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Mutations in TGM1 in Ecuadorians with autosomal recessive congenital ichthyosis

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To the Editor

There have been few genetic studies of autosomal recessive congenital ichthyosis (ARCI) in South America, and none has been performed in Ecuador.¹ A broad program led by the Miss Ecuador Organization to help people with ichthyosis in Ecuador has been organized by faculty members of the Catholic University of Guayaquil, and a cohort of 11 apparently unrelated Ecuadorian kindred from the coastal province of Manabí was selected for genetic analysis on the basis of clinical findings.

Photographs of those individuals revealed that they had a strikingly similar phenotype. All showed ectropion, large, thick, dark, plate-like scales, palmoplantar keratoderma, and alopecia. Because mutations in transglutaminase-1 (TGM1) are the most common cause of ARCI, we sequenced the exons and exon/intron boundaries of TGM1.

Polymerase chain reaction products were analyzed using Sanger sequencing of forward and reverse strands. The resulting traces were analyzed using Sequencher 9.0 (Genecodes).

TGM1 mutations were identified in all 11 cases (Table 1). Nine had homozygous mutations, and two had compound heterozygous mutations. All mutations, except a novel deletion of a single nucleotide in exon 13 (c.2149delC), have been reported previously in lamellar ichthyosis. The novel deletion mutation results in a frameshift, which leads to the premature termination of the translation product (p.Leu716Phefs*33). It is located between two previously reported mutations causing lamellar ichthyosis, suggesting that this domain is critical for normal enzymatic activity.^{2,3} Significantly, nine patients share the same mutant allele (c.1184G>A) with seven homozygous, suggesting that this mutation arose within the Ecuadorian population in the distant past with subsequent affected cases being the descendants of a founding individual. This mode of transmission is supported by the high rate of intermarriage within this population.

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Table 1

TGM1 mutations in patients with ichthyosis from Ecuador

Cases	Type	Mutations	Amino acid change
Patients 1–7	Homozygous	c.1184G>A	p.Arg396His
Patient 8	Homozygous	c.425G>A	p.Arg142His
Patient 9	Homozygous	<u>c.2146delC</u>	p.Leu716Phefs*33
Patient 10	Compound heterozygous	c.1184G>A/ <u>c.2146delC</u>	p.Arg396His/p.Leu716Phefs*33
Patient 11	Compound Heterozygous	c.1184G>A/c.2275C>T	p.Arg396His/p.Arg760X

This table demonstrates each patient case, what type of mutation the patient has, where the mutation occurred, and the resulting amino acid change. The previously unreported mutation is underlined.