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Complex Mosaic Ring Chromosome 11 Associated with Hemizygous Loss of 8.6 Mb of 11q24.2qter in Atypical Jacobsen Syndrome

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Comparative genomic hybridization · Deletion 11q · *FLI1* · Jacobsen syndrome · Ring chromosome · Thrombocytopenia Paris-Trousseau type

Abstract
Jacobsen syndrome (JBS) is a contiguous gene deletion syndrome involving terminal chromosome 11q. The haploinsufficiency of multiple genes contributes to the overall clinical phenotype, which can include the variant Paris-Trousseau syndrome, a transient thrombocytopenia related to *FLI1* hemizygous deletion. We investigated a boy with features of JBS using classic cytogenetic methods, FISH and high-resolution array CGH. The proband was found to have a mosaic ring chromosome 11 resulting in a hemizygous 11q terminal deletion of 8.6 Mb, leading to a copy number loss of 52 genes. The patient had a hemizygous deletion in the *FLI1* gene region without apparent thrombocytopenia, and he developed diabetes mellitus type I, which has not previously been described in the spectrum of disorders associated with JBS. The relationship of some of the genes within the context of the phenotype caused by a partial deletion of 11q has provided insights concerning the developmental anomalies presented in this patient with atypical features of JBS.

Jacobsen syndrome (JBS; OMIM 147791, http://omim.org/) is a contiguous gene deletion syndrome involving terminal chromosome 11q. JBS has also been reported with a familial unbalanced 11q translocation, a ring chromosome 11, and a pericentric 11q inversion associated with partial deletion. The deletion size ranges from ~7 to 20 Mb, with the proximal breakpoints usually starting within or distal to subband 11q23.3 and extending to the telomere [Mattina et al., 2009].

The spectrum of clinical symptoms is variable, and this may depend on both the size or the deleted region in 11qter and the type of chromosome aberration involved. Typical clinical features can include pre- and postnatal growth retardation, psychomotor delay, characteristic facial dysmorphism, and thrombocytopenia or pancytopenia [Sheth et al., 2014]. A subset of JBS patients has mal-

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Table 1. List of clinical features observed in JBS present in the proband

Common dysmorphic features in JBS	Proband
Craniofacial	
High prominent forehead	+
Facial asymmetry	–
Trigonocephaly	+
Narrow forehead	+
Flat occiput	+
Ophthalmic	
Telecanthus	+
Downslanting palpebral fissures	–
Strabismus	+
Palpebral ptosis	+
Bushy double eyebrows	+
Epicanthal folds	–
Eyelid or iris coloboma	–
Cataract	–
Nasal	
Short nose	+
Broad nasal bridge	+
Anteverted nares	+
Prominent columella	+
Ear	
Small ears	+
Low-set ears	–
Hypoplastic lobus	+
Oral	
Long and flat philtrum	+
Carp-shaped mouth	+
Thin upper lip	+
Retrognathia	+
High-arched palate	+
Dental anomalies	+
Neck	
Short neck	+
Webbed neck	–
Hands	
Cutaneous syndactyly	–
Finger pads	+
Abnormal palmar creases	+
Hypoplastic hypotenar regions	+
Clinodactyly of the 5th finger	+
Brachydactyly	–
Camptodactyly	+
Feet	
Flat feet	+
Large and long first toe	+
Talipes equinovarus	+
Crowded toes or syndactyly	–
Cardiac	
Cardiac involvement (ventricular septal defect)	+
Hematological	
Thrombocytopenia/pancytopenia	–

formations of the heart, kidney, gastrointestinal tract, genitalia, skeleton, and central nervous system. Ocular, hearing, hormonal and immunological problems such as late-onset combined immunodeficiency associated with hypogammaglobulinemia, pancytopenia, and low T-helper cell counts may also be present [Trkova et al., 2012]. Nearly all described JBS patients are born with Paris-Trousseau syndrome, a transient neonatal thrombocytopenia associated with hemizygosity of chromosome 11q which usually includes the *FLI1* gene [Hart et al., 2000].

We report an atypical case of JBS without thrombocytopenia with a complex mosaic karyotype involving a monosomy 11, a monocentric ring, and a larger dicentric ring chromosome 11 by G-banding analysis. Array CGH identified a hemizygous deletion of 8.6 Mb which includes a loss of 52 genes from distal 11q, including the *FLI1* gene. This patient developed diabetes mellitus type I which has not previously been described in the spectrum of disorders associated with JBS. The relationship of some of the genes within the deleted region of 11q is considered in the context of the developmental anomalies presented in this patient.

