Jacobsen Syndrome: Surgical Complications due to Unsuspected Diagnosis, the Importance of Molecular Studies in Patients with Craniosynostosis

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Abstract

Jacobsen syndrome (JBS) is an uncommon contiguous gene syndrome. About 85–92% of cases have a de novo origin. Clinical variability and severity probably depend on the size of the affected region. The typical clinical features in JBS include intellectual disability, growth retardation, craniofacial dysmorphism as well as craniosynostosis, congenital heart disease, and platelet abnormalities. The proband was a 1 year/3-month-old Mexican male. Oligonucleotide-SNP array analysis using the GeneChip Human Cytoscan HD was carried out for the patient from genomic DNA. The SNP array showed a 14.2-Mb deletion in chromosome 11q23.3q25 (120,706–134,938 Mb), which involved 163 RefSeq genes in the database of genomic variation. We report a novel deletion in JBS that increases the knowledge of the variability in the mutation sites in this region and expands the spectrum of molecular and clinical defects in this syndrome.

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Jacobsen syndrome (JBS; OMIM 147791), also known as terminal 11q23.3q25 deletion, is an uncommon contiguous gene syndrome with about 200 cases reported worldwide. JBS has a prevalence of 1 in 100,000 newborns with a female predominance of 2:1 [So et al., 2014]. About 8–15% of cases are caused by a deletion from a parental balanced chromosome translocation or other rearrangements, whereas 85–92% have a de novo origin [Grossfeld et al., 2004; Van Zutven et al., 2009]. Clinical variability and severity depend on the size and the location of the deleted region. The typical clinical features in JBS include intellectual disability (97%), growth retardation (68–75%), craniofacial dysmorphism (>40%), congenital cardiac malformations (56%), and platelet abnormalities (88.5–94%). Kidney (8–13%), gastrointestinal (18%), genitalia (36–60%), and brain (51–65%) defects, as well as skeletal dysplasia (14%) can also be present. Behavioral and psychiatric disorders, hearing, immunological and hormonal problems have also been observed [Grossfeld et al., 2004; Manolakos et al., 2009; Mattina et al., 2009; Seppänen et al., 2014; Akshoomoff et al., 2015; Favier et al., 2015]. Several patients with

Fig. 1. Features of the patient. **a** Patient at the age of 6 months. **b**, **c** Patient at the age of 1 year and 3 months.
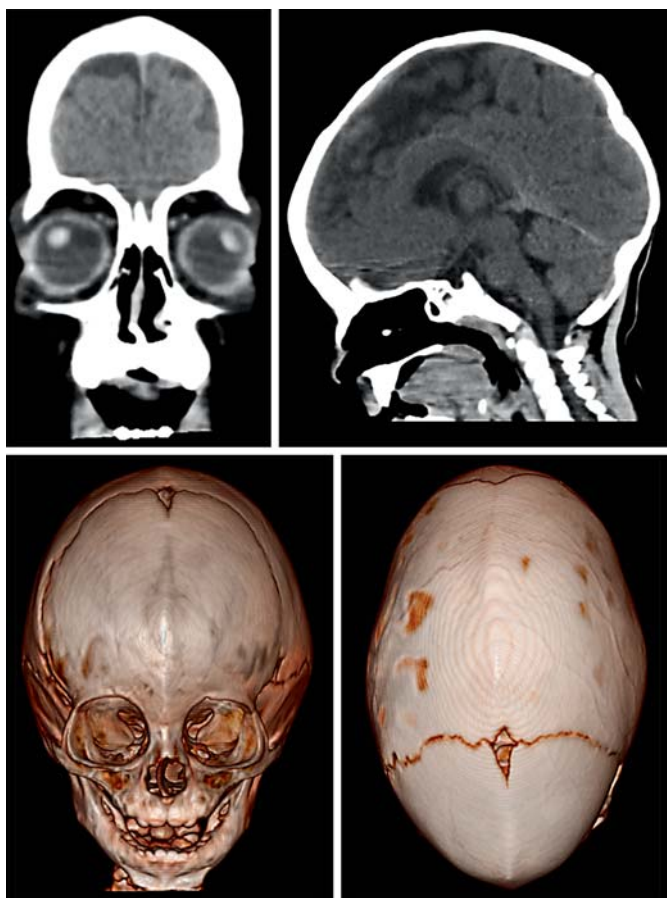

Fig. 2. CT of the brain. Cortico-subcortical atrophy, sagittal and metopic synostosis are observed.

