

Utilizing patient-derived colon organoids to explore the effect of genetically determined ERAP2-proficiency upon proinflammatory stimulation

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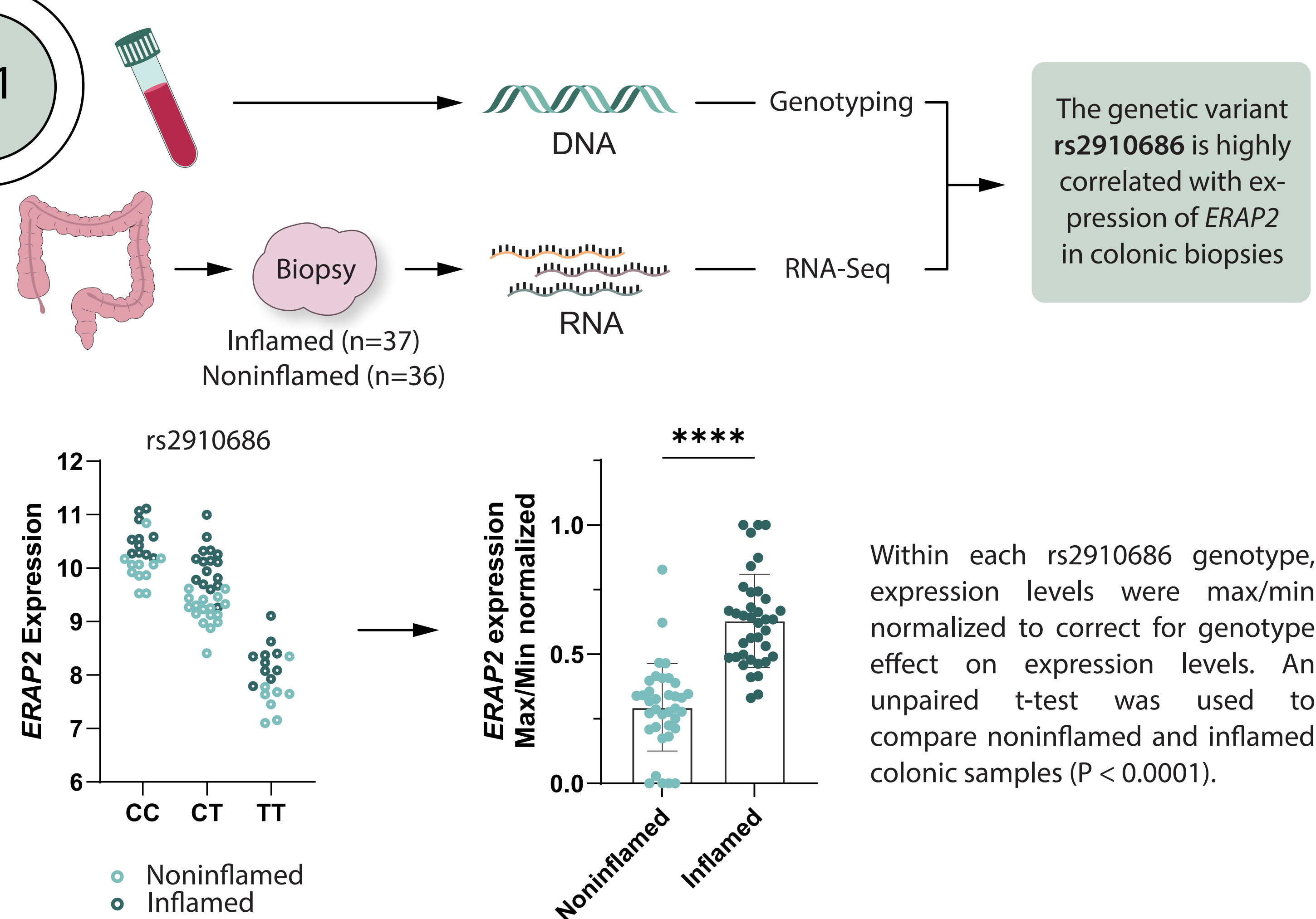
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BACKGROUND

A positive family history of inflammatory bowel disease (IBD) remains the strongest risk factor for development of disease, underpinning genetic factors in IBD etiology. Genetic variants in Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) have been associated with numerous inflammatory conditions, including IBD. How ERAP2 contributes to IBD pathogenesis is however unresolved. To investigate the effect of genotype on ERAP2 expression in different disease states, patient material from a IBD cohort was used to correlate genotype to ERAP2 expression in inflamed and noninflamed colonic biopsies. As the epithelial involvement in IBD pathogenesis is getting increasingly recognized, we set out to explore the impact of epithelial ERAP2 presence upon inflammatory encounter using human-derived colonoids as a model system.

