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Deletion of 8q24 in an Adult with Mild Dysmorphic Features, Developmental Delay, and Ketotic Hypoglycemia

Benjamin D. Solomon¹, Eileen Lange², Jay Shubrook³, F. John Service⁴, Gail Herman⁵, Rajaram J. Karne⁶, Phillip Gorden⁷, Maximilian Muenke¹, and Constantine A. Stratakis^{2,*}

¹Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

²Section on Endocrinology and Genetics, Program on Developmental Endocrinology & Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

³Department of Family Medicine, Ohio University College of Osteopathic Medicine, Athens, Ohio, USA

⁴Department of Endocrinology, Mayo Clinic, Rochester, MN, USA

⁵Center for Molecular and Human Genetics, The Research Institute at Nationwide Children's Hospital and Department of Pediatrics, The Ohio State University, Columbus, OH, USA

⁶Division of Endocrinology, Diabetes & Metabolism, Department of Medicine, Ohio State University Medical Center, Columbus, OH, USA

⁷Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

Abstract

We present a 56-year-old female with a history of carbohydrate intolerance and ketotic hypoglycemia, dysmorphic features, mild developmental delay, lymphedema, altered pain sensation, and frequent fractures, who was found to have a heterozygous 8.09 Mb deletion of chromosome 8q24.11q24.13 containing more than 39 genes, as well as a duplication of 20q11.23 containing one gene. The deleted region overlaps that of two previously reported patients, who share a subset of clinical characteristics with the patient described here. Some of this patient's clinical features are consistent with the loss of genes in the deleted region. The diagnostic work-up of this patient clearly demonstrates the evolution of genetic testing techniques.

Keywords

8q; 8q24; Microdeletion

Introduction

The availability of new genetic technologies allows clinicians to make diagnoses in patients with previously unexplained developmental delay, dysmorphic features, and multisystem anomalies [Shaffer et al., 2007]. The patient we describe had a multisystem disorder of

* To whom correspondence should be addressed: *Constantine A. Stratakis, MD, D(Med)Sci*, SEGEN, PDEGEN, NICHD, NIH, Building 10, CRC (East Laboratories), Room 1-3330, 10 Center Dr., MSC1103, Bethesda, Maryland 20892, USA. Tel. 301-496-4686/496-6683, fax: 301-402-0574/480-0378, stratakac@mail.nih.gov.

unknown etiology. She was investigated multiple times over several decades prior to the performance of a chromosome microarray analysis which identified a cytogenetic defect. A later higher-resolution microarray better defined the breakpoints.

This patient was found to have a single copy loss involving chromosome 8q24.11q24.13 as well as duplication of 20q11.23 containing one gene. The 8q24 region contains the *TRP1* and *EXT1* genes. Heterozygous mutations in *TRPS1* result in trichorhinophalangeal syndrome type I and in *EXT1* cause multiple exostoses syndrome. Deletions of both *TRPS1* and *EXT1* can cause Langer-Giedion syndrome (also called trichorhinophalangeal syndrome type II) [Ahn et al., 1995; Lüdecke et al., 1995; Momeni et al., 2000]. (Central features of trichorhinophalangeal syndrome type I include mild growth deficiency, thin nails, cone-shaped epiphyses and other skeletal anomalies, and a characteristic craniofacial appearance including sparse hair, large and prominent ears, a bulbous nose, a long philtrum, and a narrow palate. Patients with trichorhinophalangeal syndrome type II have similar facial features, but also have multiple exostoses, more pronounced cognitive impairment, and may have loose/redundant skin in infancy [Jones, 2006].) The patient described here has some phenotypic findings commonly associated with the two trichorhinophalangeal syndromes, although she does not fit clearly into either clinical pattern, and her medical problems include manifestations not previously described as related to genes in this region. She also shares features with two previously reported patients with overlapping deletions of 8q24. The first was a 12-year-old male with dysmorphic features, seizures, and multiple exostoses [Wuyts et al., 2002]; the second was a 9-year-old male with dysmorphic features, frequent infections, and multiple exostoses [McBrien et al., 2008]. The patient described here has some similar dysmorphic features to these two previously reported patients, including thick eyebrows, the appearance of hypertelorism, a broad nose with a rounded/bulbous nasal tip, a long philtrum and thin upper lip and angulated ear helices. All three patients had frank but overall relatively mild neurocognitive impairment.

Patient Description

Clinical History

The patient is a 56-year-old Caucasian female with a history of mild developmental delay who was seen at the National Institutes of Health due to a history of carbohydrate intolerance and ketotic hypoglycemia. The patient and her referring physicians reported lifelong eating difficulties. Her fasting blood glucose ranged typically between 30 and 50 mg/dL. She described symptomatic hypoglycemia when her glucose was lower than 30 mg/dL and discomfort (headaches and fainting episodes) as her glucose increased above 60 mg/dL. After numerous unfruitful medical evaluations in childhood, the patient and her family eventually selected a high protein, low carbohydrate diet, which seemed to reduce symptoms.