11q23.3q25 deletions ranging in size from 2.8 to 14 Mb revealed by molecular karyotyping have been reported, but only 17 patients have complete clinical data [Wenger et al., 2006; Bernaciak et al., 2008; Tyson et al., 2008; Manolakos et al., 2009; Ji et al., 2010; Wu et al., 2010; Ye et al., 2010; Guerin et al., 2012, Trkova et al., 2012; Sheth et al., 2014; So et al., 2014; Xu et al., 2014; Malia et al., 2015; Maruani et al., 2015; Yamamoto et al., 2015]. The purpose of this study is to report the SNP microarray-based molecular characterization of a patient with a mild phenotype of JBS and a 11q23.3q25 deletion. We compared previous cases with molecular karyotyping and found that genotype-phenotype correlation was not present. This study also highlights the surgical complications due to unsuspected diagnosis and emphasizes the importance of molecular studies in patients with craniosynostosis.

Case Report

The proband, a 1 year/3-month-old Mexican male, is the third child of healthy, unrelated and young (34 and 30-year-old) parents. Family history was negative for intellectual disability or congenital malformations. No history of prenatal exposure to teratogens or maternal illness was recorded. After an uneventful pregnancy, he was born by abdominal delivery at 37 weeks' gestation with a weight of 2,950 g (10–25th centile), a length of 51 cm (75th centile). OFC was not recorded. Apgar scores were 8 and 9 at 1 and 5 min. He did not require special neonatal management. Dolichocephaly with craniosynostosis was detected at 2 months by the parents. At the age of 5 months, he underwent sagittal suterectomy which led to bleeding with hypovolemic shock and required a blood transfusion. Blood analyses showed normal platelet in numbers (134,000) with

medium platelet volume of 8.3 fl (7.5–10 fl), all other blood test results were within normal parameters. On physical examination (at 1 year and 3 months), his weight was 9,200 g (3rd percentile), length was 76 cm (10–25 percentile), and the OFC was 46.5 cm (25–50 percentile). He had trigonocephaly, eye exotropia, reverse epicanthic folds, narrow and high palate, broad nasal bridge, hypoplastic nares, thin upper lip, bilateral single palmar crease, valgus foot, overlapping of 1st on the 2nd toe in both feet, and right cryptorchidism (fig. 1). Audiological and ophthalmologic examinations were normal. The echocardiogram was normal. Blood analysis showed normal platelet in numbers (167,000) with medium platelet volume of 11 fl (7.5–10 fl); all other blood test results were in normal ranges. At this age, he underwent metopic suterectomy with profuse bleeding and hypovolemic shock which required a blood transfusion. Urine analyses and thyroid profile were normal.

CT scans of the brain showed cortico-subcortical atrophy, sagittal and metopic synostosis (fig. 2). At 9 months, the echocardiogram detected a mild tricuspid insufficiency. Currently, the boy needs assistance when standing up and only expresses some monosyllabic utterances.

Material and Methods

Metaphase slides were prepared from peripheral blood lymphocyte cultures from the patient and his parents, using standard methods. Chromosome analysis was performed by routine GTG-banding at ~500-band resolution.

Oligonucleotide-SNP array analysis using the GeneChip Human Cytoscan HD was carried out for the patient following the provided protocol (Affymetrix, Santa Clara, Calif., USA) and using the Affymetrix GeneChip Scanner 3000 7G. Data were analyzed using GTYPE (GeneChip Genotyping Analysis Software, 1.0.12 version) to detect copy number aberrations. The resolution of this procedure was estimated at 1.15 kb with 2.67 million probes.

