PgmNr 2460: Founder effects and genotype/phenotype correlations in homozygous cases of autosomal recessive congenital ichthyosis.

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Autosomal recessive congenital ichthyosis (ARCI) is a phenotypically and genetically heterogeneous skin disease. It is an ultra-rare disease with less than one patient in 50,000 people and can be caused by mutations in more than twelve different genes, with approximately 20% of the cases without mutations in a currently known candidate gene. The main pathophysiological feature is an impaired skin permeability barrier function, which leads to a disturbance of the cutaneous water homeostasis. A clear correlation between genetic causes and clinical picture has not been described to date, in part because of pronounced allelic heterogeneity and a vast majority of compound heterozygous cases. We have therefore collected cases from populations with a large percentage of consanguineous families, mainly from Saudi Arabia, Yemen, and Pakistan. We have assessed various approaches to identify candidate genes and mutations, including SNP-based homozygosity mapping, gene panel sequencing and whole exome sequencing. Interestingly, we found likely pathogenic variants in known candidate genes in all 19 families studied here, and these variants were identified in only five different genes, namely *TGM1*, *ABCA12*, *CYP4F22*, *NIPAL4*, and *ALOXE3*. Variants included both known and previously unknown mutations and nonsense, splice site, and missense variants. Patients from Saudi Arabia and Pakistan were assigned to potential founder mutations in *TGM1*, *ALOXE3*, and especially *NIPAL4*, respectively. Importantly, based on detailed clinical data including recent treatment information, we defined clear genotype/phenotype correlations. We attributed *TGM1* and *ABCA12* mutations to the most severe forms of lamellar and erythematous ichthyoses, respectively, almost regardless of treatment, and identified the phenotypic spectrum of ARCI associated with variants in each of the other genes. A detailed clinical analysis will be completed and specified. Our results contribute to the mutational spectrum of ARCI and revealed significant insights into genotype/phenotype correlations. The findings are instrumental for defining a fast and convenient procedure to make a diagnosis considering the patient background and the laboratory facilities available.