Prolidase Deficiency in a Mexican-American Patient Identified by Array CGH Reveals a Novel and the Largest *PEPD* Gene Deletion

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Key Words

Chromosome microarray analysis · Deletion mutation · Novel mutation · *PEPD* · Prolidase deficiency

Abstract

Prolidase deficiency (PD) is a rare genetic disorder caused by mutations in the peptidase D (*PEPD*) gene, affecting collagen degradation. Features include lower extremity ulcers, facial dysmorphism, frequent respiratory infections, and intellectual disability, though there is significant intra- and interfamilial variability. Twenty-eight mutations have been previously reported, all either small deletions/duplications or point mutations discovered by enzyme or DNA assays. PD has been reported in patients of various ethnic backgrounds, but never in the Mexican-American population. We describe the first Mexican-American patient with PD, who presented with typical facial features, developmental delay, microcephaly, and xerosis. Chromosome microarray analysis (CMA) revealed a homozygous deletion in the region of 19q13.11, estimated to be between 124.79 and 195.72 kb in size, representing the largest *PEPD* gene deletion reported to date and the first discovered by CMA.

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Prolidase deficiency (PD; OMIM 170100) is a rare autosomal recessive inborn error of amino acid metabolism that affects collagen degradation, with an estimated incidence of 1–2 cases per 1,000,000 births [Lupi et al., 2008]. PD was first described by Goodman et al. [1968] and has a wide phenotypic spectrum with no evidence for genotype-phenotype correlation [Falik-Zaccai et al., 2010]. Common clinical features include facial dysmorphism, chronic ulcerations of the lower extremities, intellectual disability, and recurrent respiratory tract infections. The symptoms are caused by the reduction or loss of prolidase activity due to mutations in the peptidase D (*PEPD*; OMIM 613230) gene located in chromosome 19q13.11, which has multiple functions including involvement in the latter stages of catabolism of dietary and endogenous proteins rich in proline or hydroxyproline, such as collagen. Clinical manifestations are often detectable in early childhood, but late-onset cases have also been reported [Lupi et al., 2008].

Patient and Methods

Clinical Report

Our patient is a 6-year-old boy born to consanguineous parents (parents' fathers are second cousins) of Mexican descent. The remainder of the family history is unremarkable. Our patient presents with microcephaly (OFC = 48 cm, –8 SD) and with

Fig. 1. A aCGH Genoglyphix plot of chromosome 19 showing probes (blue dots) located at $-3.0 \log_2$ ratio. **B** UCSC plot showing the deletion involving all 15 exons and 14 introns of the *PEPD* gene.

normal height (126 cm, 80th percentile) and weight (23 kg, 50th percentile). He has dysmorphic facial features including synophrys, proptosis, hypertelorism, downslanting palpebral fissures, a prominent nose, thin vermilion of the upper lip, prognathism, and low anterior and posterior hairlines. His skin examination revealed prominent supragluteal fat pads and diffuse xerosis. He has receptive and expressive language delay despite a normal hearing evaluation. He receives speech and occupational therapies, verbalizes ~15 words and uses some sign language. He walked at the age of 19 months and currently walks and runs without difficulty. Other medical problems include constipation. Abdominal ultrasound revealed splenomegaly that was not detected on physical examination. His parents deny any history of ulcerations of the skin, recurrent pulmonary infections, or other recurrent infections.

Molecular Cytogenetic Analysis

Chromosome microarray analysis was performed using the array comparative genome hybridization (aCGH) method labeled with 2 different fluorophores for the patient extracted DNA and a sex-match control DNA and then hybridized onto NimbleGen CGX-12 v1.0 12-plex hg 18 based on the human genome build 18 following the manufacturer's protocol. The resolution of aberration is 10–50 kb for a detectable deletion of minimum size. The $\log_2$ ratio of the 2 different labeled patient and control DNA were analyzed and calculated using Genoglyphix database analysis (Signature, Spokane, Wash., USA).