Results

The proband's karyotype after GTG-banding was 46,XY,del(11)(q23q25) in 50 analyzed metaphases compatible with the diagnosis of JBS. Parental karyotypes were normal. The SNP array showed a 14.2-Mb deletion in chromosome 11q23.3q25 (120,706–134,938 Mb) which involved 163 RefSeq genes in the database of genomic variation, DGV database (http://projects.variation.tcag.ca/variation/hg38/); 62 genes are in the OMIM database (fig. 3), 8 of these genes *(TECTA, SCN3B, CDON, ST3GAL4, KIRREL3, KCNJ5, ETS1,* and *NTM)* have a heterozygous defect, and 13 genes have been associated to a recessive phenotype *(SC5D, UBASH3B, CLMP, CHEK1, SLC37A2, FEZ1, HYLS1, STT3A, FOXRED1, KCNJ1, ST14, JAM3,* and *ACAD8)*. The final cytogenetic result was 46,XY,del(11)(q23.3q25), arr [hg38] 11q23.3q25 (120,706,758–134,938,470)×1 dn.

Discussion

The diagnosis of our patient was JBS; clinically, our patient had mild motor delay, craniosynostosis, craniofacial dysmorphism, and a normal count and size of thrombocytes at 5 months of age. At 15 months of age, discretely larger thrombocytes, mild tricuspid insufficiency, cortico-subcortical atrophy, and cryptorchidism were observed. To date, 17 cases ranging in size from 2.8 to 14 Mb with 11q23.3q25 deletions revealed by molecular karyotyping and complete clinical data have been reported (table 1). These cases present craniofacial dysmorphism; developmental delay or intellectual disability; blood, growth and heart disorders, and brain defects similar to our case (table 1).

The 14.2 Mb-deletion of our patient includes 62 OMIM genes, 8 of them with a heterozygous expression pattern (table 2). Apparently, the platelet defect detected at 15 months, motor delay and mild tricuspid regurgitation could have a relationship with the *ST3GAL4, KIRREL3* and *ETS1* genes, respectively, although these findings are not always present in JBS with happloinsufficiency of these genes [Grewal et al., 2008; Ji et al., 2010; Bae et al., 2011; Luukkonen et al., 2012; Trkova et al., 2012; Sheth et al., 2014; So et al., 2014].

The principal genes involved in the Jacobsen phenotype seem to correspond to the *ST3GAL4, KIRREL3, NFRKB, FL1,* and *ETS1* genes. The *FLI1* gene, involved in the vascular and megakaryocyte differentiation, has been related to thrombocytopenia, although it has a recessive pattern [Spyropoulos et al., 2000; Trkova et al., 2012]. It is important to mention that the *FLI1* gene defect is the major cause of Paris-Trousseau syndrome (PTS); in vitro studies demonstrate that overexpression of *FLI1* in CD34(+) cells from PTS patients restores the megakaryopoiesis, indicating that *FLI1* hemizygous deletion contributes to the PTS hematopoietic defects [Raslova et al., 2004; Favier et al., 2015]. The *ETS1* and *NFRKB* genes have also been associated with thrombocytopenia, but there are no confirmatory studies. It is noteworthy that the *ST3GAL4* gene associated with thrombocytopenia has not been mentioned in any previous study; we consider that thrombocytopenia could be related to this gene defect in JBS [Grossfeld et al., 2004]. However, not all cases with a deletion in the *ST3GAL4* gene are diagnosed with thrombocytopenia [Ji et al., 2010; Trkova et al., 2012, Sheth et al., 2014; So et al., 2014]. This denotes that there is no genotype-phenotype correlation in JBS (table 1).

