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

Marina Eskin-Schwartz1,2,3,*, Vadim Dolgin2,*, Uri Zilberman4, Ilana Aminov2, Elena Didkovsky5, Anna Pikovsky6, Galina Ling7, Idan Cohen3, Ohad S. Birk1,2,3

1Genetics Institute at Soroka University Medical Center, 2The Morris Kahn Laboratory of Human Genetics 3Faculty of Health Sciences, Ben-Gurion University of the Negev, 4Pediatric Dental Unit, Barzilai Medical Center, Ashkelon, Israel, 5Institute of Pathology, Rabin Medical Center, Petah Tiqwa, Israel, 6Oral Medicine Unit, Department of Oral and Maxillofacial Surgery, Soroka University Medical Center, 7Pediatric Gastroenterology Unit, Saban Pediatric Medical Center, Beer-Sheva, Israel,*Equal contribution.

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.

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.

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.