Results

Molecular Cytogenetic Results

Based on the $\log_2$ ratio, the results revealed an interstitial biallelic deletion involving the *PEPD* gene (fig. 1). This deletion is characterized by a copy loss of 5 oligonucleotide probes in the region of 19q13.11. This abnormality is estimated to be a minimum size of 124.79 kb and a maximum size of 195.72 kb due to gaps in the regions represented on the microarray with genomic coordinates: arr[hg18] 19q13.11(38,569,683–38,704,639)×0. Because of the biallelic deletion, the patient has a homozygous deletion in *PEPD*, which is known to be associated with PD.

FISH of the BAC clone RP11-1101H9 (205 kb with 62% within region of interest) directed onto 19q13.11 was obtained from Empire Genomics (Buffalo, N.Y., USA) and performed on the patient and his sister. FISH results showed 2 copies of diminished signals (compared to those found in the sister) in 50 interphase and 20 metaphase cells of the patient's peripheral blood (fig. 2B), indicating a biallelic deletion, confirming the aCGH findings. FISH of the same BAC clone performed on 50 in-

Fig. 2. **A** Interphase cell of the sister showing 1 normal and 1 diminished signal (arrows) of the RP11-110H11 probe (SpectrumOrange™) in the presence of 2 normal signals of the centromere of chromosome 20 (SpectrumGreen™) used as an internal control. **B** Interphase cell of the patient showing 2 diminished signals of the probe. **C** Partial metaphase cell of the sister showing 1 diminished and 1 normal signal of the SpectrumOrange probe.

terphase and 20 metaphase cells of the sister showed one diminished signal indicating a monoallelic deletion (fig. 2A, C).

Biochemical Analysis

By ion exchange method, urine amino acid analysis revealed elevated methionine (195 mM/M creatinine; normal <50 mM/M creatinine) as well as unidentified peaks causing interference with the peaks of isoleucine, leucine and tyrosine. Using gas chromatography-mass spectrometry, urine organic acid analysis revealed imidodipeptiduria. Carbohydrate-deficient transferrin analysis was also performed to rule out a congenital disorder of glycosylation, given the physical finding of supragluteal fat pads. The result was normal.

Discussion

To date, ~90 patients with PD have been described, 67 of which have been molecularly characterized revealing 28 distinct mutant alleles [Tanoue et al., 1990, 1991; Ledoux et al., 1994, 1996; Kikuchi et al., 2000; Forlino et al., 2002; Lupi et al., 2004, 2006, 2008; HersHKovitz et al., 2006; Wang et al., 2006; Falik-Zaccai et al., 2010; Klar et al., 2010; Butbul Aviel et al., 2012; Caselli et al., 2012; Pandit et al., 2013; Besio et al., 2015]. The *PEPD* gene is over 130 kb long and is comprised of 15 exons. Of the 28 mutations, there are 14 point mutations; 5 splice site mutations; 6 small deletions causing either a missing amino acid, a premature stop codon, or involving an intron; 1 larger deletion of 774 bp causing complete elimination of

exon 14; 1 small duplication leading to a truncated enzyme, and one 3-bp insertion resulting in distortion of the enzyme (table 1). The current gene deletion is the largest yet reported. Additionally, all prior mutations were identified by enzyme or DNA assays, making this the first deletion identified by aCGH. The Databases of Decipher and International Standards for Cytogenomic Arrays have no patients with pure complete or intragenic *PEPD* deletions. All documented patients within 19q13.11 region have several genes including *PEPD*, and the Database of Genome Variants shows no variants.

Prolidase is a dipeptidase necessary for the final step of collagen degradation. It splits imidodipeptides with C-terminal proline or hydroxyproline, making proline available for reutilization in collagen synthesis [Myara et al., 1984; Klar et al., 2010]. In PD, this enzyme has decreased or complete loss of activity, giving rise to imidodipeptiduria and a variety of clinical manifestations. In our patient, the urine amino acids showed ‘interfering peaks’ which are consistent with prolidase peptide deficiency. The urine organic acids were able to identify imidodipeptides.

