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PURE DISTAL 11q DELETION WITHOUT ADDITIONAL GENOMIC IMBALANCES IN A FEMALE INFANT WITH JACOBSEN SYNDROME AND A DE NOVO UNBALANCED RECIPROCAL TRANSLOCATION

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Summary: *Pure distal 11q deletion without additional genomic imbalances in a female infant with Jacobsen syndrome and a de novo unbalanced reciprocal translocation*
We report a neonate with pure deletion of distal 11q (11q23.3→qter) and Jacobsen syndrome. The patient had growth restriction, petechiae, thrombocytopenia, dilation of renal pelvis, congenital heart defects, and seizures. Array comparative genomic hybridization revealed a 15.8-Mb deletion from 11q23.3 to 11q25 without genomic imbalances in other chromosomes. Cytogenetic analysis revealed a karyotype of 46,XX,der(7)(7pter→7q32),der(11)(11pter→11q23.3::7q32→7qter). The parental karyotypes were normal. This is the first report of pure distal 11q deletion without additional genomic imbalances in a patient with Jacobsen syndrome and a de novo unbalanced reciprocal translocation.

Key-words: 11q deletion - Jacobsen syndrome - Reciprocal translocation.

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INTRODUCTION

Jacobsen syndrome (JBS) (OMIM 147791) is a contiguous gene syndrome caused by partial deletion of chromosome 11q23→qter, and may manifest clinical features of developmental delay, psychomotor retardation, craniofacial dysmorphisms of trigonocephaly, hypertelorism, a broad and flat nasal bridge, a carp-shaped mouth, micrognathia and low-set malformed ears, congenital heart defects of ventricular septal defects, truncus arteriosus and aortic arch defects, renal anomalies of renal duplication and hydronephrosis, ocular malformations of ptosis, colobomas, cataracts, glaucoma, strabismus and telecanthus, limb anomalies of talipes equinovarus, clino- or camptodactyly and syndactyly, a short neck, widely-spaced nipples, and thrombocytopenia or pancytopenia (6, 12, 15). JBS occurs in 1/100,000 births and has a female: male ratio of 2:1 (6, 12, 15-16). JBS may result from partial deletion of chromosome 11q associated with mirror duplication of the

other chromosome in case of an unbalanced translocation. Pure distal 11q deletion without additional genomic imbalances in case of a *de novo* unbalanced reciprocal translocation is unusual. Herein, we report such a case.

CASE REPORT

The 9-day-old female newborn was transferred to the medical center from a local hospital because of cyanosis, congenital heart defects, respiratory failure, petechiae, thrombocytopenia and seizures after birth. She was the third child of a 43-year-old healthy father and a 30-year-old healthy mother. Her 5-year-old brother and 3-year-old sister were both normal, and there was no family history of congenital malformations. Polyhydramnios was noted during the pregnancy. She was delivered at 37 weeks of gestation with a body weight of 2,530 g (< 3rd centile), a body length of 46.5 cm (3rd-15th centile) and a head circumference of 32.5 cm (3rd-15th centile). On examination, she had microcephaly, down-slanting palpebral fissures, epicanthic folds, a broad nasal ridge, a short nose, low-set posteriorly rotated ears, thin fingers and petechiae (Fig. 1). Brain ultrasound revealed bilateral ventriculostriatal vasculopathy and mild brain edema, renal ultrasound revealed dilation of renal pelvis, and cardiac ultrasound revealed mitral atresia, a single ventricle, a small left atrium, truncus arteriosus, total anomalous pulmonary venous returns and persistent left superior vena cava. Hematological studies showed thrombocytopenia with a platelet count of $63\times10^3/\mu L$ (normal: $140\text{-}450\times10^3/\mu L$). The prothrombin time was 14.3 seconds (normal: 8-12 seconds), and the activated partial thromboplastin time was 48.7 seconds (normal: 23.9-35.5 seconds). Cytogenetic analysis revealed a karyotype of 46,XX,der(7)(7pter→7q32),der(11)(11pter→

Figure 1. (A) and (B) The craniofacial appearance of the proband.