Clinical Case

The proband is a 13-year-old boy referred to the clinical genetics service with dysmorphic features (table 1), intellectual disability, and behavioral issues. He is the first-born child to a nonconsanguineous and healthy 17-year-old mother and 24-year-old father. There was no previous history of genetic diseases or diabetes in either of the parental families. The pregnancy was uncomplicated until 36 weeks' gestation, when a cesarean section had to be performed due to fetal distress and a tight nuchal cord. His birth weight was 2,560 g, his height 47.5 cm, his OFC 33 cm, and his APGAR score 8/9. During the perinatal period, a foot deformity that was classified as metatarsus adductus was diagnosed, and a serial casting was performed. His developmental milestones were delayed.

Learning difficulties and behavioral problems, characterized by attention deficit and hyperactivity, were reported when the patient first started school. He was referred to a pediatric neurologist for evaluation and several tests were performed, including MRI which was normal. The patient was referred for major investigation and physical examination at 13 years of age, he presented with dysmorphic features that resemble JBS (fig. 1). His weight was 64.5 kg (90–97th percentile), his height 145 cm (10–25th percentile), and his OFC 52 cm (10th percentile). In addition to being obese, the proband has hypercholesterolemia and hypertriglyceridemia and developed diabetes mellitus type I, which is an unusual finding in JBS patients without thrombocytpenia. His hormonal and immunological systems appeared to be normal, but cardiac involvement (ventricular septal defect), in keeping with JBS, was detected. However, there were no malformations of the kidney, gastrointestinal tract, or genitalia.

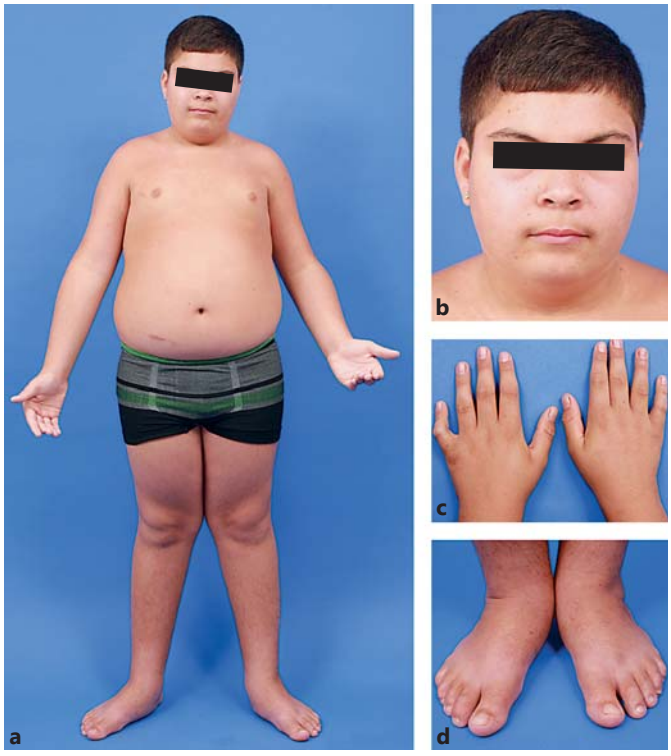

Fig. 1. Clinical features of the patient. **a** Frontal view of the patient. **b** Facial features: high, prominent, narrow forehead; trigonocephaly; flat occiput; telecanthus; strabismus; palpebral ptosis; bushy double eyebrows; short nose; broad nasal bridge; anteverted nares; prominent columella; small ears; hypoplastic lobus; long, flat philtrum; carp-shaped mouth, and a thin upper lip. **c** Hands: clinodactyly of the 5th finger and camptodactyly. **d** Feet: flat feet; large, long first toe, and talipes equinovarus.

Material and Methods

A chromosome analysis of 100 metaphases was performed from 72-hour cultures of peripheral blood lymphocytes followed by conventional GTG-banding technique (400-band level resolution). Array CGH using the 2x400K platform (Agilent Inc., Santa Clara, Calif., USA) was performed following the protocol provided by the manufacturer. Normalization, segmentation, and identification of corresponding copy number events were done using Nexus 7.0 (BioDiscovery, Santa Clara, Calif., USA). The Fast Adaptive States Segmentation Technique (FASST2) was used to a significance threshold of 1.0E–5 with a maximum space between adjacent probes of 1 kb. Copy number alterations reported were based on genome build GRCh37/hg19 and were restricted to regions with 10 or more adjacent probes that differed significantly from the expected normalized values. Gain was estimated with a threshold of 0.42; high gains, threshold of 1.14; losses, –0.62, and homozygous copy loss, –1.1. FISH was performed with probes sureFISH (Agilent) G100333-Red 11q25 (region: 133,935,398–134,140,426) and G100071-Green 11qtel (region: 134,649,534–134,945,261), as recommended by the manufacturer's protocol.