PD exhibits significant inter- and intrafamilial phenotypic variability [Falik-Zaccai et al., 2010]. Among patients with molecular characterization, skin abnormalities are the most common feature, present in 79% of patients, including ulcerations, telangiectasias, photosensitivity, dry skin, pseudo-psoriasis, or nonspecific dermatitis. Other features include dysmorphism (71%), intellectual disability or developmental delay (69%), frequent or serious infections (53%), splenomegaly (41%), bony abnormalities (19%), systemic lupus erythemato-

Table 1. List of molecularly characterized PD patients and their clinical manifestations

Patient ID	Exon	Intron	Mutation	Effect on protein	Clinical phenotype			FD	SM	additional features	Ethnicity/ residence	Reference
					skin ulcers	ID/ DD	FI					
1 ^a	2		202-2A→T/202-2A→T	absent exon 3; alternative splicing	+	+	+	+	-	microcephaly, short stature, osteopenia, genu valgum	Turkey	Besio et al., 2015
2 ^a	2		202-2A→T/202-2A→T	absent exon 3; alternative splicing	+	+	+	+	-	microcephaly, short stature, genu valgum	Turkey	Besio et al., 2015
3	3		329+4del/329+4del		+	-	-	+	-	microcephaly, short stature	Turkey	Besio et al., 2015
4	3		329+4del/329+4del		+	+	+	+	-	microcephaly, osteopenia	Turkey	Besio et al., 2015
5	4		IVS4-1G→C/null allele	absent exon 5	+	+	+	-	-		Okiahoma	Ledoux et al., 1994
6	6		IVS6-2A→G/IVS6-2A→G	absent exon 7	+	+	+	-	-	SLE	Canada	Ledoux et al., 1994
7	7		IVS7-1G→A/IVS7-ss1G→A	alternative splicing	+	+	+	+	+	anemia, telangiectasia, photosensitivity	Italy	Forlino et al., 2002
8	7		IVS7-1G→A/IVS7-1G→A	alternative splicing	+	-	+	+	-	telangiectasia	Italy	Forlino et al., 2002
9	8		611dupIAGGCCACCGTGA/611dupIAGGCCACCGTGA	frameshift and premature stop codon	+	+	+	+	+	FTT	Turkey	Lupi et al., 2006
10	8/12		551G→A/833G→A	Arg184Gln	-	-	-	-	-	asymptomatic at birth, no other data	Canada	Ledoux et al., 1996
11	8		551C→T/551C→T	Arg184X	+	+	+	+	-	joint dislocations, partial deafness, visual disturbance	Japan	Kikuchi et al., 2000
12	8		605C→T/605C→T	Ser202Phe	-	+	+	+	+	hepatomegaly, elevated IgE, brachydactyly, craniosynostosis	Druze/Israel	Hershkovitz et al., 2006
13 ^b	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis	Moslem/Israel	Falik-Zaccai et al., 2010
14 ^b	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis	Moslem/Israel	Falik-Zaccai et al., 2010
15 ^b	8		605C→T/605C→T	Ser202Phe	-	+	-	+	-	dermatitis, asthma	Moslem/Israel	Falik-Zaccai et al., 2010
16 ^b	8		605C→T/605C→T	Ser202Phe	-	+	-	+	-	dermatitis, asthma	Moslem/Israel	Falik-Zaccai et al., 2010
17 ^b	8		605C→T/605C→T	Ser202Phe	-	+	+	+	-	FTT, died at age 20 months of respiratory failure	Moslem/Israel	Falik-Zaccai et al., 2010
