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8q21.11 Microdeletion in Two Patients with Syndromic Peters Anomaly

Hannah Happ¹, Kala F. Schilter^{1,2}, Eric Weh¹, Linda M. Reis¹, and Elena V. Semina^{1,2,3,*}

¹Department of Pediatrics and Children's Research Institute, Medical College of Wisconsin, Milwaukee, WI, 53226 USA

²Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI, 53226 USA

³Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, WI, 53226 USA

Abstract

Peters anomaly is a form of anterior segment dysgenesis characterized by central ocular opacity and corneo-lenticular adhesions. Isolated and syndromic Peters anomaly can be observed and demonstrate significant genetic heterogeneity. We report the identification of overlapping 8q21.11 deletions in two patients with syndromic Peters anomaly via whole exome sequencing and chromosomal microarray analyses. Microdeletions of 8q21.11 were recently reported in ten patients with highly variable phenotypes involving craniofacial features, ptosis, intellectual disability, abnormalities of the hands/feet and other defects; sclerocornea and/or microphthalmia were reported in three cases. The two additional cases presented in this report expand the phenotypic spectrum of 8q21.11 microdeletions to include Peters anomaly (seen in both patients) and persistent primary dentition (seen in one patient with a larger deletion). The two novel deletions include the *ZFHX4* and *PEX2* genes, which are also affected in all three previous cases involving ocular anomalies. Screening of remaining alleles of the *ZFHX4* and *PEX2* did not identify any additional likely pathogenic variants in either patient, suggesting dominant (haploinsufficiency) mechanism for the identified deletion. This report provides further insight into the phenotypes associated with 8q21.11 deletions and, for the first time, reports Peters anomaly as an additional ocular feature; screening for copy number variations of the 8q21.11 region should be considered in patients with Peters anomaly and related syndromic features.

Keywords

8q21.11 microdeletion; copy number variation; Peters anomaly; *PEX2*, *ZFHX4*

*Corresponding author: Elena V. Semina, PhD, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509, Phone: 414-955-4996, Fax: 414-955-6329, esemina@mcw.edu.

SUPPLEMENTAL MATERIALS

Supplemental Table 1. qPCR primer sequences and coordinates.

Supplemental Table 2. *ZFHX4* and *PEX2* PCR primers and conditions.

INTRODUCTION

Peters anomaly (PA) is a form of anterior segment dysgenesis (ASD) characterized by central ocular opacity and corneo-lenticular adhesions likely due to developmental failure of separation of the lens vesicle from the corneal ectoderm [Heon et al., 1992]. PA can occur as an isolated ocular anomaly but additional systemic anomalies are present in 35–60% of cases [Heon et al., 1992; Ozeki et al., 2000]. While classic Peters Plus syndrome, in which PA (or other ASD) is accompanied by short stature, brachydactyly, intellectual disability, and characteristic facial features, is almost universally caused by mutations in *B3GALT1* [Weh et al., 2013], other forms of syndromic and non-syndromic PA show significant genetic heterogeneity [Weh et al., 2014].

In this report, we present the first identification of two independent 8q21.11 deletions in patients affected with syndromic PA. The presented data confirm the previously described disease associations, expand the phenotypic spectrum of 8q21.11 deletions, and indicate that patients with syndromic PA should be screened for 8q21.11 copy number variation.

CLINICAL REPORTS

This human study was approved by the Institutional Review Board of the Children's Hospital of Wisconsin with written informed consent obtained for every subject.

Patient 1 (Figure 1; Table 1) is a 6-year-old Caucasian female who presented with bilateral corneal opacity at birth and was diagnosed with Peters anomaly/sclerocornea with iridocorneal adhesions along with mild microphthalmia in the right eye. She was treated with Trusopt® and Lotemax® with significant clearing of the corneal opacity over time. The patient has global developmental delay with hypotonia especially affecting the lower extremities and receives speech, physical, occupational, and mobility therapy. Brain MRI showed central white matter volume loss and thin corpus callosum. In terms of craniofacial features, the patient displayed a high forehead, cupid's bow upper lip, prominent low-set ears and dental anomalies consisting of delayed eruption and persistent primary dentition (requiring extraction after the permanent teeth grew in). Other features include a single transverse palmar crease of the hand, 5th finger clinodactyly, small very flat feet, and a sacral dimple. Patent ductus arteriosus (PDA) was noted in infancy but echocardiogram at 2 ½ years of age identified a structurally normal heart with resolved PDA. Growth was normal with a height of 113 cm (25–50th centile) and weight of 22.8 kg (50–75th centile). This patient was previously reported as *B3GALT1*-negative with a Peters plus syndrome (PPS)-like phenotype [Patient 32 [Weh et al., 2013]].