In addition to the above medical history, review of systems was notable for a 30-year history of intermittent bilateral extremity swelling and a lifelong history of both decreased pain sensation and numerous fractures despite minimal trauma. Later in life, the patient was diagnosed with fibromyalgia.

Family history was notable for the fact that the patient was one of dizygotic twins; the other twin had normal cognition but was reported to have a history of diabetes mellitus and “anorexia”. Family history was otherwise noncontributory; unfortunately, none of the other family members was available for study.

On examination at 56 years, the patient appeared older than her stated age. Her height was 148 cm (~50th centile for an 11.5 year-old female), weight was 40.0 kg, BMI was 20.4 kg/

m², and head circumference measured 53 cm (~50th centile for a 12-year-old female). Her facial anomalies included sparse hair, a broad and high forehead, midface hypoplasia, a broad nose with a bulbous tip, a slightly long and smooth philtrum, and a thin vermilion border. She had 2+ lower extremity pitting edema bilaterally which was apparent to approximately the mid-shin, brachydactyly, and mild 5th finger clinodactyly (Fig. 1). Photographs from early childhood through early adulthood are shown in Fig.2. Her twin (not shown) did not show evidence of similar features on review of photographs. X-rays did not reveal any bony abnormalities other than the presence of significant osteoporosis; a full skeletal survey was not performed, but available reports showed neither exostoses nor epiphyseal coning. Other imaging studies (including ultrasound of the abdomen and pelvis, CT scan of the chest, abdomen, and pelvis, and MRI scan of the pituitary) showed no structural or other abnormalities. She had normal gastric emptying.

Metabolic Studies

Studies of her metabolism revealed that a high percentage of her resting glucose production was from gluconeogenesis. Ketones were present both during periods of hypo- and hyperglycemia. She had previously been shown to have a normal response to insulin, implying that she was able to appropriately downregulate gluconeogenesis, and had a normal response to glucagon and normal insulin surrogates, further implying that her hypoglycemia was not insulin-mediated. Glycogenolysis was intact; liver biopsy in childhood showed no evidence of glycogen accumulation, there was no history of hepatomegaly or splenomegaly, and amylo-1,6-glucosidase deficiency was excluded via glucagon administration after a long fast. Additionally she showed evidence of blood lactate elevation with fructose or alanine administration, and blood glucose elevation upon administration of alanine. While her phenotype could be consistent with glycogen storage disorder type 0 (glycogen synthase deficiency), decreased hepatic glycogen on a liver biopsy was not present in this patient; testing for GSD0 was not performed.

On further investigation (years after initially demonstrating normal insulin response), a mixed meal study and alanine tolerance test showed severe insulin resistance ascribed to her long-term self-imposed high protein, high fat, and low carbohydrate diet. Both fasting cholesterol and LDL were markedly elevated on fasting lipid profile, with total cholesterol measured at 311 mg/dL (normal range 100-200 mg/dL), and an LDL value of 227 mg/dL (normal range 65-129 mg/dL)

Genetic Testing

Chromosome analysis on peripheral blood (600 band level) showed a 46,XX chromosome complement. Results of lactate and pyruvate were within normal limits; mitochondrial DNA mutation/deletion testing (standard mutation panel performed by Baylor Medical Genetic Laboratories, Houston, TX, USA) was negative, and acylcarnitine profile, plasma amino acids and urine organic acids all showed normal results except for the presence of ketonuria. A commercial chromosome microarray analysis of 622 loci using 1887 genomic BAC clones (Signature Genomic Laboratories, Seattle, WA, USA) revealed the presence of a single copy loss of 6 BAC clones from the long arm of chromosome 8 at 8q24.11q24.12. The exact extent of the deletion, estimated at 1.67 Mb, was unknown, as the nearest proximal clone was 578 kb from the deleted region and the nearest distal clone was at a 20.5 Mb distance. The deletion was confirmed using FISH analysis with BAC clones from the region (RP11-177I14-RP114K16). Subsequently, a higher resolution microarray platform using approximately 105,000 oligonucleotide probes, with average spacing of one probe every 35 kb throughout the genomes, and one probe every 10 kb in regions known to have clinical significance (Signature Genomic Laboratories, Seattle, WA, USA) was used for clinical validation and to better define the extent of the deletion. This oligonucleotide array

revealed an 8q24.11q24.13 deletion estimated at 8.09 Mb, as well as an approximately 98.88 kb duplication of 20q11.23 containing one gene (*TGM2*), which has not been previously reported. The revised karyotype is given as: 46,XX,arr cgh 8q24.11q24.13(118,148,936-126,238,545)×1,20q11.23(36,172,168-36,271,046)×3. The deleted region contains multiple genes, including *EXT1*, but not *TRPS1*. This region is not a known region of copy number variation. As mentioned above, additional family members were not available for analysis.