18 ^c	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis	Moslem/Israel	Falik-Zaccai et al., 2010
19 ^c	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis	Moslem/Israel	Falik-Zaccai et al., 2010
20	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	hypotonia	Druze/Israel	Falik-Zaccai et al., 2010
21	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis, asthma	Druze/Israel	Falik-Zaccai et al., 2010
22	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis, asthma	Druze/Israel	Falik-Zaccai et al., 2010
23	8		605C→T/605C→T	Ser202Phe	+	+	+	+	+	SLE phenotype	Druze/Israel	Falik-Zaccai et al., 2010
24 ^d	8		605C→T/605C→T	Ser202Phe	-	+	+	+	+	dermatitis, asthma, bronchiectasis	Druze/Israel	Falik-Zaccai et al., 2010
25 ^d	8		605C→T/605C→T	Ser202Phe	-	+	+	+	+	asthma, dermatitis	Druze/Israel	Falik-Zaccai et al., 2010
26 ^c	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	dermatitis	Druze/Israel	Falik-Zaccai et al., 2010
27 ^c	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	FTT	Druze/Israel	Falik-Zaccai et al., 2010
28 ^c	8		605C→T/605C→T	Ser202Phe	-	+	-	+	+	cystic fibrosis, pseudo-psoriasis, FTT	Druze/Israel	Falik-Zaccai et al., 2010
29	8		605C→T/605C→T	Ser202Phe	-	-	-	+	-	SLE	Druze/Israel	Falik-Zaccai et al., 2010
30	8		605C→T/605C→T	Ser202Phe	-	+	+	+	+	SLE, pancytopenia, lung disease, rash	Druze/Israel	Butbul Aviel et al., 2012
31	9		634G→C/634G→C	Ala212Pro	-	+	+	+	+	SLE, FTT, microcephaly, clinodactyly, brachydactyly	Moslem Arab	Butbul Aviel et al., 2012
32	9		634G→C/634G→C	Ala212Pro	-	+	+	+	+	FTT, dermatitis, SLE phenotype	Moslem/Israel	Falik-Zaccai et al., 2010
33	10		691delTAC/691delTAC	231delTyr	+	+	+	+	-	hypotonia, irritability	Portugal	Lupi et al., 2004; Pereira and Vilarinho, 1997
34	10		691delTAC/691delTAC	231delTyr	+	-	+	+	-	elevated IgE	Portugal	Lupi et al., 2004; Lopes et al., 2002
35 ^f	11		768C→G/768C→G	Tyr256X	+	-	-	+	+	photosensitivity, elevated IgE, SLE phenotype	Moslem Arab	Klar et al., 2010
36 ^f	11		768C→G/768C→G	Tyr256X	+	-	+	+	+	telangiectasia, SLE phenotype	Moslem Arab	Klar et al., 2010
37 ^f	11		768C→G/768C→G	Tyr256X	+	-	+	+	+	fulminant hepatitis leading to infant death	Moslem Arab	Klar et al., 2010
38	11		IVS11+1G→C/null allele	absent exon 11	+	+	-	+	-	telangiectasia, photosensitivity	Italy	Forlino et al., 2002
39	11		IVS11+1G→A/IVS11+1G→A	alternative splicing	-	-	+	-	-	telangiectasia, photosensitivity	India	Lupi et al., 2008
40 ^g	11		793C→T/793C→T	Arg265X	+	+	+	+	-	hepatomegaly, eczema-like rash, asplenia, FTT	Amish/Ohio	Wang et al., 2006
41 ^g	11		793C→T/793C→T	Arg265X	+	+	+	+	+	hepatomegaly, eczema-like rash, FTT	Amish/Ohio	Wang et al., 2006

Table 1 (continued)