It is important to mention that the *BSX1* gene could be essential for global cognitive function, and when haplo-
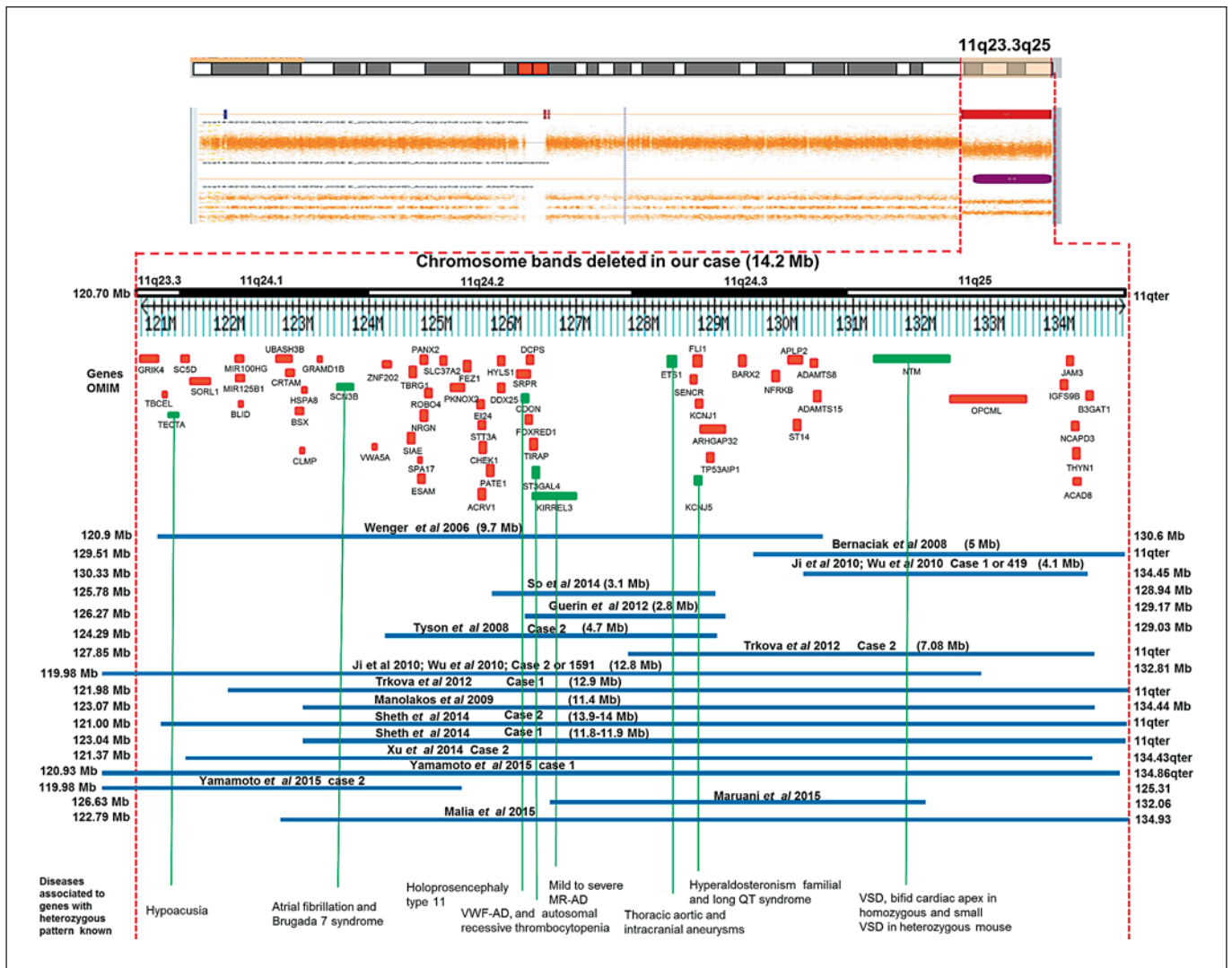
Fig. 3. CytoScan HD array and schematic representation of the result. The figure shows chromosome 11q23.3q25 and the relative position of the genes *(TECTA, SCN3B, CDON, ST3GAL4, KIRREL3, KCNJ5, ETS1,* and *NTM)* associated with heterozygous phenotypes (green) and the 13 genes *(SC5D, UBASH3B, CLMP, CHEK1, SLC37A2, FEZ1, HYLS1, STT3A, FOXRED1, KCNJ1, ST14, JAM3,* and *ACAD8)* associated with a phenotype with recessive manifes-tation in the deleted interval. The OMIM genes are shown in red. A partial molecular karyotype of the imbalance in chromosome 11 detected with the Human Cytoscan HD array is also illustrated. A single copy of the 14.2-Mb region was identified by log$_2$ ratio, copy number state and allele analysis. Some affected patients with dele-tion in the 11q23.3q25 region are also shown.