11q23.3::7q32→7qter) (Fig. 2). Oligonucleotide based-array comparative genomic hybridization (aCGH) using Human CGH 3×720K Whole-Genome Tiling v3.0 Array (Roche NimbleGen, Madison, WI, USA) revealed a 15.8-Mb deletion at chromosome 11q23.3-q25, or arr cgh (118,487,499 134,312,499 bp)×1 (UCSC hg18, NCBI, build 36, Mar. 2006) (Fig. 3). The chromosome 7 and other chromosomes did not have genomic imbalances. Polymorphic DNA marker analysis revealed a paternal origin of the 11q deletion. The infant died of heart failure at the age of 16 days. The parental karyotypes were normal.

DISCUSSION

In 85% of the reported cases of JBS, the 11q deletion is usually a *de novo* pure terminal deletion, whereas in the other 15% of the cases, the partial deletion of chromosome 11q results from familial or *de novo* unbalanced translocations, ring chromosomes, recombination of parental inversions (12). The peculiar aspect of the present case is a paternally derived pure 11q deletion associated with a *de novo* reciprocal translocation with a loss of the translocated segment of 11q (11q23.3→qter). Such an occurrence has not previously been described in patients with JBS.

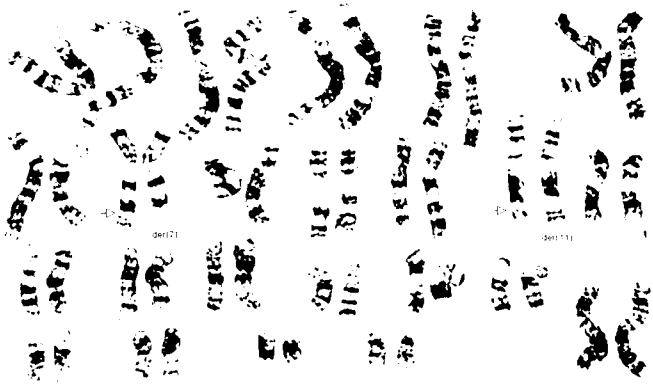

Figure 2: A karyotype of 46,XX,der(7)(7pter→7q32)(der11)(11pter→11q23.3::7q32→7qter)

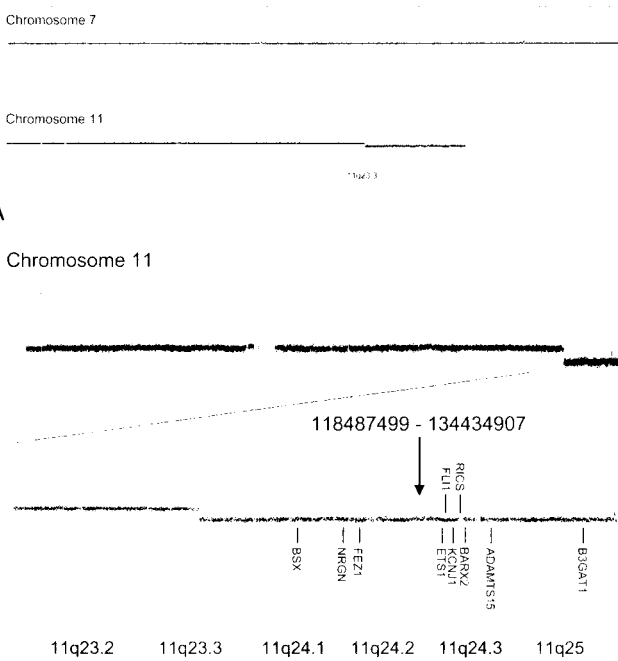

Figure 3: (A) Oligonucleotide based-array comparative genomic hybridization (aCGH) using Human CGH 3×720K Whole-Genome Tiling v3.0 Array (Roche NimbleGen, Madison, WI, USA) reveals a 15.8-Mb deletion at chromosome 11q23.3-q25, or arr cgh (118,487,499 – 134,312,499 bp)×1. The chromosome 7 does not have genomic imbalance. (B) Amplification of the ideogram and aCGH with the relevant genes associated with the phenotype. The position of genes is from UCSC the human, March 2006 assembly.

