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Original article

Subtle familial translocation t(11;22)(q24.2;q13.33) resulting in Jacobsen syndrome and distal trisomy 22q13.3: further details of genotype–phenotype maps

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Abstract. We report on 3 kindred patients with terminal 11q monosomy and distal 22q trisomy involving the *SHANK3* gene, resulting from a subtle familial translocation t(11;22)(q24.2;q13.33). The patients presented with the characteristic symptoms of Jacobsen syndrome (JBS), including: mental retardation, short stature, and craniofacial dysmorphism in all 3 cases; cardiac defects in 2 cases; and thrombocytopenia, brain abnormality, eye coloboma, recurrent infections, cryptorchidism and toe anomalies in single cases. The oldest patient also had Hashimoto disease and diabetes mellitus type 2. So far, these 2 conditions have not been reported in adult patients with JBS. Features typical for distal 22q trisomy in our patients include muscular hypotonia and prenatal failure to thrive, seen in 2 and 1 cases, respectively. We also present a family member with 11q24.2-qter trisomy and 22q13.33-qter monosomy, whose clinical phenotype is partially overlapping with several dysmorphic features of JBS. In addition, multiple pregnancy losses and infantile deaths occurred in this family, suggesting that these chromosomal imbalances may produce a lethal phenotype. FISH with a panel of BAC probes determined the accurate sizes of the deletion 11q (9.9 Mb) and trisomy 22q (0.8 Mb). To date, only 5 cases of submicroscopic 22q13.3-qter trisomy have been reported. A detailed clinical description of our patients, along with a precise cytogenetic designation of chromosomal breakpoints, allow further refinement of genotype-phenotype correlation for distal imbalances in 11q and 22q.

Keywords: chromosomal translocation, Jacobsen syndrome, partial monosomy 11q24.2, partial trisomy 22q13.33, recurrent pregnancy loss.

Introduction

The contiguous gene deletion disorder caused by a terminal deletion of the long arm of chromosome 11, also known as Jacobsen syndrome (JBS), has been described in more than 100 patients. The spectrum of clinical symptoms observed in patients with JBS is variable, and depends on the size of the deletion. The most common features of JBS include mild to moderate developmental delay, postnatal growth retardation, cardiac defects, thrombocytopenia or pancytopenia with platelet dysfunction (Paris-Trousseau syndrome), hand/foot anomalies, and dysmorphic facies (Grossfeld et al. 2004; Leegte et al. 1999; Penny et al. 1995). In the majority (70–80%) of patients affected with JBS, chromosomal breakpoints were mapped in sub-band 11q23.3 (Grossfeld et al. 2004; Michaelis et al. 1998) and clinical characterization of individuals with more distal 11q deletions is established to a lesser extent.

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Trisomies of 22q13.3-qter involving the *SHANK3* gene are exceedingly rare. To our knowledge, only 5 cases of submicroscopic 22q13.3-qter duplication have been reported in the literature. Abnormalities described in those patients included intrauterine growth retardation, short stature, microcephaly, facial dysmorphism, congenital heart defects, cleft palate, feeding difficulties with failure to thrive, developmental delay, and muscular hypotonia (Wieczorek et al. 1998; Feenstra et al. 2006; Okamoto et al. 2007). Interestingly, hypotonia and global developmental delay are also common in patients with monosomy of the telomeric 22q13 region (Phelan-McDermid syndrome) (Phelan et al. 2001). Bonaglia et al. (2006) reported that recurrent terminal deletion breakpoints in those patients are localized within the *SHANK3* gene. Abnormal *SHANK3* dosage is hypothesized to be responsible for severe cognitive deficits, including language and speech disorder, as well as autistic behavior (Bonaglia et al. 2001; Durand et al. 2007).

We report here on 3 family members with 11q24.2-qter monosomy and 22q13.33-qter trisomy, due to an unbalanced product of the familial chromosomal translocation t(11;22)(q24.2;q13.33). We also present a clinical phenotype of a reciprocal 11q24.2-qter trisomy concomitant with 22q13.33-qter monosomy, as well as depict the reproductive history of this family. Precise cytogenetic designation of chromosomal breakpoints, along with the detailed clinical description of our patients enables a further refinement of karyotype–phenotype correlation for partial trisomy of distal 22q and partial monosomy of distal 11q.