Results

Cytogenetic analysis by GTG-banding revealed mosaicism that comprised 3 distinct clonal cell populations with a karyotype mos 45,XY,–11[18]/46,XY,r(11)[78]/46,XY,dic r(11;11)[4]. The major clone comprised 78% of the metaphase cells and was characterized by a ring chromosome 11 that appeared to be formed as a result of a small 11q telomeric deletion starting at band 11q24.2 (fig 2). The second most common clone showed monosomy of chromosome 11 (18% of the metaphases), and the remaining 4% of metaphase cells had a large complex dicentric ring chromosome 11. Parental karyotypes were both normal. The analysis showed an 8.6-Mb region of hemizygous loss in 11q24.2qter (chr11:126,368,150–135,006,516), containing 52 genes *(LOC101929427*, *KIRREL3*, *KIRREL3-AS2*, *MIR3167*, *KIRREL3-AS3*, *LOC101929473*, *LOC101929497*, *MIR6090*, *ETS1*, *LOC101929517*, *SENCR*, *FLI1*, *KCNJ1*, *C11orf45*, *KCNJ5*, *TP53AIP1*, *ARHGAP32*, *BARX2*, *LINC01395*, *TMEM45B*, *NFRKB*, *PRDM10*, *LINC00167*, *APLP2*, *ST14*, *ZBTB44*, *ADAMTS8*, *ADAMTS15*, *MIR8052*, *C11orf44*, *LOC100507431*, *LOC103611081*, *SNX19*, *LOC101929653*, *NTM*, *NTM-IT*, *OPCML*, *LOC646522*, *SPATA19*, *MIR4697*, *MIR4697HG*, *IGSF9B*, *LOC100128239*, *JAM3*, *NCAPD3*, *VPS26B*, *THYN1*, *ACAD8*, *GLB1L3*, *GLB1L2*, *B3GAT1*, and *LOC283177)*. The array-CGH analysis showed no other structural genomic imbalances apart from the 11q chromosomal loss. FISH analysis using chromosome 11-specific probes showed that the ring chromosome present as the major clone had deletions in the 11q25 and 11qtel regions (fig 2).

Discussion

The literature describes 24 pre- and postnatal cases of ring abnormalities affecting chromosome 11, of which 7 cases (29%) were thought to be associated with JBS. In 3 of them, the ring chromosome 11 was present as a mosaic, and Paris-Trousseau syndrome was associated with JBS in only 2 patients [Valente et al., 1977; Niikawa et al., 1981; Cousineau et al., 1983; Romain et al., 1983; Daniele et al., 1986; Palka et al., 1986; Fagan et al., 1988; Adewale et al., 1991; Park et al., 2007; Carella et al., 2010; Hansson et al., 2012; Iourov et al., 2012; Zhang et al., 2012; Lange et al., 2015; Peng et al., 2015]. The present study is the first analysis by array CGH of a mosaic ring chromosome 11 linked to JBS of a boy without evidence of neonatal thrombocytopenia. Eight patients with ring chromosome

