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An 18-Year Follow-Up Report on an Infant With a Duplication of 9q34

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TO THE EDITOR:

We report an 18-year-follow-up study on a male subject who was first reported during infancy with multiple anomalies and a 46,XY, 12p+ karyotype [Spinner et al., 1993]. Chromosome studies at that time with chromosome painting showed extra material on chromosome 12 derived from the chromosome 9q34 band. Parental chromosome studies were normal. Shortly after birth, he was noted to have frontal bossing and ridging of the sutures with deep-set eyes and a long narrow face. He had micrognathia, a high nasal bridge, and asymmetric normally positioned ears. His limbs showed arachnodactyly and camptodactyly of the first through fourth digits bilaterally. His hand creases were poorly formed and his toes were long and overlapping. Other findings included a small penis and a hypoplastic scrotum with testes in the canal bilaterally. He was also hypotonic, had feeding difficulties, and frequent episodes of apnea and bradycardia. He developed a heart murmur at 2 weeks of age which later resolved. An echocardiogram showed that the heart was structurally normal although there was a left superior vena cava and right sided arch with an aberrant left subclavian artery.

Clinical Report: 18-Year Follow-Up

Since the initial report at 9 months of age, his most recent evaluation occurred at 19 years of age. The review of past medical history showed eye surgery at 2 years of age to correct strabismus and bilateral orchiopexy at 2 years of age. Gait disturbances were noted with planovalgus deformity of both feet at 4 years of age. He was able to stand at that time for only a few seconds without support before falling. His muscle bulk and strength were considered normal. Generalized hypotonia was noted but no pathological reflexes detected. As he became older, he was able to walk and run, but not as active as others his age. He had repair of a dislocated patella secondary to injury and joint laxity at 11 years of age. He underwent two oral surgeries at 15 years of age to remove permanent teeth secondary to a

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small jaw and dental crowding. Brain imaging (MRI) showed a Chiari I malformation with a 1.5 cm cerebellar ectopy while studies of his back showed fatty infiltration within the spinal column at L1-L3 and a possible syrinx formation at the C7-T1 level. Developmental delays were noted (e.g., he walked at 5 years) and cognitive testing showed IQ scores below normal (IQ = 55). He manifested behavioral problems requiring psychotropic medication treatment. At 19 years of age, hyperactivity, attention deficit disorder, and atypical autism were noted. Although he has a happy disposition, he can become frustrated and strikes out at others when agitated. The patient has limited speech and uses an augmented communication device along with gestures. The family history remained unremarkable with no similarly affected individuals, consanguinity, birth defects, or miscarriages.

His height at 19 years of age was 176 cm (40th centile), weight was 80.5 kg (80th centile), and head circumference was 55.5 cm (40th centile). Body mass index was 26.1 kg/m² (80th centile). Inner canthal distance was 2.7 cm (10th centile). Outer canthal distance was 7.2 cm (<3rd centile). Prominent features on examination showed a long, narrow face with a narrow bifrontal diameter, zygomatic arch, and chin. His eyes were deep-set with small and narrow palpebral fissures. He had a small mouth with dental crowding and a high arched palate with a single uvula. He had facial asymmetry with a prominent nose. His right ear was larger [7.2 cm (97th centile)] and positioned more forwardly than his left ear which measured 6.6 cm (75th centile). He was dolicocephalic with normal scalp hair texture and pattern. His abdomen was protuberant with approximately 20 purple vertical striae (8–10 cm in length) noted laterally on the abdomen. There was limited range of motion of his lower extremities, and hypotonia of his upper extremities. He was ambulatory and continued to have a broad-based gait. His feet were long and narrow with increased space between the first and second toes. Pes planus was observed but without plantar creases. Cutaneous syndactyly of the second and third toes was noted as well as broad first toes with the remaining toes in flexed position. A small sacral dimple was noted with a 1 cm hemangioma. He had arachnodactyly, cutaneous syndactyly of the third and fourth fingers, and hyperflexibility. He also had clinodactyly of the second and fifth digits of the left hand and poorly formed creases throughout. There was predominance of arches on the fingertips. His hand length was 18.8 cm (90th centile) and middle finger length was 7.8 cm (75th centile) (Fig. 1A,B).

To further define the chromosome rearrangements and location of breakpoints on chromosomes 9 and 12, the Affymetrix 6.0 SNP genotyping microarray was performed commercially (Fig. 2A,B). The Affymetrix microarray represents approximately 900,000 SNPs and 940,000 copy number probes throughout the human genome. The array findings showed a 13.79 Mb duplication (126.42–140.20 Mb from the pterminus) at 9q33.3-q34.3 and a 155 kb deletion at 12p13.33 (0–155.00 kb from the pterminus). Over 150 genes have been identified in this region on chromosome 9q, but only one known gene (*IQSEC3*) in the deleted region on chromosome 12p (www.genome.ucsc.edu).

