Identification of a novel homozygous missense mutation in the Phospholipase C, delta-1 gene associated with leukonychia in a Middle Eastern patient

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BACKGROUND

Hereditary leukonychias (HLs) are rare nail disorders that present with partial or complete nail plate whitening,[1,2] due to abnormal keratinization of distal nail matrix cells, with numerous intracellular vacuoles with less dense keratin that appear white with light reflection.[2] Some cases are due to Phospholipase C, delta-1 (PLCD1) gene mutations, encoding an enzyme regulating energy metabolism signaling, Ca^{2+} homeostasis, and intracellular movement.[1] We present a case of leukonychia associated with a novel homozygous missense PLCD1 gene mutation.

Abbreviations used:

ADHD: attention deficit hyperactivity disorder
HLs: Hereditary leukonychias
PLCD1: Phospholipase C, delta-1

Report of case

A 39-year-old male born in Kuwait presented with fingernail whitening since age 17. A nail clipping 1 year prior was inconclusive. There was no family history of similar findings. Of note, his parents were first cousins of Israeli descent. The patient sought diagnosis and treatment because he was stigmatized in his home community.

Medical history was significant for hereditary hemochromatosis, pre-diabetes, chronic pain following traumatic injury in 2015, depression, anxiety, and attention deficit hyperactivity disorder.

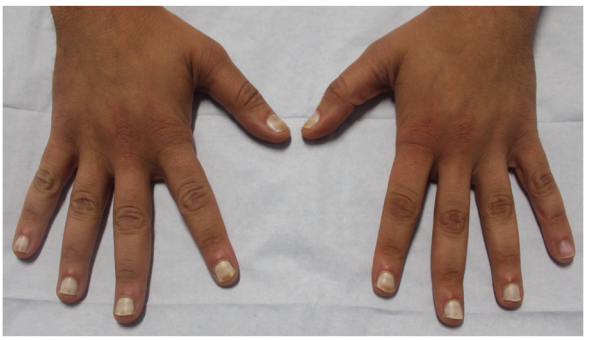

Fig 1. Clinical image of fingernails with *white* discoloration of all fingernails except the *left* fifth fingernail.

Medications included amitriptyline, atomoxetine, buspirone, desvenlafaxine, diclofenac, hydroxyzine, famotidine, and tramadol. Clinical examination was significant for normal toenails and white discoloration of 9/10 fingernails, which did not fade with

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Statement of ethics: The authors obtained written consent from patients for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors. As this is a case report, ethical approval is not required for this study in accordance with the Weill Cornell Institutional Review Board.

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Table I. Summary of hereditary leukonychias cases linked to distinct mutations in PLCD1

Cases	Affected family members	Mutations	Nail Involvement
Shen et al, 2021[1] Chinese family	6 cases of HL (2 males and 4 females)	G to A transition at nucleotide position 1384 (c.1384G > A); Heterozygous missense mutation c.770G > A; substitution of codon for arginine at amino acid position 257 to histidine (p.R257H)	Koilonychia present in 5/6 family members. 1/6 family members koilonychia initially, then progressed to leukonychia.
Xue et al, 2019[2] Chinese Han pedigree study	Mother and son affected	Missense mutation c.1451A > G in exon 9 of PLCD2 gene	Leukonychia and koilonychia
Kiuru et al, 2011[3] Pakistani study of 4 families[3]	Family A and B had consanguineous marriages or recessively inherited leukonychia. Families D and E demonstrated autosomal dominant inheritance.	Family A: Autosomal recessive mutation c.1720C > T and p.Arg437X Family B: Autosomal recessive mutation c.1792-10delTGRAGTGGCC mutation. Family C: Autosomal dominant mutation c.1720C > T, p. Ala574Thr Family D: Autosomal dominant; c.625T > C, p. Cys209Arg	Leukonychia
Khan et al, 2018[5] Pakistani family	Mother and 5 children[4]	Pathogenic missense mutation c.1390G > A, p.Glu464Lys in PLCD1 with an autosomal dominant pattern.	Leukonychia and koilonychia
Zhang et al, 2023[6] Chinese family	Mother and daughter[5]	p.E462K, p.E464K, and p.D484G in PLCD1	Leukonychia and koilonychia

HL, Hereditary leukonychia; *PLCD1*, Phospholipase C, delta-1.

pressure (Fig 1). He had no cysts involving the scalp, trunk, or extremities.

