations might explain the discrepancy between the benign