Patients, materials, methods

Clinical reports

Patient 1 (V:4, Figure 1a, Table 1) – the proband – is a 4-year-old boy born by vaginal delivery after an uneventful pregnancy (G3P3) at 40 weeks gestation to a nonconsanguineous and healthy 23-year-old mother and a 30-year-old father. At birth, his weight was 2300 g (<3rd percentile), length 47 cm (<3rd percentile), head circumference 33.5 cm (10th–25th percentile), and Apgar scores were 5, 5, and 7 (at 1, 3, and 5 min, respectively). Physical examination showed right cryptorchidism, hypospadias, small penis, muscular hypotonia, and cardiac murmur. Cardiac

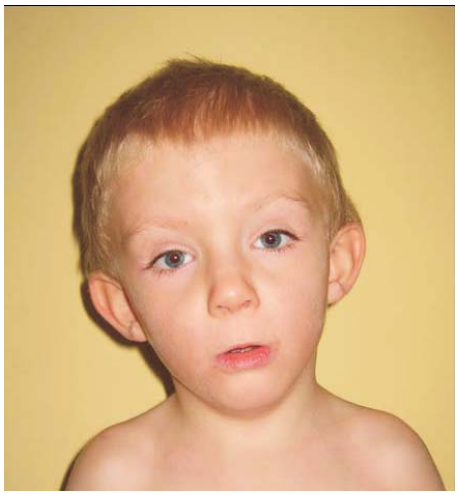

Figure 1a. Proband (Patient 1) at the age of 4 years

sonography revealed a trace atrial septal defect (ASD), which closed spontaneously a year later. Result of a karyotype analysis performed at the age of 2 years was normal (resolution of 450 bands per haploid genome). Developmental milestones were delayed (sitting and walking achieved at 10 and 16 months, respectively). The boy was first investigated in the genetic clinic at the age of 4 years. His measurements were: weight 13.4 kg (<3rd percentile), length 94 cm (<3rd percentile), head circumference 49 cm (3rd percentile). He presented with facial dysmorphic features typical of JBS. Triangular face, ocular hypertelorism, down-slanting palpebral fissures, bilateral ptosis, divergent strabismus, scanty eyebrows, short nose with wide nasal bridge and anteverted nares, thin upper vermillion boarder, flat philtrum, abnormal dentition with extremely short upper and shortened lower incisors (Figure 1b), and low-set dysplastic pinnae were noted. According to psychological evaluation, mental retardation was moderate, with severe speech delay. Expressive speech delay was more pronounced than receptive. In addition to this, attention deficit hyperactivity disorder (ADHD) was recognized. Repeated laboratory examinations of complete blood count,

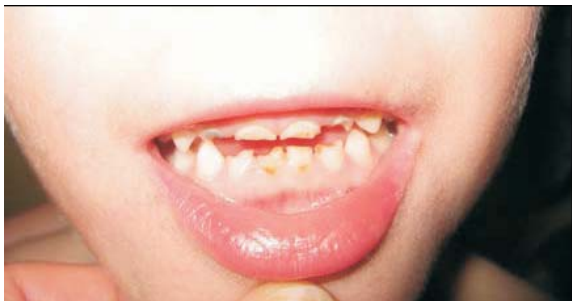

Figure 1b. Abnormal dentition with shortened upper and lower incisors

Table 1. Clinical characterization of the presented cases with reference to the most frequent symptoms described in partial 11q monosomy (Grossfeld et al. 2004) and partial 22q13.3 trisomy (Feenstra et al. 2006; Okamoto et al. 2007)

