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Phenotypic Spectrum of Autosomal Recessive Congenital Ichthyosis Due to *PNPLA1* Mutation

L.M. Boyden[1,*], **B.G. Craiglow**[2,3,*], **R.H. Hu**[2], **J. Zhou**[2], **J. Browning**[4], **L. Eichenfield**[5], **Y.L. Lim**[6], **M. Luu**[7], **L.M. Randolph**[8], **M. Ginarte**[9], **L. Fachal**[10], **L. Rodriguez-Pazos**[11], **A. Vega**[10], **D. Kramer**[12], **G. Yosipovitch**[13], **H. Vahidnezhad**[14], **L. Youssefian**[14], **J. Uitto**[14], **R.P. Lifton**[1], **A.S. Paller**[15], **L.M. Milstone**[2], and **K.A. Choate**[1,2,16]

[1]Department of Genetics, Yale University School of Medicine, New Haven, CT

[2]Department of Dermatology, Yale University School of Medicine, New Haven, CT

[3]Department of Pediatrics, Yale University School of Medicine, New Haven, CT

[4]Department of Dermatology, Baylor College of Medicine, San Antonio, TX

[5]Department of Dermatology, University of California San Diego, San Diego, CA

[6]Department of Dermatology, National Skin Centre, Singapore, Singapore

[7]Divisions of Dermatology, Children's Hospital of Los Angeles, Los Angeles, CA

[8]Medical Genetics, Children's Hospital of Los Angeles, Los Angeles, CA

[9]Department of Dermatology, Complejo Hospitalario Universitario, Santiago de Compostela, Spain

[10]Fundación Pública Galega de Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica-USC, CIBERER, IDIS, Santiago de Compostela, Spain

[11]Servicio de Dermatología, Complejo Hospitalario Universitario de Vigo, Vigo, Spain

[12]Department of Dermatology, Hospital Luis Calvo Mackenna, Santiago, Chile

[13]Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, Miami, FL

[14]Department of Dermatology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA

[15]Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL

[16]Department of Pathology, Yale University School of Medicine, New Haven, CT

Correspondence: Keith A. Choate, Department of Dermatology, Yale University School of Medicine, PO Box 208059, New Haven, Connecticut 06520, USA. keith.choate@yale.edu.

*These authors contributed equally to this work.

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Dear Editor

The ichthyoses are rare skin disorders linked by the common finding of scale and concomitant barrier function abnormalities. Recently, mutations in *PNPLA1* which encodes patatin-like phopholipase domain containing 1, and plays a role in the formation of the epidermal lipid barrier, have been identified as rare cause of non-syndromic ARCI[1–6].

We identified subjects with *PNPLA1* mutations within our registry of 732 ichthyosis kindreds. DNA was isolated from blood, and either multiplex targeted next generation sequencing (NGS) of 42 genes known to cause disorders of keratinization or WES (Supplementary Table 1) was performed. Fourteen unrelated ARCI probands were found to be compound heterozygous or homozygous for mutations in *PNPLA1* which were confirmed with Sanger sequencing. *PNPLA1* mutations segregated with disease in all kindreds, five of which were consanguineous (Supplementary Figures 1–14).

A total of 16 different *PNPLA1* mutations were observed, including two which result in early termination, a splice site mutation, and 13 missense substitutions at conserved residues (Figure 1, Supplementary Figure 15). All missense mutations are within the more highly conserved N-terminal half of the protein, and all but two are clustered within the patatin domain. Two subjects are homozygous for missense mutations at S53, the nucleophilic serine in the putative lipid hydrolase site, and one is homozygous for a missense mutation at D172, the other critical residue in the catalytic dyad.

The phenotypes of all subjects with *PNPLA1* mutations are described in Table 1, with representative clinical photos provided in Supplementary Figures 1–14. At birth, seven subjects presented with a collodion membrane (one with vernix-like hyperkeratosis), and eight showed generalized erythema and/or scaling. Mature phenotypes include scale that may be fine or plate-like, and erythema ranging from minimal to severe (Figure 2). The presence and degree of ectropion and palmoplantar keratoderma are variable, although they are either absent or mild in the majority of subjects. Only seven of 19 subjects were born with a collodion membrane.

Generally, the spectrum of phenotypic severity appears difficult to correlate with specific *PNPLA1* genotypes. While some subjects with the same genotype exhibit consistent clinical features, there are other subjects with identical or similar mutations who show notable variation in phenotype. For instance, the affected siblings of kindred ICH162 (Supplementary Figure 2), both of whom are compound heterozygous for the same missense mutations, vary significantly in the severity of their presentations. ICH162-1 was born collodion and developed plate-like scale, palmoplantar keratoderma, and severe ectropion, whereas her sister had generalized scale and erythema at birth with no collodion membrane, and now has fine white scale; mild ectropion presented only within the past two years at age 80.