The present case had a large 15.8-Mb deletion encompassing the region of 11q23.3→qter and a breakpoint (118,487,449 bp) centromeric to the *CBL* gene (118,582,200 – 118,684,869 bp) and telomeric to D11S924 (116,598,922 – 116,599,171 bp). The present case had a paternal origin

of the deletion. It has been suggested that there is parental bias towards the 11q deletion in JBS (13, 15). For example, the origin of the 11q deletion is more likely to be paternal when the breakpoint is telomeric to D11S924, while there is maternal bias when the breakpoint is centromeric to D11S924. The paternal origin of the 11q deletion in association with a breakpoint telomeric to D11S924 in the present case is consistent with the previous observations. The present case had a breakpoint close and centromeric to the proto-oncogene *CBL2*. The *FRA11B* folate-sensitive fragile site has been localized to the $p(CCG)_n$ trinucleotide repeat in the 5' untranslated region of *CBL2* at 11q23.3 (8-9). It is hypothesized that imprinting is involved in the methylation and the expansion of the CCG repeat at the *FRA11B* (9, 12, 15).

The present case was associated with petechiae, thrombocytopenia, dilation of renal pelvis, complex congenital heart defects and seizures after birth, and had haploinsufficiency of the genes of *BSX* at 11q24.1, *NRGN* and *FEZ1* at 11q24.2, *ETS1*, *FLI1*, *KCNJ1*, *RICS*, *BARX2*, and *ADAMTS15* at 11q24.3, and *B3GAT1* at 11q25.

FLI1 (OMIM 193067), a proto-oncogene, is responsible for FLI1, a member of the ETS family of transcription factors. Dysregulation of FLI1 will cause neoplasms. For instance, transcriptional activation of *FLI1* gene by chromosomal translocation of t(11;22)(q24;q12) will generate FLI1/EWS fusion protein and cause Ewing sarcoma, and insertional activation of the *FLI1* gene by leukemia virus will cause erythroleukemia (1-2). On the other hand, FLI1 is required for vascular integrity and megakaryocytic development (7). Heterozygous deletion of the *FLI1* gene has been noted in Paris-Trousseau thrombocytopenia (5). Thrombocytopenia in patients with JBS is due to dysmegakaryopoiesis caused by hemizygous loss of the *FLI1* gene (12).

ETS1 (OMIM 164720) is responsible for ETS1, a member of the ETS family of transcription factors. *ETS1* is expressed in the endocardium and neural crest during early cardiac development in mice (20). Ye *et al.* (20) found that gene-targeted deletion of *ETS1* in mice caused ventricular septal defects and abnormal ventricular morphology, and proposed that the cardiac lesions in patients with JBS is associated with hemizygosity for the *ETS1* gene due to 11q deletion.

KCNJ1 (OMIM 600359) is responsible for an inward-rectifying apical potassium channel expressed in the thick ascending limb of Henle and throughout the distal nephron of the kidney. Homozygous or compound heterozygous mutations of the *KCNJ1* gene are associated with antenatal Bartter syndrome (17). *ADAMTS15* (OMIM 607509) is responsible for ADAMTS15, a member of the large ADAMTS family of zinc-dependent protease which is expressed in fetal liver and kidney (4). Deletion of *KCNJ1* and *ADAMTS15* may contribute to the renal

anomalies associated with JBS (18).

BARX2 (OMIM 604823), a homeobox gene, is expressed in neural and craniofacial structures during development (10). *FEZ1* (OMIM 604825) is involved in axonal outgrowth and fasciculation (3). *NRGN* (OMIM 602350) is expressed only in brain (11). *B3GAT1* (OMIM 151290) is responsible for a neuronally expressed HNK1 carbohydrate epitope that contains a sulfoglucuronyl residue. The HNK1 epitope is widely expressed in cerebral cortex, hippocampus and cerebellum (19). *RICS* (OMIM 608541) is responsible for a neuron-associated GTPase-activating protein that may regulate dendrite spine morphology and strength by modulating Rho GTPase activity (14).

In summary, we present pure distal 11q deletion without additional genomic imbalances in a female infant with JBS and a *de novo* unbalanced reciprocal translocation. Neonatal observation of growth restriction, petechiae, thrombocytopenia, pelvic dilation and congenital heart defects should alert JBS and prompt cytogenetic investigation of partial 11q deletion.

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