insufficiency of *BSX1* is present, this could result in severe mental retardation. In addition, a deletion of neuro-granin, a gene essential for synaptic plasticity and long-term potentiation, participates in the auditory attention deficit in most patients with 11q deletion [Coldren et al., 2009].

On the other hand, a previous report states that there is no correlation between the deletion size of 11q and the presence of autism, implicating a critical region in 11q, that includes the *RICS*, a gene encoding Rho GTPase-ac-tivating protein [Akshoomoff et al., 2015].

We consider that some genes, e.g. *KCNJ5* or *SCN3B*, have a negative dominant effect [Wang et al., 2010; Yang et al., 2010]; this leads to a mild or null defect in the phe-notype. Nevertheless, it is important to take into account the effects of haploinsufficiency of all affected genes in the

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Table 1. Comparison of clinical features in 17 cases of 11q23q25 deletion with molecular karyotyping

Reference	Growth/motor or intellectual delay[a]	Craniofacial dysmorphism[b]	Blood[c]	Heart[d]	Neurology disorder/brain image[e]	Other characteristics[f]	Size deleted, Mb	Molecular karyotyping	Sex/age
Present case	+/+	+	bleeding at 5 m by cranioplasty, borderline upper platelet at 8 m	mild tricuspid insufficiency	cortico-subcortical atrophy	cryptorchidism	14.2	SNP array	F/1 year
Wenger et al., 2006	+/+	+	thrombocytopenia at birth and 3 m, atypical megakaryocytes at 3 m	ADS, PDA, PAS, double outlet right ventricle	no expressive language at 2 y	exotropia, ptosis	9.7	BAC array	F/2 years
Bernaciak et al., 2008	–/+	+, mild	–	–	hyperintense white matter, hyperactivity, aggressiveness, pain indifference	–	5.4	aCGH	F/4 years
Tyson et al., 2008 Case 2	–/+	+	anemia	–	speech delay, white matter lesions	mild bilateral hearing loss	4.7	aCGH	M/7 years
Manolakos et al., 2009	–/–	+, mild	anemia, platelet aggregation and bleeding time abnormal	mitral valve regurgitation	speech delay, hypotonic	mild bilateral hearing loss, 5th finger short	11.4	SNP array	M/7.5 years
Guerin et al., 2012	–/+	+, mild	anemia, at 4 m thrombocytopenia spontaneous resolution, platelet ATP and dense granules decreased, giant granules present	VSD	ASD	–	2.8	aCGH	F/4 years
Trkova et al., 2012 Case 1	+/–	+	–	NR	NR	renal pelvis dilatation, right duplex renal system	12.9	SNP array	F/18 months
Case 2	+/–	+	severe thrombocytopenia at 4 w, anisocytosis and borderline macrocytosis at 8 m	NR	IV hemorrhage	short humerus and femur, left hypoacusia	7.08	SNP array	M/8 months
Ji et al., 2010; Wu et al., 2010 Case 1	+/+	+	–	–	+	–	4.1	SNP array	M/7 months
Case 2	–/+	+	–	+	NR	skeletal defects	12.8	SNP array	F/2 years
So et al., 2014	–/+	+, mild	–	–	PVNH, seizure, headaches	transverse limb defect, DM2, osteoarthritis	3.1	aCGH	F/67 years
Sheth et al., 2014 Case 1	+/+, mild motor <4 y, severe intellectual	+	–	VSD, tricuspid valve tags	hypotonia, speech delay, thin CC, white matter affected	broad, short and slight webbing neck, syndactyly, clinodactyly	11.9	aCGH	F/6.5 years