Frequent clinical findings in:partial 11q monosomy partial 22 q trisomy	Patient 1 (male)	Patient 2 (female)	Patient 3 (female)	Phenotype of 11q deletion (according to Grossfeld et al. 2004)	Phenotype of dup22q(q13.3-qter) (according to Feenstra et al. 2006 and Okamoto et al. 2007)
Developmental delay	+	+	+	85%	5/5
Growth deficiency/short stature	+	+	+	68%	5/5
Cardiac defect	+	-	+	56%	2/5
Abnormal brain MRI	+	-	-	51%	1/5
Thrombocytopenia/Paris-Trousseau syndrome	–	–	+/–	94% / 93%	NR
Toe abnormalities	–	–	+	83%	NR
Cryptorchid testes	+	NA	NA	58%	NR
Recurrent infections	–	–	+	54%	NR
IGF-1 deficiency	–	–	–	50%	NR
Chronic constipation	–	–	–	42%	NR
Small for gestational age	+	–	–	NR*	2/5
Muscular hypotonia	+	–	+	NR	3/5
Cleft palate(high-arched palate)	–	–	–	NR	2/5 (2/5)
Microcephaly	–	–	–	NR	4/5
Sparse and fine hair	–	–	–	NR	2/5
Facial dysmorphism:					
Hypertelorism	+	+	+	92%	4/5
Down-slanting palpebral fissures	+	+	+	83%	2/5
Wide nasal bridge	+	+	+	91%	3/5
Prominent forehead	+	–	+	62%	4/5
Micro- and/or retrognathia	–	+	+	36%	1/5
Low-set malformed pinnae	+	+	+	81%	3/5
Thin vermillion boarder	+	+	+	84%	NR
Strabismus	+	+	–	67%	NR
Ptosis	+	+	+	58%	NR
Scanty eyebrows	+	+	–	50%	NR
Short nose	+	+	–	69%	NR
Anteverted nostrils	+	+	+	64%	NR
Dental anomalies	+	–	+	50%	NR
Prominent upper lip	–	–	–	NR	2/5

Clinical findings common for both 11q monosomy and 22q13.3 duplication syndromes are bolded; features described solely in dup22q13.3 are in italics; symptoms exclusive for 11q- are shown in normal type. NA = not applicable; NR = not reported;* single parameters occasionally below 3rd percentile

platelets (ranging from 15.0 to 39.5×10^9 L^{-1}), bleeding time test (BTT), TSH, and IGF-1 (76.5 ng mL^{-1} at 5 years of age) were normal. Abdominal ultrasound, hearing tests, and EEG were unremarkable. Ophthalmologic examination confirmed strabismus divergens. MRI of the brain revealed an area of hypomyelination/dysmyelination or vascular lesion of the right hemisphere, small foci of perivascular gliosis, and posterior fossa arachnoid cyst.

Patient 2 (V:1, Figure 2, Table 1) – first cousin of the proband – is a girl delivered vaginally (G1P1) from a breech presentation at 41 weeks gestation to a young, healthy and nonconsanguineous couple (20-year-old mother and 21-year-old father). The pregnancy was uneventful. Birth measurements were: 2800 g (3rd–10th percentile), length 52 cm (75th–90th percentile), head circumference 35 cm (50th–75th percentile), and Apgar score was 10 at 1 min. Cardiac murmur was noted, but echocardiography excluded the presence of congenital heart anomaly. In infancy, muscular hypotonia and failure to thrive were conspicuous. Motor development was normal, but speech was markedly delayed. Chromosome study (400 bands) was normal. The girl was operated on at the age of 6 years for congenital bilateral ptosis. Upon the first clinical genetic examination at the

