Genotype Of Autosomal Recessive Congenital Ichthyosis From A Tertiary Care Center In India

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Autosomal recessive congenital ichthyosis (ARCI) refers to non-syndromic ichthyosis presenting with phenotypes such as harlequin ichthyosis, collodion baby, lamellar ichthyosis (LI), bathing suit ichthyosis (BSI), congenital ichthyosiform erythroderma (CIE), and ichthyosis prematurity syndrome. There are 13 causative genes identified so far - TGM1, ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, LIPN, NIPAL4, PNPLA1, SDR9C7, SLC27A4, SULT2B1, and ST14 with phenotypical differences between each of them described from various populations. However, there is limited data on the genotype or phenotype of ARCI from India.

The objective of our study was to characterize the genotype in ARCI and to correlate with the phenotype. In this prospective observational study, patients with a clinical diagnosis of ARCI were recruited. DNA was extracted from peripheral blood and analyzed for the 13 described ARCI genes by next-generation sequencing using an in-house panel. The variants identified were confirmed by Sanger sequencing and compared with known genetic variants and pathogenicity assessment tools to establish pathogenicity. Phenotype-genotype correlation was performed. Among the 28 patients recruited, we identified 12 patients with CIE phenotype (42.9%), 8 with LI (28.6%), 5 with a mixed phenotype (17.9%), and 3 with BSI (10.7%). Pathogenic and likely pathogenic variants were identified in 22 (78.6%) patients, involving 7 known ARCI genes. These included TGM1 mutation in 6 (21.4%), ALOX12B in 4 (14.3%), ALOXE3 in 4 (14.3%), NIPAL4 in 3 (10.7%), PNPLA1 in 3 (10.7%), ABCA12 in 1 (3.6%) and CERS3 in 1 (3.6%). Novel mutations were identified in 59.1% of patients. Exon 10 was involved in 66.7% TGM1 mutations and exon 3 in 66.7% PNPLA1 mutations suggestive of hot spots.

This was the first systematic study to establish the genotype of ARCI in the Indian population with the identification of novel pathogenic variants in over half the study population.