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Letter to Editor

Cohen syndrome coincident with epidermolytic palmoplantar keratoderma caused by novel KRT9 gene mutation: A rare case report

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To the editor,

Cohen syndrome represents an exceptionally rare clinical autosomal recessive hereditary disorder,[1] characterized by developmental delays, intellectual impairment, microcephaly, and other anomalies. Whereas epidermolytic palmoplantar keratoderma (EPPK) is an infrequent autosomal dominant genetic skin condition,[2] with a prevalence of approximately (1.0–1.4)/100,000.[1] It manifests clinically as diffuse thickening of the palmoplantar epidermis, resulting in wax-like yellowish plaques. Clinical reports concerning the co-occurrence of Cohen syndrome and a novel mutation in the KRT9 gene leading to EPPK are notably scarce, as the occurrence of autosomal dominant mutations in the KRT9 gene has been linked to EPPK. In this report, we presented a singular case of Cohen syndrome combined with a newly discovered mutation in the KRT9 gene, resulting in EPPK (Fig. 1), aiming to enhance understanding of the pathogenic genes and clinical phenotypes associated with this condition.

A 9-year-old child with intellectual disability, emotional instability, and aberrant behavior was admitted to the hospital for ten days. The patient exhibits delayed language development and poor communicative abilities. At the age of 3, they were initially evaluated for language developmental delay, and at 5, they received a diagnosis of autism spectrum disorder. Ten days ago, the patient's restlessness notably intensified, exhibiting a propensity for loud outbursts, wall-pounding, which could persist for 4-5 h. Furthermore, they exhibited self-directed aggression towards their grandmother, engaged in frequent self-talk, and experienced disrupted sleep patterns at night. The patient was hospitalized for assessment with the diagnosis of “intellectual developmental disorder”. Dermatological examination revealed thickening and yellowing of the skin's keratin layer on the palms and soles. Laboratory investigations and cranial magnetic resonance imaging showed no abnormal findings. Whole exome sequencing results identified mutations in the VPS13B gene, specifically c.11728C>T (p.Pro3910Ser) and c.1671C>G (p.Asp557Glu), as well as a heterozygous mutation in the KRT9 gene, c.488G>A (p.Arg163Gln) (Table 1). Subsequently, the patient received a definitive diagnosis of Cohen syndrome combined with EPPK.

The remarkable aspect of this particular case lies in the fact that, in addition to presenting with intellectual disability and delayed psychomotor development accompanied by thickening and yellowing of the skin's keratin layer on the palms and soles, the affected child also exhibits emotional instability and aberrant behavior. This combination of symptoms can easily lead to misdiagnosis as

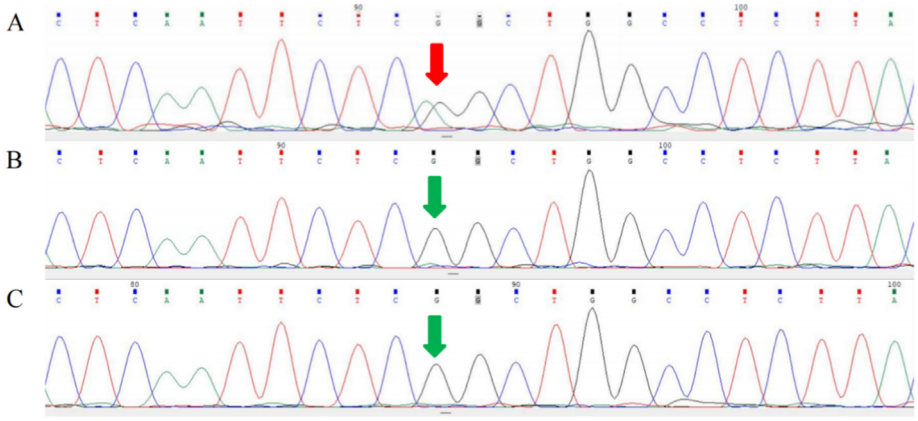

Fig. 1. Sequencing chromatograms of the KRT9 gene in the patient (1A) and their father (1B) and mother (1C). The red arrows indicate the mutation sites.。 .

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Table 1
Nucleotide sequence variations associated with the clinical phenotypes of the subjects. EPPK: epidermolytic palmoplantar keratoderma; AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; N/A: currently unknown.

Gene (Reference Transcript)	Genome Position (GRCh37/hg19)	Variation Information	Subregion	Associated Disease	Inheritance Mode	Mutation Source
KRT9 (NM_000226.3)	chr17:39727757	c.488G>A p.Arg163Gln	Exon1	EPPK	AD	Novel Mutation
VPS13B (NM_017890.4)	chr8:100883833	c.11728C>T p.Pro3910Ser	Exon61	Cohen Syndrome	AR	N/A
	chr8:100155221	c.1671C>G P.Asp557Glu	EXon13	Cohen Syndrome	AR	N/A

a psychiatric disorder, posing a significant challenge for clinicians in their diagnostic process. Moreover, the heterozygous mutation in the KRT9 gene, specifically c.488G>A (p.Arg163Gln), represents a novel genetic variant, enriching the repository of genetic information associated with EPPK and thereby advancing clinicians' understanding of this condition.

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Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2023.08.206.

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