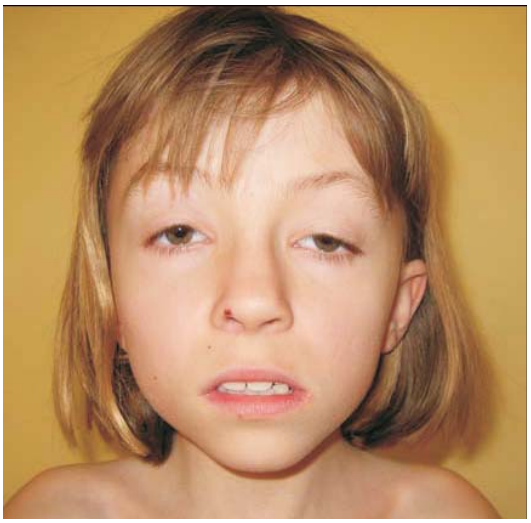

Figure 2. Patient 2 at the age of 9½ years

Figure 3. Patient 3 at the age of 24 years

age of 9.5 years, her stature was proportionally short: weight was 22 kg, length 123 cm (both <3rd percentile), and head circumference 50.5 cm (3rd percentile). Facial dysmorphism included triangular face, hypertelorism, down-slanting palpebral fissures, bilateral ptosis, sparse eyebrows, short nose with wide nasal bridge and anteverted nares, thin vermillion boarder, flat philtrum, micrognathia, and low-set dysplastic ears. Mild mental retardation was observed. Ophthalmologic investigation disclosed bilateral hypermetropia (+1.5 Dsph), strabismus convergens, and bilateral choroidal coloboma. On laboratory tests, complete blood count, platelets (1.53×10^9 L^{-1}), BTT, blood glucose, TSH, GH, and IGF-1 (220 ng mL^{-1} at the age of 10 years) were normal. MRI of the brain, abdominal ultrasound, and hearing tests were inconspicuous.

Patient 3 (IV:5, Figure 3, Table 1) – the proband's aunt – was first seen in our genetic clinic at the age of 24 years. She was born by vaginal delivery after an uneventful pregnancy (G3 P3) at 42 weeks gestation. The parents were young (24-year-old mother and 25-year-old father), healthy, and nonconsanguineous. Birth weight was 2900 g (10th percentile), length 50 cm (25th–50th percentile), head circumference 35 cm (50th percentile), and Apgar score 10 at 1 min. Neonatally, there were feeding difficulties and hypotonia. Psychomotor development was markedly delayed, with independent sitting and walking achieved at 18 and 24 months of age, respectively. Throughout her first few years of life, the girl suffered from recurrent respiratory infections and failed to thrive. Result of a karyotype analysis (400 bands) performed at that time was normal. Heart sonography at 10 years revealed mild aortic stenosis (AS) and mild to moderate tricuspid valve insufficiency (TI). X-ray disclosed kyphoscoliosis of thoracic and lumbar segments of the vertebral column. Laboratory tests showed repeated mild thrombocytopenia (from 10.6×10^9 $L^{-1}$to 13.2×10^9 L^{-1}), with occasional results within the normal range (the highest $1.66 \times 10^9 L^{-1}$). The other hematological values, as well as BTT and IGF-1 (125 ng mL^{-1} at 24 years) were normal. At 20 years, she exhibited the clinical symptoms of hypothyroidism. TSH appeared to be increased and an ultrasound scan of the thyroid gland was suggestive of Hashimoto disease. At 23 years, the patient developed type II diabetes mellitus. Physical examination at the age of 24 showed: weight 57 kg (50th percentile), short stature 152 cm (<3rd percentile), head circumference 55 cm (10th–25th percentile), and borderline BMI (24.7 kg m^{-2}). Facial abnormalities consisted of triangular face, hypertelorism, down-slanting palpebral fissures, bilateral ptosis, wide nasal bridge with anteverted nostrils, thin upper vermillion boarder, flat philtrum, low-set malformed pinnae, abnormal dentition with short incisors, and retrognathia. Brachydactyly of the feet affecting 3rd, 4th, and 5th toes, and generalized hirsutism were noted. According to psychological assessment, she presented with moderate mental retardation. MRI of the brain disclosed the presence of the cavum septum pellucidum, which was described as a normal variant. Hearing test showed mild right hypoacusis. Ophthalmologist diagnosed bilateral myopia (–1.5 Dsph). Abdominal ultrasound was unremarkable.

Patient 4 (III:2, Figure 4) – the proband's maternal grandmother's sister – was investigated at 43 years of age. She had proportionate short stat-

ure and severe mental retardation with absent speech. She presented with facial dysmorphic features, such as hypertelorism, bilateral ptosis, low-set dysplastic ears, short and smooth philtrum, thin vermillion boarder, and shortened upper incisors. Complete blood count was normal.

Review of the history of the proband's family revealed the presence of a congenital heart defect (partial atrioventricular septal defect) in his older brother (V:2), successfully operated at 3 years of age. Upon investigation in the genetic clinic at the age of 7 years, the proband's brother exhibited no signs of facial dysmorphism and demonstrated normal psychomotor and somatic development. Results of his karyotype and FISH studies were normal.