Interestingly, we report two families that appear to display dominant inheritance, but in which sequencing revealed *PNPLA1* mutations consistent with recessive inheritance. In kindred ICH201 (Supplementary Figure 3), which was previously published as autosomal dominant ichthyosis [7], there are actually two different recessive *PNPLA1* genotypes in

affected individuals. The proband (ICH201-1) is compound heterozygous for A34T and S140P, while her two affected children (ICH201-3 and ICH201-4) are both homozygous for S140P, having presumably inherited a second copy of this mutation from their unaffected father. Mutation A34T has been previously been observed with homozygous inheritance in a prior report of a kindred from Galicia, Spain [8]. Kindred ICH201 is also from Galicia, and collection of the extended family history revealed additional family members with ichthyosis (the proband's deceased sister and a deceased nephew from another sister), despite no known history of consanguinity. These observations suggest that A34T and S140P may be founder mutations present at low frequency in Galicia, a region in which founder mutations in *TGM1* have also been reported [9]. Kindred ICH454 (Supplementary Figure 7) also is notable for an affected parent with two affected children and the resulting appearance of dominant inheritance. In this family, all three are homozygous for the same *PNPLA1* mutation as a result of the consanguineous union of the proband and a first cousin who is a heterozygous carrier.

Two of the missense mutations we report are distal to the patatin domain (aa16-185, Figure 1). Mutation C216R is homozygous in the three affected members of kindred ICH454 (described above), and mutation P235L is homozygous in subject ICH592-1, a child of first cousins of Turkish descent born with a collodion membrane and now exhibiting fine white scale and minimal erythema (Supplementary Figure 11). These mutations suggest that residues outside the canonical ezymatic region may nevertheless be critical to protein function.

In a cohort of 450 ichthyosis subjects in whom we have made a genetic diagnosis employing targeted NGS of 43 genes or WES, the 14 unrelated probands with pathogenic *PNPLA1* mutations we report here show *PNPLA1* to be an important, if relatively rare, cause of ARCI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ARCI	autosomal recessive congenital ichthyosis
LI	lamellar ichthyosis
CIE	congenital ichthyosiform erythroderma

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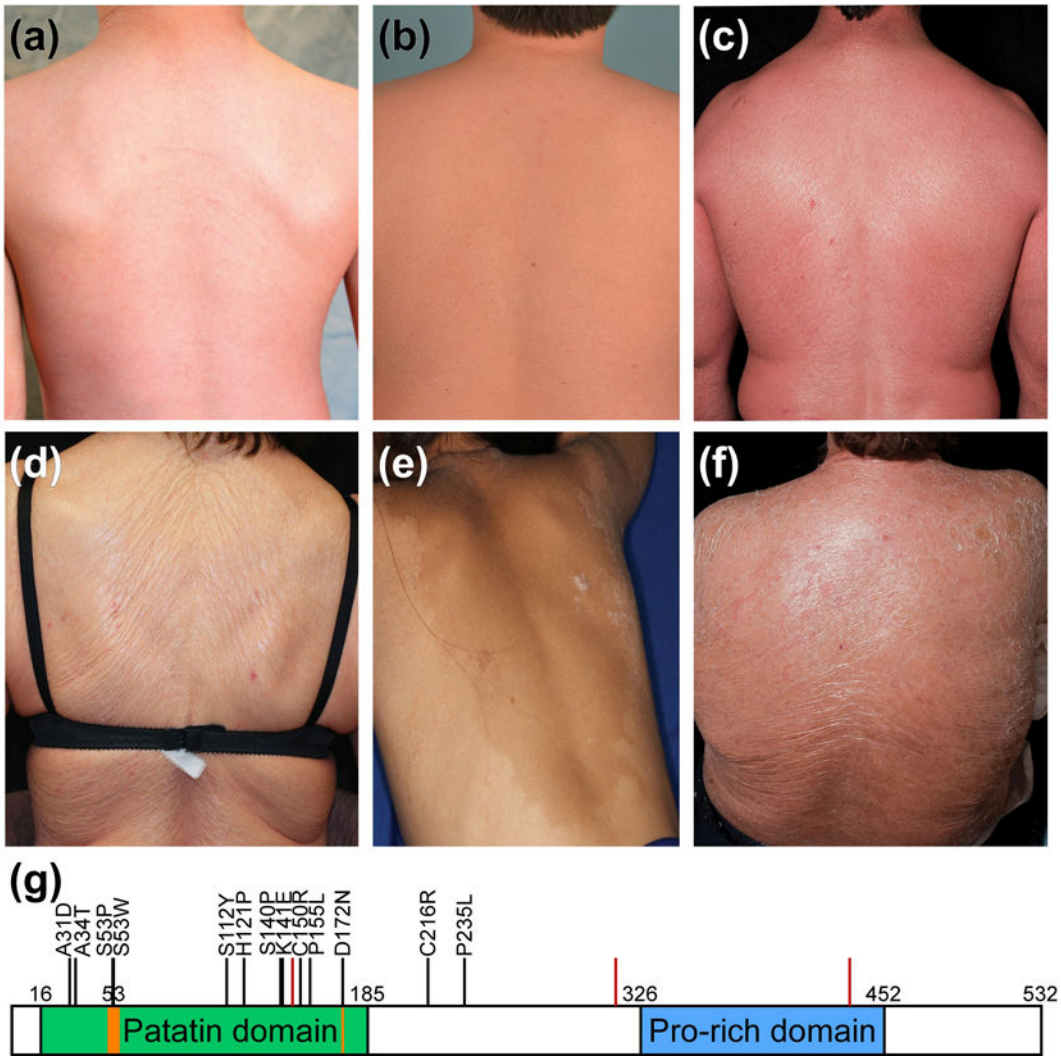

