**DISSECTING THE COMPLEX CONNECTIONS BETWEEN NOTCH1 AND SERCA2 PROTEINS IN THE DARIER’S DISEASE: A PARADIGMATIC GENETIC NETWORK IN THE PATHOGENESIS OF A MENDELIAN GENODERMATOSIS**

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Keywords: Darier Disease, genodermatosis, NOTCH1 signaling pathway

**Background/Objectives:** Darier’s Disease(DD) is a rare, dominantly inherited genodermatosis with the loss of desmosomal adhesion and abnormal keratinization, caused by variants in *ATP2A2*. *ATP2A2* encodes for a SERCA2 protein, an ubiquitously expressed cellular pump responsible for calcium translocation from cytosol to endoplasmic reticulum. The molecular mechanism underneath *ATP2A2* alterations is not known. Intriguingly, in other disease models SERCA2 is a master regulator of NOTCH1 signaling and SERCA2 inhibition causes NOTCH1 pathway inactivation. The project aims to define a DD transcriptional profile and the genetic, biochemical and physiological impact of DD *ATP2A2* alterations on NOTCH1 signaling and/or on other new pathways.

**Methods:** we collected patients’ skin biopsies: i)to perform transcriptomic RNA-sequencing analysis on affected and unaffected subjects; ii)to generate keratinocytes and fibroblasts primary cells for expression analysis and immunofluorescence assays of the NOTCH1-downstream effector targets (*HES1*, *HEY1*, *c-MYC*); iii)to investigate *NOTCH1* signaling deregulations through immunohistochemistry on FFPE bioptic samples. Furthermore, we generated plasmids containing patients’ specific *ATP2A2* variants to evaluate their impact on the *NOTCH1* signaling and the proteins interaction by performing *in vitro* functional and biochemical assays.

**Results:** We define a DD transcriptomic gene signature, focused on metabolic, ribosomal and immunological deregulations. We pointed out a molecular dependency of *NOTCH1* pathways and *ATP2A2* defects through the effects evaluation of patient-specific variant overexpression and by *ex vivo* assays based on patient-derived primary cell lines and tissue IHC.

**Conclusions**: By understanding the molecular network between SERCA2 and NOTCH1 in DD, novel and effective therapeutic approaches may be developed and tested in DD.