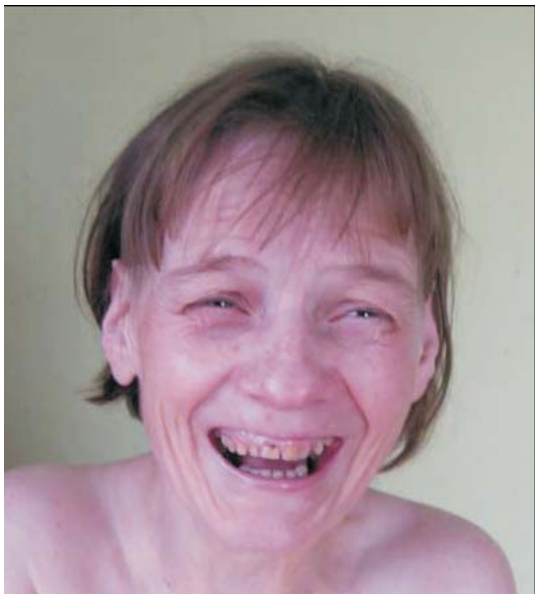

Figure 4. Patient 4 at the age of 43 years

The second pregnancy of the proband's mother resulted in a premature male (V:3) delivered vaginally at 28 weeks gestation. His weight was 470 g (<3rd percentile), length 36 cm (10th–25th percentile), head circumference 25 cm (25th–50th percentile). Apgar score was 1 at 1 min, but after external heart massage with intubation and oxygen supplementation it raised to 4, 5 and 7 (at 3, 5 and 10 min, respectively). The neonate died on day 2. An autopsy revealed ventricular septal defect (VSD) and bilateral suprarenal hemorrhage.

The pedigree of the family was striking (Figure 5). Patient 3's mother (III:4) had 11 siblings, but 5 of them died shortly after birth (III:9,10,13–15) and 2 in infancy (III:5,6), all for unknown reasons. She also had 2 severely mentally retarded sisters, one of whom (Patient 4, III:2) was examined by us. The other sister died at the age of 49 years prior to referral to our genetic clinic. Furthermore, out of 13 pregnancies of maternal grandparents of Patient 3's mother, 12 resulted in spontaneous abortions (II:1–12).

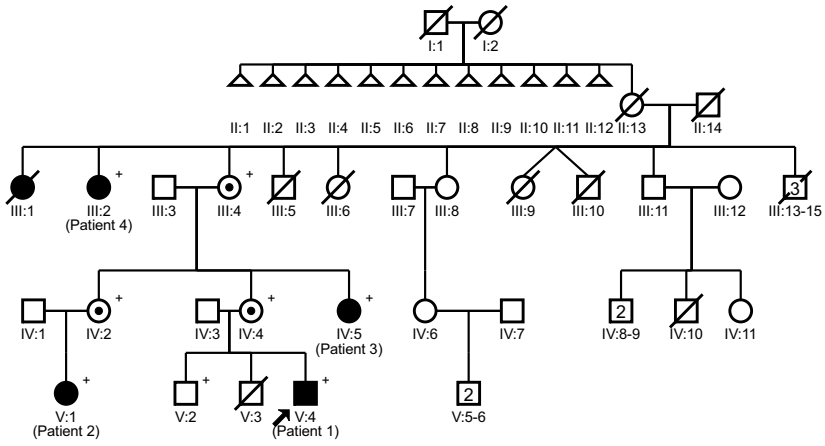

Figure 5. Family pedigree with FISH results. Patients with mental retardation and facial dysmorphism are marked by solid symbols. V:1, V:4, and IV:5 are patients with symptoms of Jacobsen syndrome with der(11)t(11;22)(q24.2;q13.33). III:2 is a patient with der(22)t(11;22)(q24.2;q13.33); III:4, IV:2, IV:4 are healthy mothers, the carriers of a balanced translocation t(11;22)(q24.2;q13.33), shown by black dots inside the symbols. II:1-12 were spontaneous abortions; + indicates family members available for karyotype and/or FISH testing.