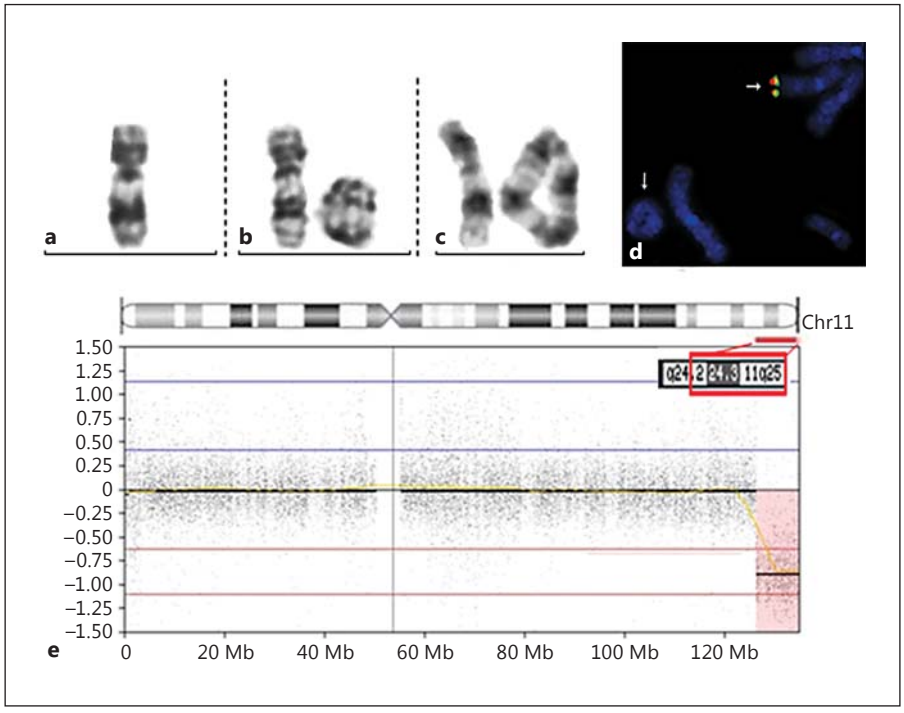

Fig. 2. Partial karyotypes, FISH and array analysis. **a** G-banding shows monosomy of chromosome 11. **b** Ring chromosome 11 in major clone. **c** Dicentric ring chromosome 11. **d** FISH analysis of chromosome 11 and ring chromosome (bottom arrow) shows the absence of 11q25 (red signal) and 11qtel (green signal) genomic regions (top arrow). **e** Copy number variation analysis by array-CGH shows an 8.6-Mb deletion in chromosome 11q24.2qter.

11 were studied by array CGH previously. Three of them were related to JBS, and all were female [Hansson et al., 2012; Iourov et al., 2012; Peng et al., 2015].

The deleted region of 11q that is associated with intellectual disability contains the genes *SNX19*, *THYN1*, *OPCML*, *VPS26B*, *NCAPD3*, and *NTM*. Deletion of the *NTM* gene, related to the development of the nervous system, has been associated with cognitive function. *JAM3* and *ETS1*, suggested as candidate genes for the JBS cardiac phenotype, were also deleted.

Four genes have been related to thrombocytopenia when hemizygously deleted *(FLI1*, *ETS1*, *NFRKB*, and *JAM3)* [Trkova et al., 2012]. It is noteworthy that our patient has not developed this hematologic phenotype. Therefore, our patient is the first report of a male with JBS without thrombocytopenia, but presenting with monosomy of the genes *FLI1, ETS1, NFRKB*, and *JAM3*. At present, there are no other reports of males with *FLI1* haploinsufficiency and normal platelet function and count.

Thrombocytopenia is predominant in males. Females do not appear to present with thrombocytopenia, even when the *FLI1* gene is deleted [Hansson et al., 2012; Sheth et al., 2014]. Interestingly, more than 80% of the patients reported with r(11), and 70% with 11q deletion are female. One possible explanation for gender preference with this disorder is that the sex chromosome complement may influence the expression of chromosome 11qter, perhaps by modifying the susceptibility to develop thrombocytopenia in female patients [Peng et al., 2015].

Our patient also developed diabetes type I. However, as of now, there do not appear to be candidate genes within the deleted region to explain this phenotype. Another patient with diabetes was reported in the literature, but she presented with type II diabetes [Lange et al., 2015].

Most features of JBS may be caused by deletion of different sets of contiguous genes. The relative difference in the phenotypic expression may depend on the genetic background and gene-gene interactions. Structural rearrangements within the ring chromosome could also lead to changes in gene expression, modifying the associated clinical characteristics. The symptoms and clinical findings of 11q deletion are considered nonspecific, and incomplete penetrance for specific phenotypes may explain the high variability between patients [Sheth et al., 2014].

Partial monosomy 11qter in mosaic and the presence of a ring chromosome is complex for prenatal genetic counseling. Deletions in the ring chromosome, the ring instability, and epigenetic factors also must be considered in the evaluation of the genetic consequences. It is not possible to define the phenotype of the 11q partial monosomy accurately due to the heterogeneity in size and position of the deletions. In addition, variable phenotypic ef-

fects may arise because of modifier genes or compensatory gene expression of alleles in the normal chromosome 11. The phenotype is not only due to haploinsufficient genes; it is the result of complex epigenetic, gene-gene, and gene-environment interactions.

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Statement of Ethics

All the performed procedures were in accordance with the ethical standards of the institutional and national research committee (process CONEP 13153/2006). Informed consent was obtained from the parents according to our institutional protocol.

Disclosure Statement

The authors have no conflicts of interest to declare.

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