Overlap between the deletion in our patient and that of previously reported patients with deletions in this region are shown in Fig. 3 [Wuyts et al. 2002;McBrien et al., 2008]. Three genes are found in the overlapping deleted region common to the three patients: *SLC30A8* (*ZNT8*), *MED30* (*THRAP6*), and *EXT1*.

Discussion

The availability of chromosome microarray analysis, coupled with recent research on the function of genes in the 8q24 deleted region, helps explain some of the clinical manifestations seen in this patient. First, there are a number of possibly interacting genetic etiologies for her frequent fractures. *Col14a1* null mice demonstrate abnormal fibrillogenesis, and *TNFRSF11B* encodes osteoprotegerin, which has a critical role in osteoclast regulation; homozygous mutations can result in juvenile Paget disease [Cundy et al., 2002; Whyte et al., 2002; Ansorge et al., 2009]. We further assume that her carbohydrate intolerance, which itself likely has a genetic explanation not easily explained by the 8q24 deletion, contributed to poor bone health. Second, the patient had a long history of abnormal response to pain. *ENPP2* codes for autotaxin, which is involved in neuropathic pain signaling. Animal models suggest that heterozygous mutations in this gene result in altered pain response [Inoue et al., 2008]. Deletion of *SNTB1*, which encodes a dystrophin-associated protein, may also contribute to neuromuscular disease in this patient, though this gene has not yet been implicated in known human disease [Ahn et al., 1994].

The patient's metabolic derangements such as carbohydrate intolerance and ketotic hypoglycemia have not previously been reported in patients with heterozygous deletions involving 8q24. *SLC30A8* (*ZNT8*) on 8q24 encodes a key autoantigen in type 1 diabetes [Wenzlau et al., 2007]. The significance of the duplication of the gene *TGM2* on 20q11.23 is unclear but may be related some of her medical issues. The gene encodes Transglutaminase 2, which, like other transglutaminases, has a role in enzymatic apoptosis through intracellular protein cross-linking [Fesus et al., 1987; Antonyak et al., 2006]. *TGM2* is the only transglutaminase expressed in the pancreas, and has been implicated in a number of human conditions, which notably include both early-onset diabetes and celiac disease [Dieterich et al., 1997; Porzio et al., 2007]. Thus, both the deletion and the duplication in this patient, as well as interacting environmental factors, may contribute to her phenotype.

The patient described here had a deletion which overlapped that of two previously-described patients [Wuyts et al. 2002; McBrien et al., 2008]; the common deleted genes include *SLC30A8* (*ZNT8*), *MED30* (*THRAP6*), and *EXT1*. Our patient's deletion is larger and extends far more distally than that of the other two patients. Common findings among the three patients include relatively thick eyebrows, the appearance of hypertelorism, a broad nose with a rounded or bulbous nasal tip, a relatively long philtrum and a thin upper lip, and angulated helices of the ears. All patients had developmental delay, though none had severe neurocognitive impairment. Unlike the other two patients, our patient did not have evidence of exostoses.

Since the three patients had deletions which included different genes, it is difficult to speculate about genotype-phenotype correlations. It would be expected that deletions of different genes in the three patients would result in distinct phenotypes. Specifically, one would expect the phenotype of the patients described by Wuyts et al. [2002] and McBrien et al. [2008] to be more similar to each other than to the patient described here, because the extent of the deletions were more similar in the former cases.

Finally, the diagnostic work-up in this patient clearly demonstrates the evolution of genetic testing techniques. Her initial karyotype was normal; a BAC microarray revealed a deletion of unclear size, and an oligonucleotide microarray further refined the breakpoints and additionally revealed a small duplication. This case thus argues for the application of newer diagnostic techniques both in the clinical and research setting.

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Figure 1. Face and extremities of the patient, showing facial manifestations at 56 years of age, including sparse hair, a broad and high forehead, midface hypoplasia, a broad nose with a bulbous tip, a long and smooth philtrum and a thin upper lip. Hand photos show brachydactyly, and clinodactyly.

Figure 2.

Photos of the patient at various ages demonstrating the progression of the facial phenotype. At younger ages, the broad and high forehead, thick eyebrows and midface hypoplasia are quite apparent, and the appearance of hypertelorism is more pronounced at younger ages. Signs of premature aging are first apparent in the photo at age 29 years. Not all ages are known. Photo a: 6 years of age; Photo b: 8 years; Photo c: 29 years.

Figure 3.

Deletions of the patient described here and two previously reported patients [Wuyts et al., 2002; McBrien et al., 2008], showing the region of common deletion (indicated by the shaded square), as well as the other proven deleted genes in the interval (in gray) and the flanking genes known not to be deleted (in black). An ideogram showing the estimated deleted regions is also depicted (bottom left).