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Case Report

Identification of two novel PNPLA1 mutations in Turkish families with autosomal recessive congenital ichthyosis

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SUMMARY: Dökmeci-Emre S, Taşkıran ZE, Yüzbaşıoğlu A, Önal G, Akarsu AN, Karaduman A, Özgüç M. Identification of two novel PNPLA1 mutations in Turkish families with autosomal recessive congenital ichthyosis. Turk J Pediatr 2017; 59: 475-482.

Autosomal recessive congenital ichthyosis (ARCI) is a group of inherited keratinization disorders that are characterized by abnormal epidermal keratinization. ARCI patients generally represent serious symptoms including collodion baby phenotype accompanied by dehydration, heat loss, electrolytic imbalance, and sepsis. ARCI shows high degree of clinical and genetic heterogeneity. To date, nine genes were shown to be responsible for ARCI phenotype. One of these genes, patatin-like phospholipase domain containing protein-1 (PNPLA1) was suggested to be involved in the synthesis of ω-O-acylceramides related to epidermal cornified lipid envelope organization. In addition to previously reported PNPLA1 mutations, we report two novel PNPLA1 mutations including one novel missense mutation c.335C>A (p.Ser112Tyr) and one novel deletion mutation c.733_735delTAC (p.Tyr245del) in Turkish ARCI patients from unrelated consanguineous families. We also report previously reported missense mutation c.514G>A (p.Asp172Asn) in Turkish ARCI patients. Novel PNPLA1 mutations were shown to be located in the catalytic patatin domain of PNPLA1 gene. Identification of novel mutations in PNPLA1 gene expands the mutational spectrum in the causative gene. Increase in the total number of cases has high diagnostic value in terms of genotype-phenotype correlation in ARCI patients.

Key words: autosomal recessive congenital ichthyosis (ARCI), PNPLA1, mutation.

Autosomal recessive congenital ichthyosis (ARCI) comprises a group of clinically and genetically heterogeneous Mendelian disorders of cornification (MEDOC) with a prevalence of less than 1/200.000.[1,2] ARCI is mainly characterized by abnormal scaling over the whole body due to the defects in epidermal keratinocyte differentiation and lipid metabolism.[3,4] The molecular mechanisms of ARCI are related to functional defects in the major components of epidermal barrier including intercellular lipid barrier, the cornified cell envelope and keratin or filaggrin degradation products.[5] The symptoms of ARCI may vary from mild to lethal conditions including hydroelectrolytic imbalance, thermal instability, dehydration, collodion baby phenotype and infection.[2,4] To date, nine different genes including TGM1[6,7], ABCA12[8], ALOXE3[9], ALOX12B[9-11], CYP4F22[12], LIPN[13], NIPAL4[14], CERS3[15,16], and PNPLA1[17] were found to be associated with ARCI.

Patatin-like phospholipase domain containing 1 (PNPLA1) gene (Gene ID 285848) is defined as one of the ARCI causing genes.[17] PNPLA1 gene contains eight exons at chromosome 6p21.31. The cloned cDNA sequence is 1,599 bp. (GenBank accession No. FJ457781) encoding a polypeptide with 532 amino acids. PNPLA1 protein has a patatin domain (residues 16–185) in the N-terminal region with serine–aspartate catalytic dyad (S53-D172) and a proline-rich domain (residues 326–451) in the C-terminal

region.[18] Mammalian patatin-like phospholipase domain containing protein family (PNPLA1-9) have critical roles in diverse aspects of signaling pathways and lipid metabolism involving triglyceride lipase, hydrolase, and transacetylase activities.[19,20] It is reported that human PNPLA1 protein is predominantly expressed in the keratinocytes of epidermal granular layer and plays role in lipid metabolism associated with cutaneous barrier formation.[17] In addition, recent studies reported that PNPLA1 function in the synthesis of omega-O-acylceramides as a transacylase and affect epidermal cornified lipid envelope organization.[21-23]

To date, 26 different PNPLA1 mutations have been reported associated with ARCI.[17, 24-27,30] In the present study, we report two novel mutations, including one missense mutation c.335C>A (p.Ser112Tyr) and one deletion mutation c.733_735delTAC (p.Tyr245del), and also one previously reported missense mutation c.514G>A (p.Asp172Asn) in PNPLA1 gene in seven ARCI patients from three consanguineous Turkish families.