Chromosome microarray and whole exome with mitochondrial sequencing, performed prior to his dermatology visit, due to a recent diagnosis of hereditary hemochromatosis, showed homozygosity for an autosomal recessive variant, c. 1055G > A, p. (R352Q) associated with PLCD1-related nonsyndromic leukonychia.

DISCUSSION

Our patient had leukonychia associated with a homozygous missense mutation in the PLCD1 gene. PLCD1, a key enzyme in the cellular signaling pathway, has 15 exons,[1] and is localized and abundant in the human nail matrix using proteomic analysis.[3]

In this case, the patient's leukonychia is classified as "true" leukonychia, which is due to an intrinsic matrix or nail plate abnormality with whitening of the nail plate that does not fade with pressure. In contrast, "pseudo"-leukonychia describes whiteness of the superficial nail plate, which also does not fade with pressure. "Apparent" leukonychia involves pathology of the subungual tissues and will fade with pressure due to the temporary reduction of nail plate edema and improved visibility of blood vessels.[4]

Using genome-wide linkage analysis, Shen et al[1] identified 2 novel mutations in PLCD1 in a Chinese family with HL (Table I). All 6 patients (2 males and 4 females) presented with koilonychia in childhood, and 5/6 patients had distal brown discoloration of their nails.[1] One patient had a sporadic case of leukonychia with koilonychia with mutation c.770G > A (p.R257H) (Table I).[1] In another study examining HL in a Chinese Han pedigree with 2 affected individuals (mother and son), whole-exome sequence analysis identified a new missense mutation in exon 9 of the PLCD1 gene (Table I).[2]

Another study of 4 families of Pakistani origin displaying features of HL since birth used Affymetrix 10K chip technology to establish linkage to chromosome 2p21.3-p22 and identified another set of pathogenic mutations in PLCD1 (Table I).[3] Two of the families had consanguineous marriages or recessively inherited leukonychia features, while the other 2 families displayed dominant inheritance.[3] PLCD1 was localized to the nail matrix and the nail bed.[3] In another study of a Pakistani family presenting with leukonychia and koilonychia in a mother and her 5 children, whole exome sequencing identified a pathogenic missense mutation in PLCD1 with an autosomal dominant pattern (Table I).[5]

HL may present together with koilonychias.[5] Three mutations, p.E462K, p.E464K, and p.D484G in PLCD1 have been linked to koilonychia and leukonychia in 3 families with HL (Table I).[6] Notably, our patient did not present with koilonychia.

Other causes of leukonychia include drug exposure, hepatic cirrhosis, and renal disorders. Trazadone is associated with leukonychia, which our patient took following appearance of the leukonychia, so this would not explain his nail changes.[4] His abdominal MRI revealed no iron overload or liver abnormalities. A recent creatinine level was within normal limits. None of the patient's other medications or comorbidities are associated with leukonychia.

In an investigational study that performed whole-exome DNA sequencing of blood samples from 5 affected individuals and subsequent Sanger sequencing of 35 affected family members, PLCD1 variants were associated with development of trichilemmal cysts.[7] Notably, our patient and his family members did not have any trichilemmal cysts.

In sum, we describe a case of leukonychia with a novel pathogenic variant of PLCD1. Our case differs from others in that family members were unaffected. Although not all cases of leukonychia require genetic testing, cases in which multiple family members have similar clinical presentation may warrant a genetics referral. Further research is needed to identify inheritance modes and associated presentations, as well as treatments.

Conflicts of interest

Ms Conway, Henry, Drs Cohen, and Ricardo have no conflicts of interest. Dr Lipner has served a consultant for Orth-Dermatologics, Hoth Therapeutics, Moberg Pharmaceuticals and Belle Torus Corporation.

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