Patient ID	Exon	Intron	Mutation	Effect on protein	Clinical phenotype			SM	additional features		Ethnicity/ residence	Reference
					skin ulcers	ID/ DD	FI	FD				
42 ^g	11		793C→T/793C→T	Arg265X	+	-	+	+	+	hepatomegaly, eczema-like rash	Amish/Ohio	Wang et al., 2006
43 ^g	11		793C→T/793C→T	Arg265X	+	-	+	+	+	hepatomegaly, eczema-like rash	Amish/Ohio	Wang et al., 2006
44	12		826G→A/826G→A	Asp276Asn	+	-	-	-	+		Middle East	Tanoue et al., 1990; Lapière and Nussgens, 1969
45	12		826G→A/826G→A	Asp276Asn	+	+	+	-	-	hypotonia, eczema-like rash, joint laxity, cortical and cerebellar atrophy on MRI/brain	Chinese	Tanoue et al., 1990; Lombbeck et al., 1986
46 ^h	12		909_910insGCC	Q303_K304insA	+	-	-	-	-		Kashmir	Pandit et al., 2013
47 ^h	12		909_910insGCC	Q303_K304insA	+	-	-	-	-		Kashmir	Pandit et al., 2013
48	12		874delT/874delT	premature stop codon	+	-	+	-	-	osteopenia	Turkey	Besio et al., 2015
49	12		977G→A/977G→A	Trp325*	+	+	+	+	-	genu valgum	Spain	Besio et al., 2015
50	12/14		977G→A/1342G→A	Trp325*/Gly448Arg	+	+	+	+	-	short stature, genu valgum	England	Besio et al., 2015
51	12/14		826G→A/1342G→A	Asp276Asn/Gly448Arg	+	+	+	+	-	perianal eczema	Denmark	Lupi et al., 2006
52	12/14		833G→A/1342G→A	Gly278Asp/Gly448Arg	+	+	+	-	-	FTT	Denmark	Lupi et al., 2006
53 ⁱ	13		1103T→G/1103T→G	Leu368Arg	-	+	-	+	+	FTT	Druze/Israel	Falik-Zaccai et al., 2010
54 ⁱ	13		1103T→G/1103T→G	Leu368Arg	-	+	-	+	+	FTT	Druze/Israel	Falik-Zaccai et al., 2010
55	13/14		1133delACG/1301delT	Asp378del/frameshift and premature stop codon	+	+	+	+	+	short stature, microcephaly	Italy	Caselli et al., 2011
56 ^j	14		1234G→A/1234G→A	Glu412Lys	+	-	-	+	-	elevated IgE, hemoglobin O trait, eczema-like rash, dry skin	Turkey	Lupi et al., 2006;
57 ^j	14		1234G→A/1234G→A	Glu412Lys	-	-	-	-	-	eczema-like rash, dry skin	Turkey	Ayug et al., 2006
58	14		1342G→A/null allele	Gly448Arg	+	+	+	-	-	slow skin healing after injury	Canada	Ledoux et al., 1994
59	14		1342G→A/1342G→A	Gly448Arg	+	+	+	+	-		UK	Ledoux et al., 1994
60 ^k	14		1342G→A/1342G→A	Gly448Arg	+	+	+	+	+		Italy	Forlino et al., 2002
61 ^k	14		1342G→A/1342G→A	Gly448Arg	+	+	-	-	-		Italy	Forlino et al., 2002
62	14		1342G→A/1342G→A	Gly448Arg	+	+	-	-	+	SLE	Italy	Lupi et al., 2006
63 ^l	14/15		1342G→A/1354G→A	Gly448Arg/Glu451Lys	+	+	+	+	-	osteopenia	Poland	Besio et al., 2015
64 ^l	14/15		1342G→A/1354G→A	Gly448Arg/Glu451Lys	+	-	+	+	+	osteopenia	Poland	Besio et al., 2015
65 ^m	14		del774bp	absent exon 14	+	+	-	-	-	telangiectasia, premature gray hairs at age 13 years	Japan	Tanoue et al., 1991; Arata et al., 1979
66 ^m	14		del774bp	absent exon 14	+	-	-	-	-		Japan	Tanoue et al., 1991; Arata et al., 1979
67	15		1354delGAG/null allele	452delGlu	+	+	-	-	-	chronic liver disease	Australia	Ledoux et al., 1994
68			124,79–195,72-kb deletion		-	+	-	+	-	microcephaly, lipodystrophy, xerosis	Mexican/USA	Current paper