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Seven patients from three consanguineous families were recruited (Fig. 1). The diagnosis of all patients was made by of clinical findings and histopathological features of skin biopsies. All detailed clinical findings are summarized in Table I. This study was approved by the Ethics Committee of Hacettepe University and informed consent to participate was obtained from all patients and/or parents.

Genotype analysis of selected individuals from a cohort of three consanguineous families with ARCI was achieved using genome-wide linkage analysis and Sanger DNA sequencing methods. Affymetrix 250K SNP arrays were used in order to perform genome-wide analysis according to manufacturer's recommendations. VIGENOS Software (Hemosoft, Ankara) was used for homozygosity mapping. The affected individuals showed a homozygous haplotype in the 6p21 region comprising PNPLA1 gene. Both DNA strands from the probands were entirely sequenced for the eight exons and for the intron/exon boundaries of the PNPLA1 gene. Details of PCR procedure were previously

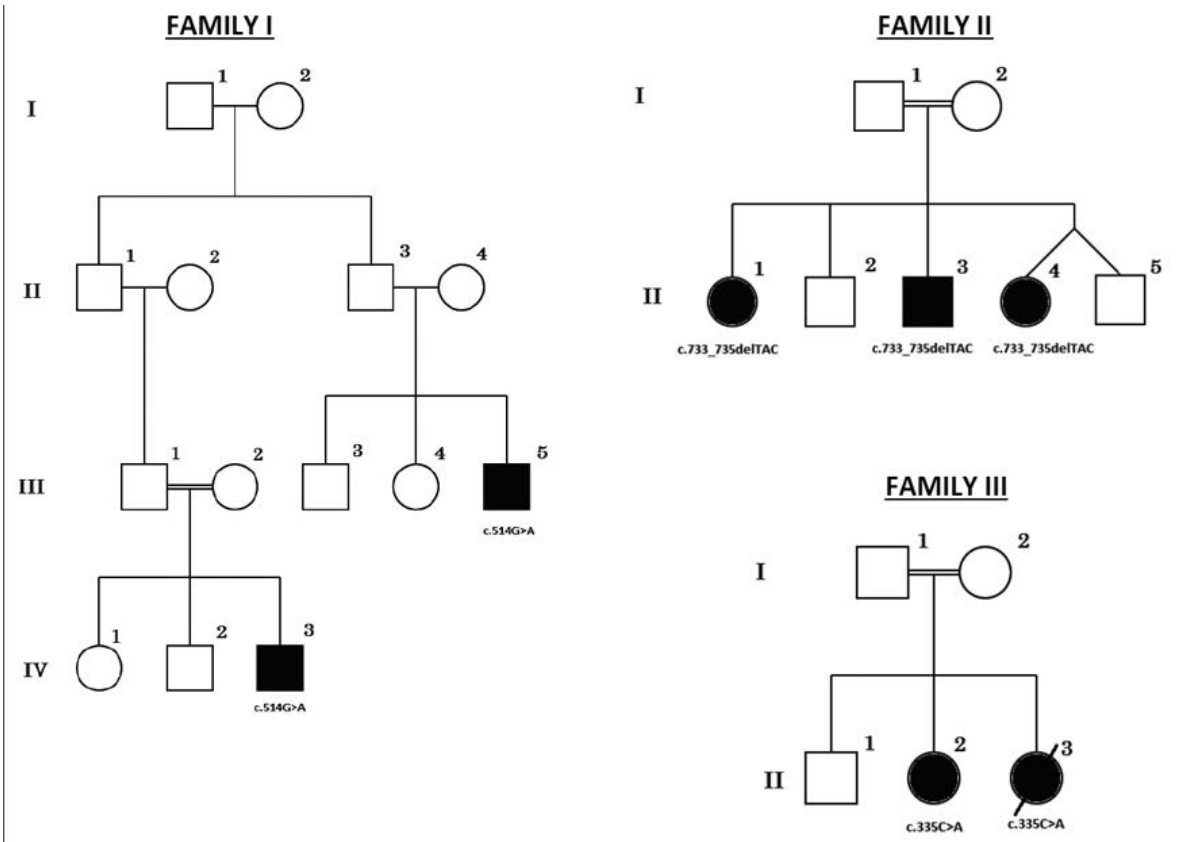

Fig. 1. Pedigree drawings of three consanguineous families with ARCI.