Genomic DNA from Patient 1 was submitted for whole exome sequencing to Axseq (Rockville, MD) and processed and analyzed as previously reported [Weh et al., 2014]. Exome sequencing data was screened for copy number variation using Copy Number Inference From Exome Reads (CoNIFER) v0.2.2 software (<http://conifer.sourceforge.net/>), used as previously outlined [Krumm et al., 2012]. Analysis of whole exome sequencing data did not identify any pathogenic variants [Weh et al., 2014]. CoNIFER analysis detected a putative 13.1 Mb deletion (hg19, chr8: 75944419–89053919). This region includes 45

characterized genes, two long intergenic non-coding RNAs, and nine uncharacterized genes (Figure 2). The deletion was verified by quantitative PCR (qPCR) using SYBR Green PCR Master Mix (Applied Biosystems/Life Technologies, Carlsbad, CA, USA) using PCR primers located within the regions of interest (Supplemental Table 1) on a Bio-Rad CFX Connect Real-Time PCR machine (Bio-Rad, Hercules, CA, USA). All experiments included a no-template control an unaffected human DNA sample along with a primer set for *RPPH1* and *NDP* for normalization and copy loss controls. Copy number changes were calculated using the 2^{-C_t} method as previously described [D'haene et al., 2010; Schilter et al., 2013]. The qPCR analysis of patient DNA confirmed diploid copy number for *PII5* and haploid copy for *HNF4G* (indicating the centromeric breakpoint is positioned between *PII5* and *HNF4G*), haploid states for *PEX2*, *ZFHX4* and *MMP16*, and diploid copy for *RIPK2* (indicating the telomeric breakpoint is positioned between *MMP16* and *RIPK2*), consistent with the CoNIFER results (data not shown). During a follow-up discussion, the family revealed the results of clinical whole genome chromosome SNP/CN microarray copy number analysis (Affymetrix 6.0) which identified a 14.51 Mb deletion of 8q21.11q21.3 (hg19, chr8:76,249,496–90,757,821; originally reported as hg18, chr8:76,412,051–90,826,943; build 36) that was present in Patient 1 (Figure 2) and absent in both parents. At the time of analysis, the identified deletion was reported as likely pathogenic but with unknown clinical significance due to a lack of previously published cases. A manual review of whole exome sequencing data did not identify any variants in the coding sequences of *PEX2* and *ZFHX4* (all exons had >10× coverage) corresponding to the remaining allele.

Patient 2 (Table 1) is a 4-month-old Asian male affected with macrocephaly and brachycephaly, down-turned corners of the mouth, thin, tented upper lip, open-mouth habitus, bilateral ear creases, broad neck, unilateral Peters anomaly, bilateral nystagmus, severe hypotonia with developmental delay, long curved toes, limitation of motion at the knees, normal growth, a small foreskin, bilateral hydrocele, and pigmentation of the navel; increased nuchal thickness and kidney dilation were noted prenatally. This patient was also previously presented as *B3GALT1*-negative with a PPS-like phenotype [Patient 5 [Reis et al., 2008]].

Copy number variation analysis performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Santa Clara, CA, USA) as previously described [Schilter et al., 2013] identified a 1.4 Mb deletion of 8q21.11–q21.12 (hg19, chr8: 77,211,654–78,624,559) which included *ZFHX4* and *PEX2*, *ZFHX4* antisense RNA 1 (*ZFHX4-AS1*), microRNA *MIR3149*, and two long non-coding RNAs, *LINC01111* and *LOC102724874* (Figure 2). The qPCR analysis was performed as above and results confirmed a single copy loss of *PEX2* and *ZFHX4* in Patient 2. qPCR analysis identified normal copy number for all probes tested in the mother; the father was unavailable. Sanger sequencing of *PEX2* and *ZFHX4* was undertaken in this patient using gene-specific primers and conditions (Supplemental Table 2). Sequencing of *PEX2* identified no rare variants. Sequencing of *ZFHX4* identified a silent change, c. 9297C>G, p.(Pro3099Pro), that was not previously observed in public databases (<http://exac.broadinstitute.org>); however, the change is predicted to be functionally benign.