Table adapted from Lupi et al. [2008] with additional information on mutations and phenotypes. Patients are unrelated unless otherwise indicated. DD = Developmental delay; FI = frequent infections; FTT = failure to thrive; ID = intellectual disability; SM = splenomegaly; ^{a, c, d, f, i} Siblings; ^{b, e, g} family related; ^{h, j, m} sisters; ^j cousins; ^k brothers.

sus (SLE; 14%), failure to thrive (16%), microcephaly (12%), hepatomegaly (9%), and asthma (7%), as outlined in table 1. Interestingly, our patient did not have a history of frequent infections or skin ulcerations despite the large deletion. Additionally, our patient has a unique finding, supragluteal lipodystrophy, which has not been previously reported in PD. For this reason, the carbohydrate-deficient transferrin studies were tested and found negative, ruling out congenital disorders of glycosylation.

Notably, SLE has been linked to PD [Bissonnette et al., 1993; Shrinath et al., 1997; Di Rocco et al., 2007] and is associated with multiple mutations [Lupi et al., 2006, 2008; Falik-Zaccai et al., 2010; Klar et al., 2010; Butbul Aviel et al., 2012]. The mechanistic relationship between these entities is not clear, but a loss of immune tolerance to lupus-associated autoantigens in PD has been hypothesized, leading to positive antinuclear antibodies and other autoantibody testing even in patients without clinical SLE [Kurien et al., 2013].

Cystic fibrosis confirmed by sweat chloride testing has also been found in patients with PD, though mutation and haplotype analysis did not show changes in the *CFTR* gene [Luder et al., 2007]. Multiple other PD patients with clinical cystic fibrosis have had normal sweat chloride testing [Mandel et al., 2000]. Despite nullisomic complete deletion in our patient, SLE or cystic fibrosis features were not observed. This suggests that the presence of a mutated protein may cause more systemic symptoms when compared to an absent protein. However, more patients with a similar size deletion would be needed to confirm this. It is also possible that SLE or chronic lung disease have not yet developed in our patient, as other cases appear to present in adolescence and adulthood.

The diagnosis in our patient was made incidentally at the age of 4 years via aCGH that was ordered due to dysmorphic features, microcephaly and developmental delay. If a mutation had not been detected, the diagnosis may not have been made, given his lack of several classically described symptoms. However, our patient does have the 3 most common features found in molecularly characterized patients: dysmorphism, developmental delay and abnormal skin findings. Therefore, we suggest that PD should be part of the differential diagnosis for any patient with characteristic facial dysmorphism, abnormal skin findings of any kind, and intellectual disability or developmental delay as they are each present in over 50% of patients.

Our patient's sister, found to be heterozygous for the same deletion, is asymptomatic. The patient's parents are

obligate carriers and are also asymptomatic. Thus, there is no evidence of haploinsufficiency of the gene, consistent with previous reports of families with multiple carriers [Falik-Zaccai et al., 2010].

The ethnic origin for previously reported patients with PD is in European countries, Canada, the US, and Middle Eastern and several Asian countries (table 1). To our knowledge, there have been no reported cases in patients of Mexican descent, making our patient the first.

In conclusion, we report a novel large deletion of the *PEPD* gene, discovered by aCGH in a Mexican-American family. Although PD is a rare disorder, it is likely underdiagnosed, particularly in patients with a mild phenotype. The marked variability in clinical presentation also creates diagnostic difficulty, and the prognosis is unpredictable. For this reason, genetic counseling, even to members of the same family, is problematic [Mandel et al., 2000]. No specific therapies can be recommended for PD. Greater awareness and improved understanding of the pathophysiology of the disease will improve the recognition and treatment of this multisystem disorder.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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