Table I. Summary of Clinical Features.

Family	Sex	Age	Collodion baby	Distribution of scaling	Scale	Erythema	Ectropion	Scalp	Palmoplantar involvement	Hypohidrosis	Nail/ teeth	Pruritus
I	M	20 yrs.	+	Generalized, including flexures	White-light brown, large lamellar	Mild, generalized	-	No	Mild palmoplantar keratoderma, accentuated palmoplantar markings	-	-/-	Mild
I	M	2 mo.	+	Generalized, including flexures	Mild-severe generalized, lamellar; octagonal lamellar on the back and legs	Mild, generalized	+	No	Mild palmoplantar keratoderma	-	-/-	Mild
II	F	8 yrs.	+	Generalized, including flexures	White-light brown, mild to moderate	Mild to moderate; face	+	Squamous pityriasiform appearance	Mild palmoplantar keratoderma, accentuated palmoplantar markings	-	-/-	Mild
II	M	5 yrs.	+	Generalized, including flexures	White-light brown	Mild to moderate; face	+	Squamous pityriasiform appearance	Mild palmoplantar keratoderma	+	-/-	Mild
II	F	5 yrs.	+	Generalized, including flexures	White-light brown	Mild to moderate; face	+	Thick scale	Mild palmoplantar keratoderma	-	+/-	Mild
III	F	2 yrs.	+	Generalized, including flexures	White-gray, mild to moderate	Disseminated, mild	+	Squamous pityriasiform appearance	Accentuated palmoplantar markings	-	+/+	Mild
III	F	20 days	+	-	White, fine	+	+	-	Accentuated palmoplantar markings	-	-/-	-

described.[17] Cycle sequencing was performed with the ABI PRISM Big Dye Terminator Cycle Sequencing Kit following the manufacturer's instructions and sequences were analyzed on the ABI PRISM 3130 DNA Analyzer. All parents were heterozygous for the mutations. Following the analysis of the patients and their relatives, it was shown that identified novel mutations co-segregated with their ARCI status. No mutations in the PNPLA1 gene were detected in a panel of 100 control DNA samples.

Family 1: Two affected patients from a consanguineous family (Family I), born as collodion babies presented with skins with generalized fine white to light-brown scales underlying erythema base. There was a mild palmoplantar keratoderma and hyperlinearity. One of the patients (III:5) had mild to severe large scales on the back. The other patient (IV:3) had mild to severe octagonal scales on the back and legs. Their nails and teeth were normal.

In this family, two affected individuals had a homozygous missense mutation (c.514G>A) in exon 4 of the PNPLA1 gene, which resulted in a G to A transition in the cDNA at position 514 downstream of the start codon (Fig. 2a). The mutation results in replacement of aspartate with asparagine at position 172 (p.Asp172Asn). The missense mutation p.Asp172Asn is localized at the site of serine–aspartate catalytic dyad (S53-D172) in the patatin domain. The mutations in PNPLA1 were modeled by using SWISS_MODEL (http://swissmodel.expasy.org) (Fig. 3). The exchange of an acidic amino acid aspartate with a uncharged amino acid glutamine at the position 172 may potentially disturb catalytic activity of the patatin domain (Fig. 3a).

Family 2: Three affected patients (II:1, II:3, II:4), diagnosed at ages 8, 5 and 5 respectively, from a consanguineous family (Family II), born as collodion babies and they had mild to moderate erythema on the face. Their skin presented generalized fine small, white and light brown scales. In flexures, brown linear thick plaques were seen. Similar lesions were present on the dorsum of hand and feet. They had palmoplantar keratoderma, pruritus and nail abnormality including toenail dystrophy and distal onycholysis. They had squamous pityriasiform appearance on the scalp. All patients in the family had large-octagonal scales on the legs.