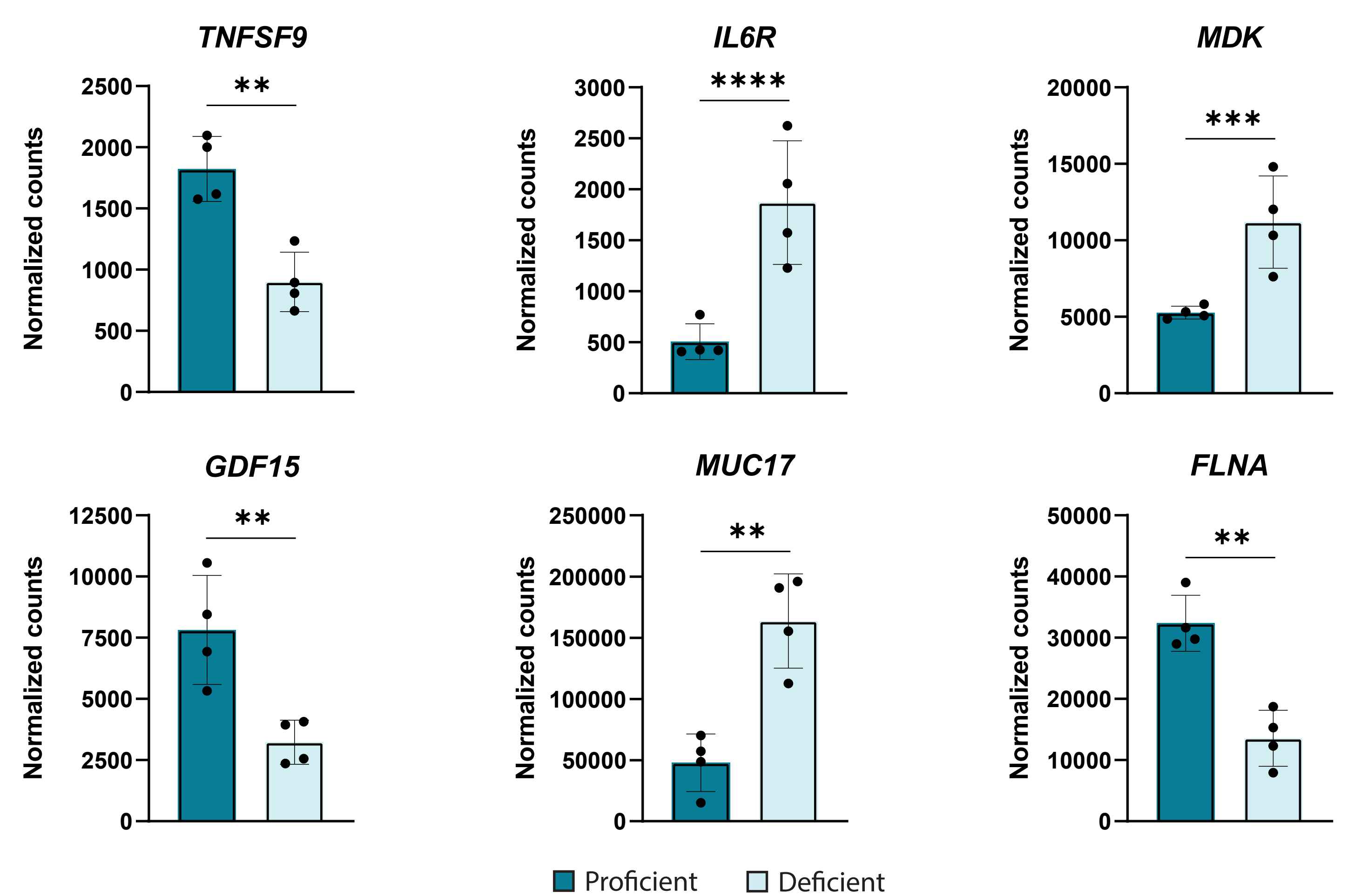
METHODS AND RESULTS

Colonic ERAP2 expression is increased in active IBD



ERAP2-proficient and -deficient colonoid donors display differential expression 24h post IFN γ stimulation

