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A 781-kb Deletion of 13q12.3 in a Patient with Peters Plus Syndrome

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To the Editor

The availability of high-resolution microarrays has greatly improved the detection of genomic rearrangements in patients with multiple congenital anomalies, developmental delays, and mental retardation [Ming et al., 2006; Stankiewicz et al., 2007; Shaffer et al., 2007; Sharp et al., 2008]. These abnormal phenotypes are commonly due to an alteration of one or more dosage-sensitive gene(s) within the affected region. Alternatively, deletions may unmask an autosomal recessive mutation carried on the non-deleted allele, which has led to the discovery of several genetic and biochemical abnormalities inherited in an autosomal recessive fashion [Ludlow et al., 1996; Garshasbi et al., 2008; Bisgaard et al., 2008]. We describe here a male patient with multiple congenital anomalies who was diagnosed with Peters plus syndrome (PPS). He was found to have a heterozygous deletion by microarray analysis that included the *B3GALT1* gene. Sequencing of *B3GALT1* demonstrated a mutation on the non-deleted allele that has been seen previously in PPS patients [Lesnik Oberstein et al., 2006; Kapoor et al., 2008; Reis et al., 2008].

The patient was evaluated at one month of age for hydrocephalus thought to be due to aqueductal stenosis, thin corpus callosum, corneal clouding, dysmorphic facial features, bilateral cryptorchidism, and a sacral dimple with tethering of the spinal cord. His birth history was significant for a premature induced vaginal delivery at 33 weeks gestational age to a 23 yo G4P1→2 female (two prior first trimester spontaneous miscarriages) due to intrauterine growth restriction and poor scores on a biophysical profile. His birth weight and length were both at the 10th centile, and his head circumference was at the 80th centile. An echocardiogram performed due to the presence of a murmur was normal except for mild peripheral pulmonic stenosis. Radiological studies included a skeletal survey that revealed platybasia and toes of equal lengths, and a renal ultrasound showing duplication of the left renal collecting system. The family history was noncontributory. His parents were non-consanguineous and of German, Irish, and Lithuanian descent. A repeat genetics evaluation at

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7 months demonstrated short stature (50th centile for 4 months), macrocephaly with a prominent forehead, short palpebral fissures (5th centile), cupped right helix, depressed nasal bridge, retrognathia, cryptorchidism, sacral dimple, rhizomelic shortening and bilateral clinodactyly of the upper extremities, and syndactyly between the 2nd and 3rd toes (Fig 1).

Due to his multiple congenital anomalies, a high-density oligonucleotide microarray was performed using the Affymetrix SNP6.0 platform (Affymetrix, Santa Clara, CA). A 781-kb heterozygous deletion was found on 13q12.3 (chr13:30,069,778-30,850,926, NCBI hg18 build), and later confirmed by fluorescence *in situ* hybridization with a probe located in the deleted region (RP11-173P16). The deletion involves five genes (Figure 2), including the *B3GALTL* gene that is implicated in PPS. We then sequenced the exons and their flanking regions and determined our patient to carry a c.660+1G>A mutation in addition to the deletion. Parental analysis confirmed them to be heterozygous carriers, with the deletion inherited from the mother and the point mutation inherited from the father.

Peters plus syndrome (OMIM 261540) is a multiple congenital anomaly syndrome where patients present with the Peters anomaly as well as several extra ocular characteristics [Maillette de Buy Wenninger-Prick and Hennekam, 2002]. The β 1,3-galactosyltransferase-like (*B3GALTL*) gene on 13q12.3 was recently discovered to be the causative gene in this syndrome [Lesnick Oberstein et al., 2006]. The protein product is a glucosyltransferase, which adds a glucose molecule to an O-linked fucose located on thrombospondin type 1 repeats of several important proteins [Heinonen et al., 2003; Hess et al., 2008]. PPS is therefore considered a new congenital disorder of O-glycosylation [Heinonen et al., 2009]. Every PPS patient with molecular analysis of the *B3GALTL* gene harbors at least one common point mutation involving the donor splice site of exon 8, c.660+1G>A [Lesnick Oberstein et al., 2006; Kapoor et al., 2008; Reis et al., 2008]. Most PPS patients analyzed are homozygous for this mutation, but there have been additional mutations identified in patients with PPS [Lesnick Oberstein et al., 2006; Reis et al., 2008]. Although PPS is a clinically heterogeneous disorder, our patient appears to have many features previously described [Maillette de Buy Wenninger-Prick and Hennekam, 2002]. New findings in our patient include platybasia of the skull and tethering of the spinal cord. However, vertebral segmentation abnormalities and spina bifida occulta have been reported [Maillette de Buy Wenninger-Prick and Hennekam, 2002; Kapoor et al., 2008].