The three affected individuals were found to have a novel homozygous deletion mutation (c.733_735delTAC) in exon 5 of the PNPLA1 gene (Fig. 2b). This mutation causes the deletion of the tyrosine residue at position 245 (p.Tyr245del). Deletion of a tyrosine amino acid may cause an alteration in the alpha helix structure that most probably alters PNPLA1 protein folding (Fig. 3b). The pathogenicity of identified mutations was evaluated by using prediction programs PolyPhen-2, SIFT and PROVEAN (Protein Variation Effect Analyzer). According to pathogenicity prediction programs, it was predicted that the p.Tyr245del mutation has deleterious effect on the function of the PNPLA1 protein. (Table II)

Family 3: Two affected sisters from a consanguineous family (Family III), born as collodion babies. One of the sisters (II:3) with similar findings to other sister died at eight months of age. The other sister (II:2) had diffuse erythema and white gray scales on her whole body. She had hyperkeratotic plaques on the knees, elbows and back of the neck. Thick dystrophic nails and brown teeth were observed. She had squamous pityriasiform appearance on the scalp.

The patients in the family were found to have novel c.335C>A mutation in PNPLA1 gene (Figure 2C). This mutation is located in the patatin domain which replaced a serine residue with a tyrosine at amino acid position 112 (p.Ser112Tyr). The exchange of hydroxyl side group of serine with aromatic side group of tyrosine may disrupt protein folding and affect catalytic patatin domain activity (Fig. 3c). p.Ser112Tyr was also predicted to have deleterious functional effects in PNPLA1 protein (Table II).

Discussion

This report and previous studies revealed that PNPLA1 mutations lead to various ARCI symptoms including collodion baby phenotype, generalized mild to severe scales with flexures, mild to moderate erythema, pruritus and palmoplantar keratoderma. We have not defined any unique ARCI symptom specific for PNPLA1 mutations. Clinical findings of our ARCI patients were commonly similar to previously

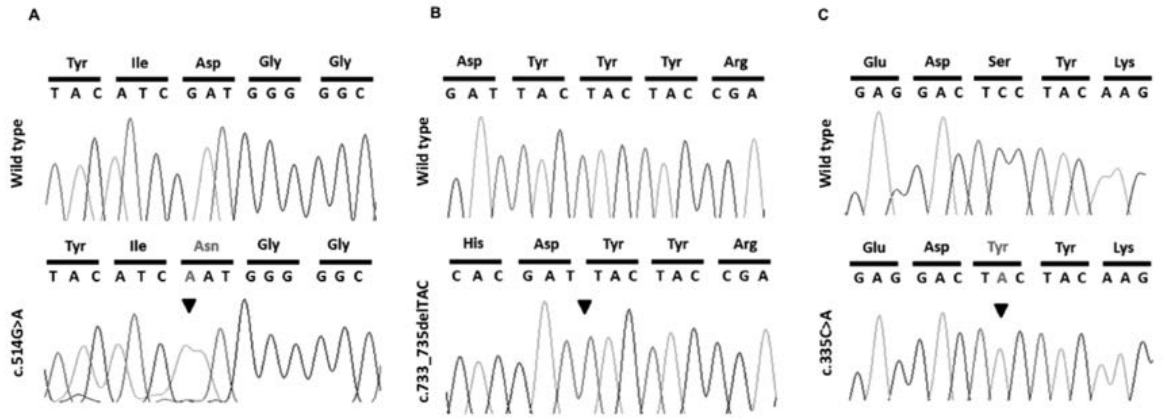

Fig. 2. Electropherograms showing the nucleotide sequence of a healthy individual (upper panels) and homozygous affected members (lower panels) with mutations (A) c.514G>A, (B) c.733_735delTAC and (C) c.335C>A.