Figure 1. Spectrum of cutaneous phenotypes and *PNPLA1* mutation sites in subjects with ichthyosis

Extent and severity of erythema and scale vary significantly and include: (**a**) ICH136-1 and (**b**) ICH431-1, mild erythema and fine white scale; (**c**) ICH201-4, moderate-severe erythema and fine white scale; (**d**) ICH162-2 and (**e**) ICH561-1, minimal erythema and plate-like scale; and (**f**) ICH201-1, moderate-to-severe erythema with plate-like scale. (**g**) PNPLA1 protein domains: patatin domain (green), lipid hydrolase catalytic dyad (orange), and proline-rich domain (blue) are indicated; numbers specify amino acid position. Locations of mutations reported herein are shown with black bars and the amino acid change (missense mutations) or red bars (splice site and frameshift mutations).

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Table 1

Characteristics of subjects with *PNPLA1* mutations.

Subject	Mutation(s)	Neonatal Presentation	Scale	Erythema	Ectropion	PPK	Consanguinity
ICH136-1	c.335C>A; p.S112Y c.464C>T; p.P155L	collodion[1]	fine white	mild	none	none	no
ICH162-1	c.92C>A; p.A31D c.464C>T; p.P155L	collodion	plate-like	minimal	severe	mild	no
ICH162-2	c.92C>A; p.A31D c.464C>T; p.P155L	Non-collodion, presented in infancy with scale and erythema	plate-like	minimal	mild[2]	mild	no
ICH201-1	c.100G>A; p.A34T c.418T>C; p.S140P	generalized scale & erythema	plate-like	moderate	mild	mild	no
ICH201-3	c.418T>C; p.S140P homozygous	generalized scale & erythema	fine white	moderate-severe	none	mild	no
ICH201-4	c.418T>C; p.S140P homozygous	generalized scale & erythema	fine white	moderate-severe	none	none	no
ICH215-1	c.514G>A; p.D172N homozygous	collodion	unknown[3]				no
ICH422-1	c.418T>C; p.S140P c.448T>C; p.C150R	collodion	fine white	mild	none	none	no
ICH431-1	c.1300del.G; p.A434fs homozygous	Non-collodion, presented at 1 month with scale and erythema	fine white	mild	none	none	no
ICH454-1	c.646T>C; p.C216R homozygous	generalized scale	plate-like	minimal	none	mild	yes
ICH454-3	c.646T>C; p.C216R homozygous	generalized scale	plate-like	minimal	none	mild	yes
ICH454-4	c.646T>C; p.C216R homozygous	generalized scale	plate-like	minimal	none	mild	yes
ICH459-1	c.362A>C; p.H121P c.438+2C>G	collodion	fine white	minimal	none	none	no
ICH561-1	c.1300del.G; p.A434fs homozygous	unknown	extremities plate-like; trunk has fine white scale	minimal	none	mild	unknown[4]
ICH590-1	c.939G>T, c.940-952del.TGGGTTCCCAAAG; p.E313Dfs homozygous	unknown	lower extremities plate-like; trunk fine white	mild-moderate	mild	none	yes
ICH592-1	c.704C>T; p.P235L homozygous	collodion	fine white	minimal	none	none	yes
ICH600-1	c.421A>G; p.K141E homozygous	generalized scale & erythema	Plate-like	minimal	none	mild	yes
ICH650-1	c.157T>C; p.S53P homozygous	generalized scale	plate-like	moderate	mild	mild	no
ICH658-1	c.158C>G; p.S53W homozygous	collodion	fine white on trunk; plate-like on lower extremities	mild-moderate	mild	none	yes

PPK: palmoplantar keratoderma; hom.: homozygous;

[1] excessive vernix;

[2] ectropion did not present until late adulthood;

[3] subject moved out of the country at age 6 weeks and was lost to follow-up;

[4] subject is adopted.