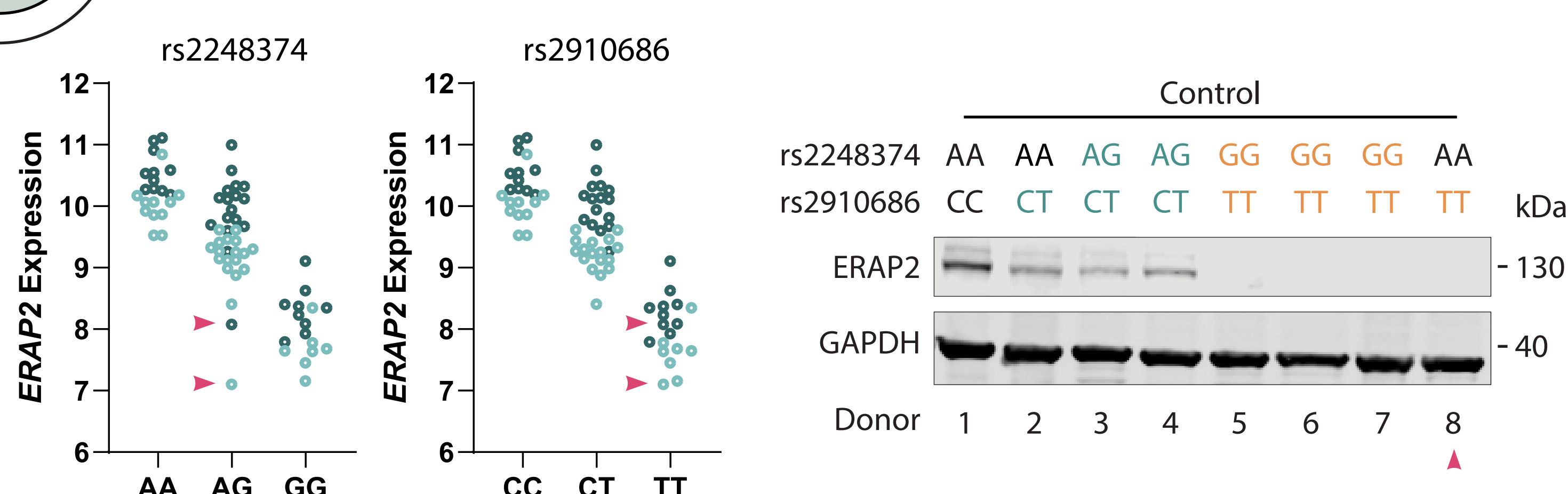
A total of 586 genes were differentially expressed between the two groups, including genes encoding proteins with regulator activity (*TNFSF9*, *MDK*, *GDF15*, *ILR6A*, *FLNA*) and the extracellular matrix structural constituent *MUC17*.



CONCLUSIONS

- ERAP2 is differentially expressed in active IBD mucosa when taking rs2910686 genotype into account
- Mechanisms independent of rs2248374 genotype can lead to ERAP2-deficiency
- ERAP2 rs2910686 genotype affects expression level of related genes upon proinflammatory stimulation
- Through genotype-based stratification of colonoid donors, we demonstrate that organoids act as a useful and physiologically relevant model system for evaluating the effects of disease-associated genetic variants

Mechanisms independent of rs2248374, a well-established determinant of ERAP2 expression, can lead to ERAP2-deficiency



Left panel: ERAP2 expression for rs2248374 (A/G) and rs2910686 (C/T) in inflamed ($n = 37$, dark green) and noninflamed ($n = 36$, light green) colon biopsies across genotype. Expression is presented as log₂ transformed normalized counts. Red arrows indicate samples where rs2248374 and rs2910686 are discordant. **Right panel:** Verification of ERAP2-proficient and -deficient colonoid donors. Genotype for rs2248374 and rs2910686 indicated for each donor. Donor 8 (rs2248374 AA, rs2910686 TT) does not express detectable ERAP2 protein.

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Precision medicine in
Inflammatory bowel disease



All authors have declared no conflict of interest
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