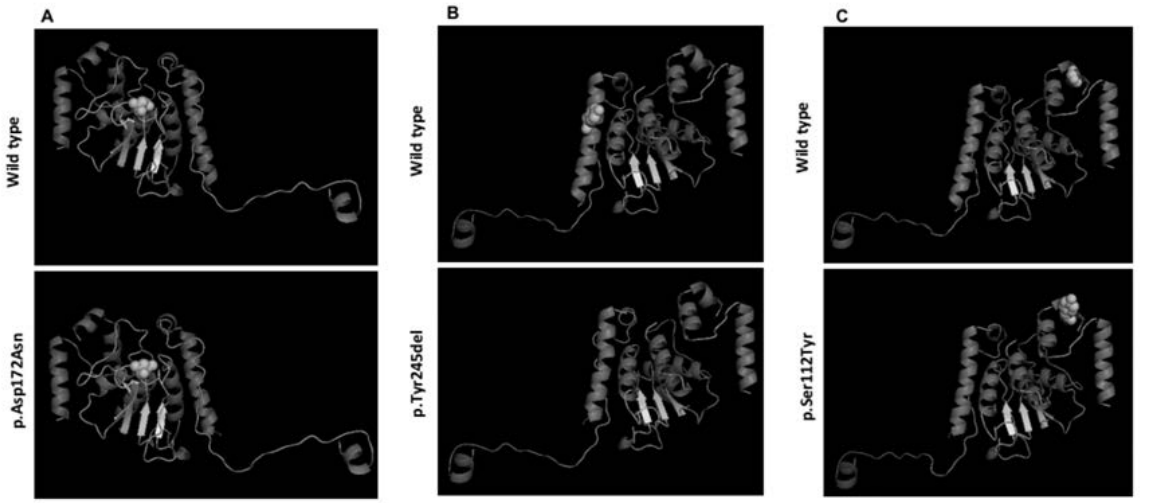

Fig. 3. 3D structure of mutated amino acid residues for mutations (A) c.514G>A, (B) c.733_735delTAC and (C) c.335C>A are shown. The models were obtained from SWISS-MODEL (http://swissmodel.expasy.org/).

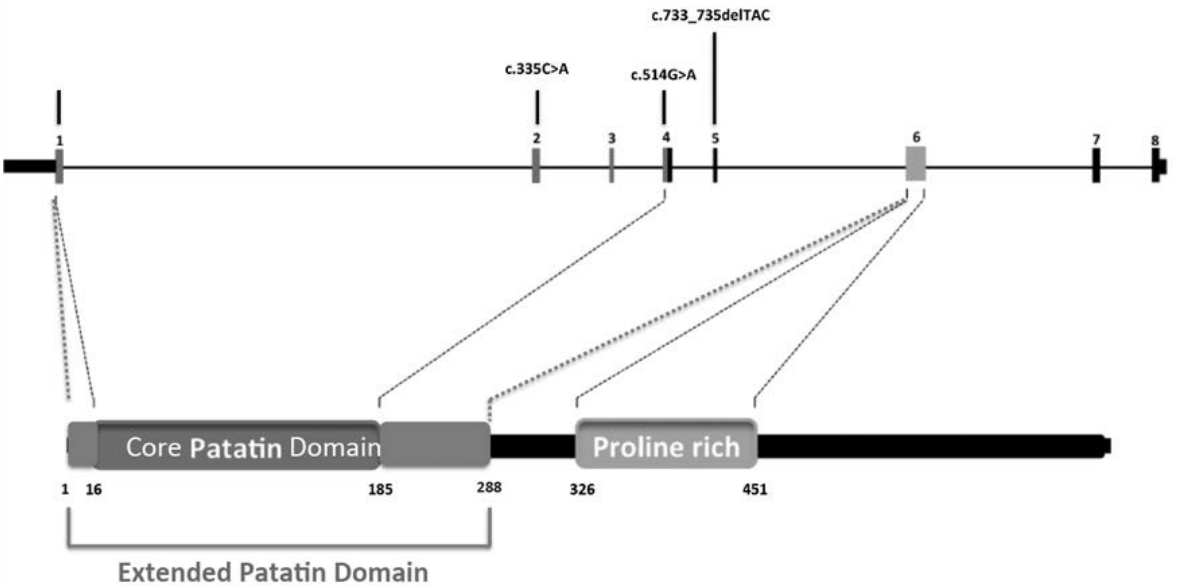

Fig. 4. The structure of PNPLA1 gene and PNPLA1 protein. PNPLA1 mutations identified by this report are shown on the gene structure.

Table II. List of Mutations Reported in the PNPLA1 Gene.