Cytogenetic analysis

Fluorescence *in situ* hybridization (FISH) study was performed with probe TUPLE-1 (Vysis), specific to the DiGeorge syndrome region. Two signals from TUPLE-1 were noted, whereas the control

22qter probe yielded 3 signals, with the additional one localized on chromosome 11q. Conventional GTG banding of parental peripheral blood lymphocytes with a high resolution of 850 bands showed in his mother an apparently balanced reciprocal translocation t(11;22) (q24.2;q13.33). Paternal chromosomes were normal. Re-evaluation of the proband's chromosomes (550 bands) revealed an abnormal karyotype with an unbalanced translocation:46,XY,der(11)t(11;22)(q24.2;q13.33)mat.

Table 2. Results of the FISH study performed in Patients 1, 2 and 3. List of the BAC clones used for the analyses with their location on chromosomes 11 and 22.

BAC clone	Band	Distance from qter *	FISH results in Patients 1, 2, and 3
Chromosome 11			
RP11-87O12	11q24.1	11.7 Mb	disomic
RP11-688B18	11q24.1	11.3 Mb	disomic
RP11-207E8	11q24.1-24.2	10.9 Mb	disomic
RP11-624A13	11q24.2	10.3 Mb	disomic
RP11-664I21	11q24.2	10.1 Mb	disomic
RP11-687M24	11q24.2	9.9 Mb	disomic (breakpoint)
RP11-100P11	11q24.2	9.8 Mb	monosomic
RP11-417F7	11q24.2	9.7 Mb	monosomic
RP11-57M13	11q24.2	9.5 Mb	monosomic
RP11-712D22	11q24.2	9.4 Mb	monosomic
RP11-115C10	11q24.2	8.4 Mb	monosomic
RP11-651F18	11q24.2	8.3 Mb	monosomic
RP11-744N12	11q24.3	6.3 Mb	monosomic
RP11-507F16	11q24.3	5.2 Mb	monosomic
RP11-678L3	11q24.3	4.2 Mb	monosomic
RP11-419F8	11q25	2.1 Mb	monosomic
Chromosome 22			
RP5-925J7	22q13.32	1.9 Mb	disomic
RP11-46J14	22q13.32	1.8 Mb	disomic
CTA-722E9	22q13.32-13.33	1.4 Mb	disomic
RP11-697C11	22q13.33	1.2 Mb	disomic
RP11-931F19	22q13.33	0.8 Mb	trisomic (breakpoint)
RP3-402G11	22q13.33	0.7 Mb	trisomic
RP11-164E23	22q13.33	0.5 Mb	trisomic
RP1-99K24	22q13.33	terminal	NP

* counted from the middle of the BAC clone
NP = not performed

GTG banding of other family members, at a resolution of at least 550 bands per haploid genome, revealed der(11)t(11;22)(q24.2;q13.33)mat in Patients 2 and 3, and der(22)t(11;22)(q24.2;q13.33) in Patient 4. Mothers of Patients 2 and 3 both were carriers of a balanced reciprocal translocation t(11;22)(q24.2;q13.33).

To determine the exact size of the deletion and duplication, a panel of 16 BAC clones specific for distal 11q, and 7 BAC probes specific for distal 22q, was identified from the existing physical maps (UCSC genome browser, http://genome.ucsc.edu). FISH was performed on PHA-stimulated peripheral blood lymphocytes according to standard protocols (Shaffer et al. 1997). Molecular cytogenetic studies performed in Patients 1, 2, and 3 mapped the chromosome 11 breakpoint to 11q24.2 between 2 overlapping BAC clones RP11-687M24 and RP11-100P11. The fluorescent signal for RP11-687M24 present on chromosome der(11) was faint, indicating that the breakpoint maps within this clone. Therefore, the size of the monosomic 11q fragment is ~9.9 Mb. The chromosome 22 breakpoint was localized in 22q13.33, between BAC probes RP11-697C11 and RP11-931F19. The fluorescent signal for RP11-931F19 on chromosome der(22) was faint, indicating that the breakpoint maps within this clone. Hence, the size of the trisomic 22q fragment was estimated as ~0.8 Mb (Table 2).