Two brothers were reported with heterozygous 1.5-Mb deletions involving *B3GALTL* and the common c.660+1G>A mutation on the other allele [Lesnick Oberstein et al., 2006]. Our patient's deletion is 781-kb, and is the smallest deletion in this region reported in the literature or online databases such as DECIPHER (<http://decipher.sanger.ac.uk/>). Comparing our deletion to the two brothers reported by Lesnick Oberstein et al. [2006], the common region of overlap includes a small area of 13q12.3 that contains 2 genes, *HSPH1* and *B3GALTL* (Figure 2). *HSPH1* encodes heat shock protein 105-kDa, a protein that is over expressed in certain cancers [Muchemwa et al., 2008] but has no association with a congenital anomaly syndrome. The other genes deleted only in our patient include *USPL1*, *ALOX5AP*, and *C13orf33*. *USPL1* is an ubiquitin-specific peptidase with unclear function, and *C13orf33* is a hypothetical protein based on DNA sequence analysis. *ALOX5AP* polymorphisms have been reported in atherosclerosis and atopic diseases [Halloway et al., 2008; Lemaitre et al., 2008], but no deletions of this gene have been implicated in human disease. Therefore, the heterozygous deletion and mutation of *B3GALTL* in our patient are the likely cause of his clinical features.

The deletion observed by Lesnick Oberstein et al. [2006] was more distal compared to our patient and contained additional genes such as *LGR8/RXFP2*, *FRY*, and *BRCA2*. It was suggested that the cryptorchidism observed in their patients may be due to

haploinsufficiency of the nearby *LGR8/RXFP2* gene, as this has been associated with cryptorchidism [Ferlin et al., 2008]. However, we did not find involvement of this gene in our patient (Figure 2). As cryptorchidism has been observed in PPS and other congenital disorders of glycosylation [Maillette de Buy Wenninger-Prick and Hennekam, 2002; Schollen et al., 2004], this specific finding in our patient is likely related to the underlying disorder rather than a positional effect of the deletion. There was also a family history of breast cancer in the family of the other deletion patients due to involvement of *BRCA2*. Our patient does not have *BRCA2* deleted, nor is there a family history of breast or ovarian cancer, again suggesting there is no positional effect of the deletion on the function of this gene. The commonly observed clinical characteristics in both our patient and the two brothers is therefore most likely due to the involvement of *B3GALTL*, yet their variable phenotypes may be caused by the multisystemic disease process seen in glycosylation defects or to the different genes associated with their respective deletions.

In summary, we present here a patient with Peters plus syndrome, who was found by microarray analysis to have a contiguous gene deletion of 781-kb on 13q12.3. Sequencing analysis of the non-deleted allele of the *B3GALTL* gene identified a previously known pathogenic point mutation. This patient involves the second reported finding of a deletion of *B3GALTL* in PPS, and is the smallest known deletion involving this specific locus. Our report also highlights the utility of microarray-based copy number analysis in the diagnosis of patients with multiple congenital anomalies, especially when the copy number abnormalities involve genes that are associated with autosomal recessive disorders.

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Figure 1. Photographs of the patient at age 7 months

Dysmorphic features included frontal prominence with occipital flattening, corneal clouding, upslanting palpebral fissures, hypertelorism, small and low-set ears with thickened and protuberant helices, and a thin upper lip with an exaggerated Cupid's bow.

Figure 2. Microarray results

An Affymetrix SNP6.0 microarray detected a heterozygous 781-kb deletion of 13q12.3 (arrow). Analysis of the deletion coordinates in the UCSC Genome Browser (<http://genome.ucsc.edu>) showed five genes to be affected, including *B3GALT1*. Overlap of our patient's deletion is shown compared to one previously described in two brothers with Peters plus syndrome [Lesnick Oberstein et al., 2006].