Alleles	Nucleotide change	Aminoacid change	Variation type	Ethnic origin	Reported previously by	Poly-Phen-2.1 (HumVar)		SIFT		PROVEAN	
Homozygous	c.335C>A	p.Ser112Tyr	Missense	Turkish	This report	0.877	Disease causing	0.01	Damaging	-3,314	Deleterious
Homozygous	c.733_735delTAC	p.Tyr245del	Deletion	Turkish	This report	-	-	-	-	-10,006	Deleterious
Homozygous	c.514G>A	p.Asp172Asn	Missense	Turkish Lurish, Azeri Kazakh	This report Vahidnezhad et al., 2016 Zimmer et. al., 2017	0.988	Disease causing	0.01	Damaging	-4,995	Deleterious
Homozygous	c.176C>T	p.Ala59Val	Missense	Morocco	Grall et. al. , 2012	1	Disease causing	0.02	Damaging	-3,126	Deleterious
Homozygous	c.391G>T	p.Glu131	Nonsense	Algeria	Grall et. al. , 2012	-	-	-	-	-	-
Homozygous	c.100G>A	p.Ala34Thr	Missense	Spanish	Fachal et. al., 2014	0.979	Disease causing	0.02	Damaging	-1,729	Neutral
Homozygous	c.387C>A	p.Asp129Glu	Missense	Pakistani Pakistani	Ahmad et. al., 2015 Lee et. al., 2016	1	Disease causing	0,02	Damaging	-3,930	Deleterious
Homozygous	c.56C>T	p.Ser19Leu	Missense	Persian	Vahidnezhad et al. 2016	1	Probably damaging	0	Damaging	-3,284	Deleterious
Homozygous	c.100G>C	p.Ala34Pro	Missense	Lurish	Vahidnezhad et al. 2016	1	Probably damaging	0.01	Damaging	-3,229	Deleterious
Homozygous	c.374C>A	p.Thr125Asn	Missense	Persian	Vahidnezhad et al. 2016	1	Probably damaging	0	Damaging	-4,829	Deleterious
Homozygous	c.421A>G	p.Lys141Glu	Missense	Kurdish, Persian	Vahidnezhad et al. 2016	0.982	Probably damaging	0.02	Damaging	-3,644	Deleterious
Homozygous	c.488.C>T	p.Pro163Leu	Missense	Arab	Vahidnezhad et al. 2016			0.07	Tolerated	-10,000	Deleterious
Homozygous	c.535C>T	p.Gln179*	Nonsense	Unknown	Zimmer et. al., 2017	-	-	-	-	-	-
Compound heterozygous	c.88G>A	p.Gly30Arg	Missense	French	Zimmer et. al., 2017	1	Probably damaging	0	Damaging	-7,348	Deleterious
	c.418T>C	p.Ser140Pro	Missense			0.957	Probably damaging	0.002	Damaging	-4,636	Deleterious
Compound heterozygous	c.418T>C	p.Ser140Pro	Missense	French	Zimmer et. al., 2017	0.957	Probably damaging	0.002	Damaging	-4,636	Deleterious
	c.421A>G	p.Lys141Glu	Missense			0.982	Probably damaging	0.001	Damaging	-3,644	Deleterious
Compound heterozygous	c.311T>C	p.Leu104Pro	Missense	French	Zimmer et. al., 2017	0.215	Benign	0.052	Tolerated	-6,510	Deleterious
	c.1143delC	p.Ser382Alafs*74	Deletion			-	-	-	-	-	-
Compound heterozygous	c.121delC	p.Arg41Glyfs*17	Deletion	Unknown	Zimmer et. al., 2017	-	-	-	-	-	-
	c.667G>A	p.Glu223Lys	Missense			0.983	Probably damaging	0.051	Tolerated	-1,470	Neutral
Compound heterozygous	c.275delC	p.Pro92Argfs*8	Deletion	Unknown	Zimmer et. al., 2017	-	-	-	-	-	-
	c.775+3A>T		Splice Site			-	-	-	-	-	-
Homozygous	c.704delC	p.Pro235Argfs*4	Deletion	German/Italian?	Zimmer et. al., 2017	-	-	-	-	-	-
Compound heterozygous	c.434T>C	p.Ile145Thr	Missense	German?	Zimmer et. al., 2017	0.986	Probably damaging	0	Damaging	-4,315	Deleterious
	c.536A>G	p.Gln179Arg	Missense			-	-	-	-	-1,734	Neutral
Homozygous	c.158C>T	p.Ser53Leu	Missense	Pakistani	Zimmer et. al., 2017	1	Probably damaging	0.009	Damaging	-5,507	Deleterious
Compound heterozygous	c.301A>G	p.Arg101Gly	Missense	Unknown	Zimmer et. al., 2017	0.968	Probably damaging	0.001	Damaging	-5,969	Deleterious
	c.275delC	p.Pro92Argfs*8	Deletion			-	-	-	-	-	-
Homozygous	c.496C>T	p.Arg166Cys	Missense	French	Zimmer et. al., 2017	1	Probably damaging	0	Damaging	-7,302	Deleterious