Table 1 (continued)

Reference	Growth/motor or intellectual delay[a]	Craniofacial dysmorphism[b]	Blood[c]	Heart[d]	Neurology disorder/brain image[e]	Other characteristics[f]	Size deleted, Mb	Molecular karyo-typing	Sex/age
Xu et al., 2014									
Case 2	–/–	–	–	single ventricle, single atrium, common atrio-ventricular valve	–	–	13.06	aCGH	fetus/24 weeks
Yamamoto et al., 2015									
Case 1	+/+	+	thrombocytopenia	–	abnormalities in the white matter	–	13.9	aCGH	F/5 years
Case 2	+/+	–	–	–	abnormalities in the white matter	ptosis, crypt-orchidism	5.3	aCGH	M/20 months
Maruani et al., 2015	–/–	–	–	–	decrease of grey matter, ASD	macrocephaly	5.4	SNP array	M/21 years
Malia et al., 2015	+/–	+	thrombocytopenia	Shone's complex	–	–	12.1	SNP array	F/36 months

+ = Phenotype present; – = phenotype absent; ADS = atrial defect septal; ASD = autism spectrum disorder; CC = corpus callosum; F = female; IV = interventricular; M = male; NR = phenotype not reported; PNVH = periventricular nodular heterotopia; VSD = ventricular septal defect. Candidate genes for the phenotype [a] *KIRREL3, BSX, NRGN, ARHGAP32*; [b] *BARX2*; [c] *ETS1, NFRKB, ST3GAL4, JAM3, FLI1*; [d] *ETS1, ADAMTS8, JAM3, ROBO4*; [e] *KIRREL3, ARHGAP32, NRGN, B3GAT1*; [f] *TECTA*: for deafness.

Table 2. Heterozygous gene defect in the deleted region 11q23.3q25

OMIM	Gene	Disease	Inheritance	Dosis
602574	*TECTA*	deafness	AD/AR	haploinsufficiency
608214	*SCN3B*	atrial fibrillation and Brugada 7 syndrome	AD	dominant negative/haploinsufficiency
608707	*CDON*	holoprosencephaly type 11	AD	haploinsufficiency
104240	ST3GAL4	reduction in plasma levels of von Willebrand factor and platelets/thrombocytopenia	AD/AR	haploinsufficiency
607761	*KIRREL3*	mental retardation	AD	haploinsufficiency
600734	KCNJ5	hyperaldosteronism familial and long QT syndrome	AD	dominant negative/haploinsufficiency
607938	*NTM*	thoracic aortic and intracranial aneurysms	AD	haploinsufficiency
164720	*ETS1*	small ventricular septal defect in mouse	AD	haploinsufficiency

AD = Autosomal dominant; AR = autosomal recessive.

phenotype as well as the presence of the epigenetic or environmental factors.

Our patient underwent surgery with severe complications (profuse bleeding) because JBS never was diagnosed. His surgery was necessary because of simple craniosynostosis, and this marks the importance of a genetic evaluation and meticulous medical semiology. Besides, it is very important to delineate the size of deletion of pa-tients with JBS using current molecular techniques. This will allow us to understand the genetic and clinical variability of the 11q phenotype.

In conclusion, the large variability in the breakpoints in 11q23q25 syndrome indicates the complexity of the JBS phenotype. In addition, an adequate medical evaluation is compulsory to avoid surgery complications.

Statement of Ethics

The protocol was approved by the Ethics Committee of the General Hospital of Mexico. Informed consent was obtained from the parents of the patient prior to the participation in the study.

Disclosure Statement

The authors have no conflict of interest to declare.

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