Screening for copy number variations of the 8q21.11 region was performed in twenty-one additional samples affected with syndromic Peters anomaly using the qPCR probes for

PEX2 and *ZFHX4*; all tested samples were found to have a normal copy number for these genes.

DISCUSSION

Palomares and coauthors [Palomares et al., 2011] recently reported eight patients with varying sizes of 8q21.11 deletions (0.66–13.55 Mb). The patients demonstrated a variable but overlapping phenotype with characteristic facial features and intellectual disability/developmental delay seen in all patients along with ptosis, hypotonia, and abnormalities of the hands/feet in most cases. Other anomalies seen in some patients included developmental ocular abnormalities (sclerocornea, microphthalmia, cataract, and/or pigmentary retinal degeneration) and various other systemic defects. Subsequent reports identified 8q21.11 microdeletions in two patients with additional features of distal arthrogryposis and ventricular septal defect in one patient and ventriculomegaly with macrocephaly in the other [Hofmann et al., 2011; Vulto-van Silfhout et al., 2013].

This report presents two additional cases affected with 8q21.11 copy number loss and complex syndromic phenotypes. The phenotypic and chromosomal anomalies of the two patients overlap the clinical features and genomic region of the above described 8q21.11 microdeletion syndrome [Palomares et al., 2011], although this phenotypic overlap was not recognized in either patient prior to molecular diagnosis. These patients are the first to be reported with Peters anomaly, expanding the phenotypic spectrum of this condition. The persistent primary dentition noted in Patient 1 is another interesting finding. Abnormal dentition was noted in one previous patient with a similarly large deletion of 8q21 (9.8 Mb; chr8:74362438–84172022), suggesting that a gene within 8q21 but outside the critical region for the syndrome may be involved in dentition. One gene within this region, *STMN2* was recently identified to be upregulated in the periodontal ligament, the connector between the tooth and alveolar jaw bone, compared to the dental follicle [Lee et al., 2013]. Two other genes within the region involved in bone metabolism, *IL7* and *PAG1*, were also shown to be expressed in periodontal ligament cells with changes in expression in response to tensile strain [Pinkerton et al., 2008; Chang et al., 2015].

The deletion in Patient 1 (14.51 Mb) is the largest reported deletion of this region. The initially described critical region (hg 19, chr8: 77226464–77766239; ~578 kb) included the zinc finger homeobox 4 (*ZFHX4*) gene, *ZFHX4* antisense RNA 1 (*ZFHX4-AS1*), and a long intergenic non-protein coding RNA 1111 (*LINC01111*) [Palomares et al., 2011]; subsequently, a 49.6 kb deletion (hg18, chr8: 77908190–77957795) which affects only the last seven exons of the *ZFHX4* gene was identified in a patient with overlapping features, further narrowing the critical region to include only *ZFHX4* [Vulto-van Silfhout et al., 2013]. Developmental ocular phenotypes (sclerocornea with microphthalmia/cataract or pigmentary retinal degeneration) were only reported in patients with deletions encompassing both *ZFHX4* and the *PEX2* gene, located ~110kb distal to *ZFHX4*, which is consistent with the copy number loss observed in Patients 1 and 2 in our study; however, not all patients with deletions including *PEX2* demonstrated developmental ocular anomalies and none had been reported with PA prior to this study [Palomares et al., 2011; Hofmann et al., 2011].

ZFHX4 is a zinc-finger homeodomain-containing transcription factor with a role in neural cell development [Hemmi et al., 2006; Nogami et al., 2005]. Further studies identified *ZFHX4* as a regulatory factor which interacts with CHD4, a core member of the nucleosome remodeling and deacetylase (NuRD) complex; *ZFHX4* was required to maintain the undifferentiated state of neuronal precursor as well as glioblastoma associated tumor-initiating cell phenotypes [Chudnovsky et al., 2014]. These data suggest that disruption of *ZFHX4* may be causative for the neural features seen in 8q21.11 microdeletion, including intellectual disability, hypotonia, behavioral anomalies, ptosis, and/or strabismus, but do not provide strong evidence for a role in ocular development. Additional data indicate that *ZFHX4* may also be associated with isolated phenotypes such as bilateral congenital ptosis. One sporadic patient with isolated congenital ptosis was found to have a de novo balanced translocation which disrupted *ZFHX4* [McMullan et al., 2002] and linkage analysis in a family with hereditary congenital ptosis suggested possible linkage to the 8q21.11–q22.1 region which includes *ZFHX4* with a LOD score of 1.16; however, sequencing and methylation-specific PCR of *ZFHX4* did not identify any causative variants in an affected family member [Nakashima et al., 2008].