Discussion

We report on 3 closely related patients – the proband (Patient 1), his cousin (Patient 2), and their aunt (Patient 3) – with an identical unbalanced translocation der(11)t(11;22) (q24.2;q13.33) resulting in partial monosomy 11q24.2-qter and partial trisomy 22q13.33-qter. We determined the sizes of the 11q deletion as 9.9 Mb, and trisomy 22q as 0.8 Mb (Table 2). Their mothers were carriers of the corresponding reciprocal translocation, detected by conventional high-resolution GTG banding.

Although our patients' phenotypes are caused by a combination of imbalances involving 2 chromosomal regions, the trisomic fragment 22q13.33-qter is very small (0.8 Mb). However, duplication of *SHANK3* gene is a strong candidate for impaired social development (Durand et al. 2007). Most of the phenotypic features observed in our patients, in particular facial dysmorphism, were suggestive of 11q monosomy syndrome (JBS). Comparison of the clinical findings seen in our patients with symptoms described for JBS as well as for 22q13.3-qter trisomy is shown in Table 1. Features that occur in both partial 11q monosomy and distal 22q13.3 trisomy include developmental delay/mental retardation, short stature, cardiac defects, brain abnormality, and such facial dysmorphic features as prominent forehead,

hypertelorism, wide nasal bridge, micro- and retrognathia, and low-set dyplastic ears. These symptoms were excluded from the attempt to establish karyotype–phenotype correlations either for partial 11q monosomy, or for 22q trisomy.

Karyotype–phenotype correlations in distal 22q13.3 trisomy

Very little is known about the clinical phenotype of the smallest 22q (22q13.3-qter) trisomy. Only 5 patients with this chromosomal abnormality have been reported to date, thus the clinical phenotype of this imbalance is currently being established. Mental retardation and short stature were present in all these patients, whereas microcephaly, prominent forehead, and hypertelorism were seen in 4 cases. Hypotonia and low-set malformed ears were observed in 3 patients, while 2 out of 5 patients suffered from intrauterine growth retardation, cardiac defects, cleft lip and/or palate, sparse and fine hair, wide nasal bridge, and prominent upper lip. Brain abnormality (white-matter lesions) and micro- and retrognathia were described only in a single case (Wieczorek et al. 1998; Feenstra et al. 2006; Okamoto et al. 2007). This phenotype exhibits a partial overlap with larger 22q distal trisomies. For example, microcephaly and sparse, fine hair are almost universal findings in pure trisomy 22q11.2-qter. Cleft lip and/or palate and muscular hypotonia are also frequently observed (Wieczorek et al. 1998; Rivera 1989; Barajas-Barajas et al. 2004; Feenstra et al. 2006). None of our patients presented with microcephaly, sparse and fine hair, and orofacial clefts, suggesting localization of the underlying genes proximal to the most terminal 0.8 Mb of 22q. Conversely, 2 out of 3 our patients suffered from muscular hypotonia, indicating a possible link of this feature with the presence of most distal 0.8 Mb trisomy 22q encompassing the *SHANK3* gene. Hypotonia is also a common finding in patients with monosomy of the telomeric 22q13 region (Phelan-McDermid syndrome, PMS) (Phelan et al. 2001). Haploinsufficiency of the *SHANK3*, which is predominantly expressed in the cerebral cortex and the cerebellum and plays a role in synaptogenesis, was proposed as a causative factor of various neurological PMS symptoms, including developmental delay, absent speech, autism, and hypotonia (Bonaglia et al. 2001; Durand et al. 2007). Moreover, Durand et al. (2007) reported on a boy with 22qter partial trisomy and autism spectrum disorder (Asperger syndrome) suggesting dosage-sensitivity of the *SHANK3* gene. Since none of our patients presented with autistic behavior, overexpression of *SHANK3* does not always result in autism. However, dosage-sensitivity of this gene could account for the frequent presence of hypotonia in both 22q13-qter monosomy and microduplication.