We researched genes in the duplicated or deleted regions that may have a role in our patient's phenotype or may be of clinical significance. For example, the *ABL1* oncogene and *TSC1* gene for tuberous sclerosis are found in the duplicated region along with *COL5A1*, the collagen type V gene with a fundamental role in fibrillogenesis [Fichard et al., 1994]. Other chromosome 9 genes included carnitine acetyltransferase, *CRAT*, a key enzyme for

metabolic pathways involved in the control of the acyl-CoA/CoA ratio in mitochondria, peroxisomes, and endoplasmic reticulum. Dynamin 1, *DNM1*, which functions in receptor-mediated endocytosis and required at an intermediate stage in coated vesicle formation with a primary role in synaptic vesicle recycling in the nerve terminal region [Van der Bliek et al., 1993]. The nuclear receptor subfamily 6, Group A, Member 1, *NR6A1*, is involved in the regulation of development, growth, and reproduction [AgoulNIK et al., 1998]. Mitogen-activated protein kinase-associated protein 1, *MAPKAP1*, is a member of a family of genes involved with phosphorylation and cell signaling [Yang et al., 2006]. Protein O-mannosyltransferase, *POMT1*, shares a sequence with yeast whereby enzymes are located in the endoplasmic reticulum and required for cell integrity and cell wall rigidity. Thyroid transcription factor 1, *TTF1*, a nuclear protein that mediates thyroid-specific gene transcription, activates transcription of human surfactant protein B in the lung [Guazzi et al., 1990]. *MRPL41*, a mitochondrial ribosomal protein L41, is one of more than 70 protein components of mitochondrial ribosomes encoded by the nuclear genome. Caspase recruitment domain-containing protein 9, *CARD9*, is a protein that participates in apoptosis signaling while the ATP-binding cassette, subfamily A, Member 2, *ABCA2*, is involved in sterol transport. Specifically, *ABCA2* may play a role in delivery of LDL-derived free cholesterol to the endoplasmic reticulum for esterification [Davis et al., 2004]. One *NOTCH1* gene, is also located in the duplicated region of chromosome 9 and mediates cell-fate decisions during development including hematopoiesis [Milner et al., 1994]. Other genes in the duplicated region of chromosome 9 that were examined included *SET*, *GLE1*, *COQ4*, *UCK1*, *LCN1*, *UBAC1*, *GRIN1*, *SURF1*, *SURF2*, and *SURF3*. Therefore, several features seen in our patient and other similarly affected individuals could be attributed to genes coding for signaling proteins, connective tissue formation, or cell integrity, metabolism, and transport.

The gene for IQ motif- and sec7 domain-containing protein 3, *IQSEC3*, is located in the deleted region of chromosome 12p in our patient. *IQSEC3* participates in activation of ARF1 which is involved in recruiting coatamer, a hepatic protein, to the membranes. The coatamer assembly helps in the transport of budding-off membranes between the endoplasmic reticulum and Golgi apparatus. In addition, features reported in the literature of monosomy chromosome 12p13.33 include microcephaly, micrognathia, variable mental retardation, and strabismus [Romain et al., 1987].

The clinical features in trisomy 9q were first reported by Turleau et al. [1975]. Four large families with seven individuals from the same geographical region reported by Allerdice et al. [1983] had the same duplication of chromosome band 9q34 secondary to an inverted insertion of chromosome 9. Similarly, Houdou et al. [1987] reported a girl with a 9q34 duplication derived from a balanced translocation in the mother. Ten years later, Spinner et al. [1993] reported our patient during infancy with a de novo duplication of 9q34-qter and monosomy 12p13.33 secondary to an unbalanced translocation. More recently, a 17-year-old female with a duplication of the 9q33.3q34.1 region was described by Gawlik-Kuklinska et al. [2007].

Only a few subjects are reported with the 9q34 duplication, although several anomalies were in common. These include dolichocephaly, an asymmetric narrow face, deep-set eyes, small

and narrow palpebral fissures, prominent beaked nose, small mouth and abnormal dental findings, arachnodactyly and digital anomalies, broad-based gait, hypotonia, and developmental delay. However, cutaneous syndactyly, hyperflexibility, low birth weight, and normally positioned digits in our patient are not in common with those reported in the literature. Thus, the phenotype observed in our patient with a 9q34 duplication does correlate with those reported in the literature thereby representing the 9q34 trisomy syndrome.

High resolution molecular cytogenetic techniques now available, such as chromosome microarray hybridization, are useful to fully characterize chromosome rearrangements. This technology allows for a more precise description of size, location, and genes involved in a chromosome region helpful in further characterizing the genetic lesion for genotype–phenotype correlations, genetic counseling, and medical management. The authors encourage the reporting of additional subjects with this rare cytogenetic syndrome using new tools for genetic testing to more precisely identify the chromosome abnormality and breakpoints.

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FIG. 1.

A: Frontal and facial views of our 19-year-old subject with 9q34 trisomy and 12p13.33 monosomy. B: Hands showing arachnodactyly, cutaneous syndactyly of the third and fourth digits, clinodactyly of the second and fifth digits of the left hand, and poorly formed creases. Feet are long and narrow with increased space between first and second toes, pes planus, cutaneous syndactyly of second and third toes, broad first toes, and flexion of other toes.

FIG. 2.

A: Chromosome microarray hybridization using the Affymetrix 6.0 SNP array showing the location of the duplication of the 9q33.3-qter region on the right. B: Chromosome microarray hybridization using the Affymetrix 6.0 SNP array showing the location of the deletion of the 12p13.3 region on the left.