The *PEX2* gene, located ~110kb distal to *ZFHX4*, is also deleted in eight of ten previously reported patients with 8q21.11 microdeletions as well as the two patients reported here [Palomares et al., 2011; Hofmann et al., 2011]. *PEX2* is a RING peroxin located in the peroxisomal membrane and is required for peroxisomal protein import through protein-ubiquitin ligase activity [Platta et al., 2009]. Homozygous or compound heterozygous intragenic mutations in *PEX2* are associated with Zellweger syndrome, a recessive peroxisome biogenesis disorder, as well as isolated autosomal recessive ataxia [Waterham and Ebberink, 2012]. Ocular features of Zellweger syndrome include cloudy cornea, congenital cataracts, glaucoma, and retinal anomalies, which overlap significantly with the eye features observed in 8q21.11 microdeletion syndrome and our patients [Waterham and Ebberink, 2012]. One paper reported cortical lens opacities that were noted biomicroscopically in parents of four patients with Zellweger syndrome; *PEX2* mutation status was not known in these families [Hittner et al., 1981]. Nonsense, missense, and frameshift mutations in *PEX2* have been identified in patients with Zellweger syndrome but whole gene deletions of *PEX2* have not been reported [Waterham and Ebberink, 2012]. Therefore, a contribution of *PEX2* to the ocular anomalies associated with the 8q21.11 microdeletion syndrome is possible but requires additional studies.

With the exception of classic Peters plus syndrome, the majority of syndromic Peters anomaly remains unexplained genetically [Weh et al., 2014]. It is interesting to note that substantial overlap exists between Peters plus syndrome and 8q21.11 microdeletion syndrome (Table 1) and, in fact, both patients presented here had been given a diagnosis of ‘Peters plus-like’ prior to identification of the deletion. The variability of the observed systemic features suggests screening for 8q21.11 microdeletions should be undertaken in patients with Peters anomaly and systemic defects that do not fit the criteria for classic Peters plus syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Facial photographs of Patient 1 in infancy (A) and at 6 years of age (B). Please note corneal opacities in infancy with partial clearing later, high forehead, cupid's bow upper lip, and prominent low-set ears.

Schematic drawing of 8q21 deletions in affected patients.

Figure 2. Schematic drawing of 8q21 deletions in affected cases. The UCSC Genome Browser (<http://genome.ucsc.edu>) view of the 8q21 region indicating positions of genes and deletions observed in each patient (red bars; chromosome 8 coordinates (hg19) for each deleted region are indicated below).

Table 1

Clinical features of 8q21del (this study and previously reported) and Peters Plus syndrome.

Features	Patient 1	Patient 2	8q21.11 microdeletion ^{a*}	Peters Plus Syndrome ^{b*}
Ptosis	ND	ND	++	–
Strabismus	–	ND	+	–
Corneal opacity	+	+	+	++
Peters anomaly	+	+	–	++
Round face	+	ND	++	+
High/prominent forehead	+	ND	++	++
Downslanting palpebral fissures	–	ND	+	–
Upper lip anomaly (thin/cupid bow)	+	+	++	++
Down-turned corners of the mouth	–	+	++	–
Highly arched palate	–	–	+	ND
Cleft lip/palate	–	–	–	+
Persistent primary dentition	+	–	–	–
Micrognathia	–	ND	++	+
Ear anomalies	+	+	++	++
Short/broad neck	–	+	+	+
Short stature	–	–	+	++
Intellectual/developmental disability	+	+	++	++
Hypotonia	+	+	+	–
Syndactyly/camptodactyly	–	+	+	–
Brachydactyly	–	–	–	++
Abnormal palmar creases	+	ND	+	–
Joint contractures	–	+	+	–
Congenital heart defect	–	–	–	+
Genital tract anomalies	–	+	+	+
Urinary tract anomalies	–	–	–	+

^a based on 10 cases presented in Palomares et al. 2011, Hofmann et al. 2011 and Vulto-van Silfhout et al. 2013

^b *B3GALT1*-positive Peters Plus syndrome (46 cases as reviewed in Weh, et al. 2013)

* for these columns ‘++’ indicates present in 75% of patients, ‘+’ indicates present in ~30–60% of patients, and ‘–’ indicates rarely or never reported;

ND: not determined; features seen at a similar frequency in both conditions are noted in bold font