# Spatial Transcriptomics in Darier Disease

Master's Thesis in Bioinformatics

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# Abstract

Darier disease (DD) is a genetic skin disorder caused by *ATP2A2* mutations that disrupt SERCA2-mediated calcium homeostasis, leading to epithelial stress and impaired epidermal integrity. This thesis integrates bulk RNA sequencing with single-cell spatial transcriptomics using the CosMx Spatial Molecular Imager to characterize the molecular and spatial consequences of ATP2A2 dysfunction. Bulk RNA-seq revealed a strong IL-17/IL-36–driven inflammatory program, keratinocyte hyperproliferation, and loss of differentiation and lipid-metabolism pathways. Spatial transcriptomics resolved these global signatures into discrete keratinocyte states—including inflamed suprabasal, differentiated, and hyperproliferative basal populations—and demonstrated fragmentation of the basal layer alongside the formation of compact epithelial–immune aggregates. Spatial analysis further showed that Darier disease is characterized by spatially restricted cytokine-responsive activation rather than diffuse inflammation across the epithelium. This work highlights the value of integrating bulk and spatial transcriptomics to dissect complex skin diseases and identifies epithelial-intrinsic cytokine pathways as potential therapeutic targets.

# Declaration of GAI use

Throughout this project, I used generative AI tools (ChatGPT and Copilot) to support conceptual understanding, inform the selection and execution of analytical methods—including R code generation—and enhance the writing process by offering critical feedback on clarity, logical flow, and completeness.

# For the reader,

In this thesis, supplementary figures are hyperlinked to their placement in the end of the document, where you'll also find hyperlinks that'll take you back to the main text.

# Abbreviations

| | |
|---|---|
| *ATP2A2* | Gene encoding SERCA2 |
| DD | Darier Disease |
| SERCA2 | Sarco/endoplasmic reticulum $Ca^{2+}$-ATPase 2 |
| LS | Lesional skin |
| NL | Non-lesional skin |
| FFPE | Formalin-fixed paraffin-embedded |
| ER | Endoplasmic reticulum |
| UPR | Unfolded protein response |
| RNA-seq | RNA sequencing |
| DGE | Differential gene expression |
| GSEA | Gene set enrichment analysis |
| HVG | Highly variable genes |
| PCA | Principal component analysis |
| UMAP | Uniform Manifold Approximation and Projection |
| kNN | k-nearest neighbors |
| VST | Variance stabilizing transformation |
| FDR | False discovery rate |
| NES | Normalized enrichment score |
| DEGs | Differentially expressed genes |
| CosMx SMI | CosMx Spatial Molecular Imager |
| ISH | In situ hybridization |
| MERFISH | Multiplexed Error-Robust FISH |
| NK | Natural killer cells |
| DC | Dendritic cell |
| IL | Interleukin (IL-1, IL-17, IL-36, etc…) |

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