Innovation and Research Week
שבוע חדשנות ומחקר

CLDN1 ARG81His founder variant causes Ichthyosis, leukocyte vacuoles, alopecia and sclerosing cholangitis (ILVASC) syndrome in North African Jews.

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Background

Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis (ILVASC), is an extremely rare disease of autosomal recessive inheritance, resulting from loss of function of the tight junction protein claudin 1, encoded by *CLDN1*. Its clinical presentation is highly variable, even among patients harboring the same causative variant, and is characterized by liver and ectodermal involvement. Although most ILVASC cases described to date were attributed to homozygous truncating variants in CLDN1 gene, a single missense variant CLDN1 p.Arg81His, associated with isolated skin ichthyosis phenotype, has been recently reported in a family of Moroccan Jewish descent.

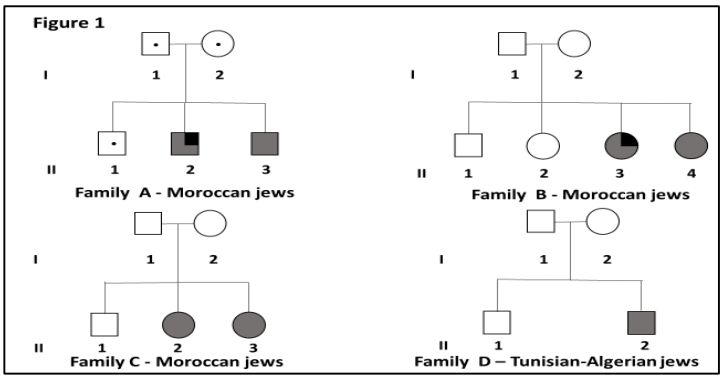
Aims

1. We set out to refine the phenotype caused by the CLDN1 p.Arg81His variant
2. to determine its carrier rate among Moroccan Jews
3. to examine possible founder origin of this variant.

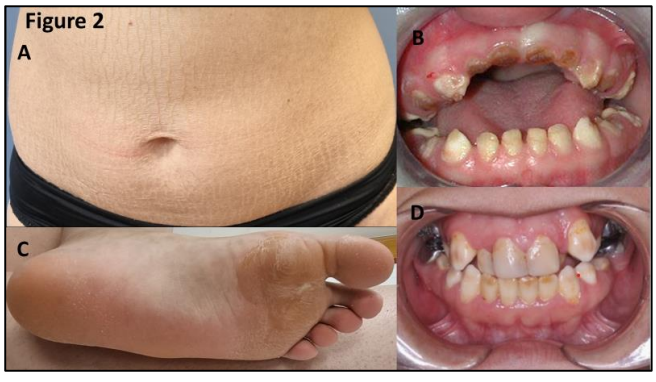
Methods

1. Light and transmission electron microscopy of the affected skin
2. Sanger sequencing
3. RFLP
4. Haplotype analysis by SNP arrays.

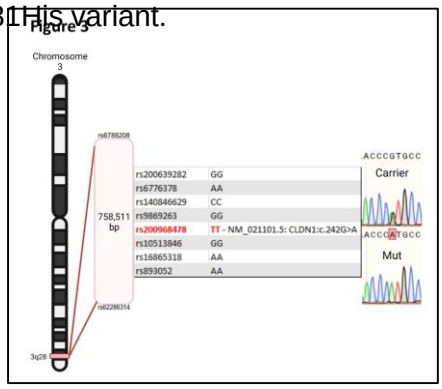
Results



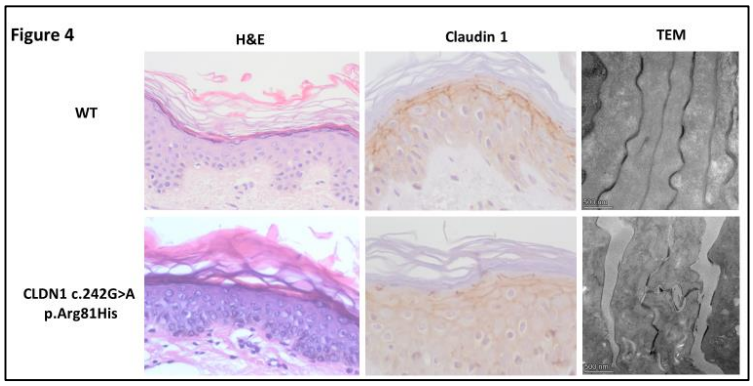
We have encountered 7 patients with ILVASC from four non consanguineous families of North African Jewish ancestry, harboring bi-allelic CLDN1 p.Arg81His variant.



Affected subjects displayed findings characteristic of ILVASC: abnormal cornification, amelogenesis of teeth, dysmorphism and variable hepatobiliary involvement.



SNP analysis showed CLDN1 p.Arg81His variant to represent founder variant shared by Moroccan Jews. RFLP analysis revealed carrier rate of 1:220 for this founder in this population.



Light microscopy showed diminished claudin 1 staining of the affected skin. Transmission Electron Microscopy revealed disrupted tight junction architecture and epidermal cell separation.

Discussion and Conclusions

Our findings emphasize the existence of diverse extra-cutaneous findings in individuals with ILVASC syndrome associated with the CLDN1 p.Arg81His variant, show this variant to cause patchy architectural disruption of epidermal tight junctions on TEM and to represent founder variant in North African Jews.