reported symptoms.[25] Generally, the symptoms of ARCI patients with PNPLA1 mutations are relatively milder than the other forms of ARCI especially caused by TGM1 and ABCA12 mutations.[25]

ARCI causing genes play important roles in differentiation of epidermal keratinocytes and/or formation of epidermal lipid barrier. Previously, ARCI causing genes CERS3, ALOX12B, CYP4F22 and ALOXE3 were reported to play role in ceramide metabolism during epidermal lipid barrier formation.[28,29] Recently, PNPLA1 protein was reported to play role in acylceramide synthesis by catalyzing esterification of omega-hydroxyceramide with linoleic acid in epidermal cornified envelope formation.[21-23] As PNPLA1 protein plays important role in epidermal lipid barrier formation, mutations in PNPLA1 gene lead to ARCI pathology.

p.Asp172Asn mutation that we identified in 2 ARCI patients in a Turkish consanguineous family was previously reported by Zimmer A et al.[25] and Vahidnezhad H et al.[30] in Kazakh, Azeri and Lurish patients. This mutation is located at the catalytic site of PNPLA1 as Ser53 and Asp172 form catalytic dyad of patatin domain. Zimmer A et al.[25] had also reported homozygous p.Ser53Leu mutation that is located at the position of Serine 53 of catalytic dyad in patatin domain. The pathogenic mutations located at catalytic site of the protein appears frequently in ARCI patients from different ethnic background.

p.Ser112Tyr mutation which is also located at patatin domain of the protein is the novel mutation reported first time in this report. Two Turkish ARCI patients had homozygous p.Ser112Tyr mutation in a consanguineous family and this mutation probably impairs functionality of PNPLA1 and leads to ARCI pathology. In addition, we report a novel deletion mutation p.Tyr245del which leads to deletion of a tyrosine amino acid at position 245. Actually, the p.Tyr245del mutation is located between core patatin domain and proline rich domain of PNPLA1 gene. Recently, it was suggested that in addition to core patatin domain PNPLA1 protein may have a functional extended patatin domain involving N terminal residues 1-288.[25] Consistently, the p.Tyr245del mutation is exactly located at the extended patatin domain of the protein. Clinical findings of our ARCI patients reveal that the p.Tyr245del mutation in the extended patatin domain may be relevant to PNPLA1 function.

To date, twenty-six mutations in PNPLA1 gene were identified in ARCI patients from a cohort of families from various ethnic background including African-Czech, German, Swedish, Algeria, French, Pakistani Kazakh, Spanish, Morocco, Persian, Lurish, Kurdish, Arab and Azeri.[17, 24-27,30] In this study, we report novel PNPLA1 mutations identified for the first time in Turkish ARCI patients. All PNPLA1 mutations identified in ARCI patients were summarized in Table II. Nearly all reported PNPLA1 mutations including our results are localized in the core patatin domain or extended patatin domain (Fig. 4). The other mutations located outside of patatin domain lead to early stop codon and form truncated protein which cause either loss of PNPLA1 functionality or change intracellular localization of protein. So, extended patatin domain is a disease causing mutation hot spot in the PNPLA1 gene and this domain is essential for functionality of the gene. Moreover, since almost all reported gene variations reside in the patatin domain, it draws almost all attention to functional sequence and its effect on the dysfunction of the epidermal keratinocytes.

It was assumed that the frequency of PNPLA1 mutations among ARCI patients is approximately 3%.[25] ARCI is a very rare genetic disease and in this case differential analysis has high diagnostic value. The increase in frequency and spectrum of PNPLA1 mutations show the necessity of PNPLA1 mutation analysis in ARCI patients especially in newborns with ichthyosis.

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