Karyotype–phenotype correlations in 11q24.2 partial monosomy

Terminal deletions of the long arm of chromosome 11 produce a clinically distinguishable phenotype, known also as JBS. The spectrum of this chromosomal condition include developmental delay/mental retardation, short stature, thrombocytopenia with Paris-Trousseau syndrome, pancytopenia, congenital heart defects, brain abnormalities, cryptorchidism, digit anomalies, IGF deficiency, recurrent infections, and specific facial dysmorphism described in more detail in Table 1 (Jacobsen et al. 1973; Penny et al. 1995; Lewanda et al. 1995; Leegte et al. 1999; Grossfeld et al. 2004; Haghi et al. 2004). In about 70–80% of patients reported to have JBS, breakpoints were localized in sub-band 11q23.3, within the CCG repeat of heritable folate-sensitive fragile site (FRA11B) (Jones et al. 1994; Michaelis et al. 1998; Grossfeld et al. 2004). Thus, the most frequently observed size of the deletion was approximately 15.8 Mb. On the basis of breakpoint analyses in clinically well-described individuals, Grossfeld et al. (2004) proposed critical regions for some of the most common JBS features. Clinical characteristics of our patients are consistent with the maps for cryptorchidism, recurrent infections, and thrombocytopenia, presented by Grossfeld et al. (2004). Although only 1 out of 3 our patients presented with recurrent infections and mild and transient thrombocytopenia (Patient 3), the others did not, most probably due to reduced penetrance of these features. Moreover, in JBS, platelets usually increase with age, so one cannot exclude that in our patients platelet counts were low in infancy and improved substantially to normal or near-normal levels (Aalfs et al. 1999; Grossfeld et al. 2004). On repeated examinations of our patients, no bleeding propensity suggestive of persistent platelet dysfunction (Paris-Trousseau syndrome), typical for JBS, was observed. However, detailed studies of platelet functioning that could rule out Paris-Trousseau syndrome were not performed.

Furthermore, we suppose that our findings enable further refinement of karyotype–phenotype correlations for some JBS symptoms, such as den-

tal anomalies, seen in Patients 1 and 3, and several other dysmorphic features (Table 1). We suppose that the responsible chromosomal loci may lie telomeric to BAC clone RP11-687M24. In addition, according to Grossfeld et al. (2004), ptosis and ocular coloboma were associated only with the largest 11q deletions. That finding contrasts with the presence of congenital ptosis in all 3 our patients, as well as of ocular coloboma in Patient 2. Therefore, it is possible that some genetic modifiers lying distal to the underlying genes on 11q may exist.

Only a few of the patients (7 out of 110) studied by Grossfeld et al. (2004) were 18 years old or more. Thus, the information on the phenotype of JBS in adults is limited. We provide a clinical description of another adult, a 24-year-old woman (Patient 3). Despite the features previously described for 11q monosomy syndrome, our patient suffered from Hashimoto disease (age: 20) and developed diabetes mellitus type 2 (age: 23). These 2 conditions have not been reported in JBS patients and may comprise either occasional findings or be a part of an adult JBS phenotype.

The pedigree of the family described here revealed multiple (12 overall) spontaneous abortions, as well as 8 neonatal and infantile deaths. This could be due to the fact that both major chromosomal imbalances occurring in this family (11q- along with distal dup22q and dup11q concomitant with 22q-) frequently produce a lethal phenotype. Thus it is possible that severe and life-shortening congenital malformations could be more frequent in fetuses and neonates than in older individuals. Interestingly, craniofacial dysmorphism of our Patient 4 with 11q24.2-qter trisomy and concomitant 22q13.33-qter monosomy exhibited partial overlap with several dysmorphic features of JBS. For example, hypertelorism, bilateral ptosis, short and smooth philtrum, thin upper lip, and shortened upper incisors seen in Patient 4, were also present in Patients 1, 2 and 3. Partial similarity of the dysmorphic traits observed either in distal 11q monosomy or 11q trisomy could provide a hint on the existence of dosage-dependent gene(s) lying within this region.

In conclusion, our study, although limited to 4 patients, provides further refinement of karyotype–phenotype correlations, especially for partial 22q13.3 trisomy, but also for partial 11q monosomy. A growing number of clinically well-characterized patients (such as those reported here), along with detailed breakpoint mapping should enable identification of specific genetic loci underlying various clinical symptoms of both chromosomal conditions.

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