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UNDERSTANDING THE IMPACT OF DOWNSTREAM OF KINASE 4 (DOK4) DAMAGING GENETIC VARIANTS IN THE PATHOGENESIS OF PEDIATRIC INFLAMMATORY BOWEL DISEASE (IBD).

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Background: IBD is a chronic inflammatory disorder of the gastrointestinal (GI) tract whose precise pathological mechanisms remain elusive. It is thought that in pediatric IBD, pathogenic exposure does not appear sufficient to cause disease, thus genetic variations are critical to disease pathogenesis. The Muise Lab uses genetic sequencing of patients with IBD from all over the world to identify crucial genetic variations that are critical to IBD development.
We report two patients with IBD from unrelated families with mutations in *DOK4*. Both patients had profound extra-intestinal disease complicating their IBD. Downstream of kinase (DOK) proteins are a family of adaptor molecules that are important in regulating cell signaling, especially in immune cells. They are known to suppress MAPK and PI3K/AKT pathways, whose dysregulation result in cancer. *DOK4* has not been extensively studied, but research suggests that this gene produces two isoforms. It is known to have negative regulatory effects on immune cell activation but is also expressed across various other tissues, where its function is yet to be determined.
Aims: We hypothesize that these variations in *DOK4* lead to immune cell dysregulation, which manifests in both gastrointestinal and systemic chronic inflammatory disease. Through this study, we aim to elucidate the mechanism of novel genetic defects in *DOK4*.
Methods: It will be critical to understand how variants within both patients are contributing to the onset of IBD through *in vitro* studies. Therefore, we will characterize and quantify how changes in expression of DOK4 alters essential cell signaling pathways. We have established immortalized cell lines from patients bearing these mutations to specifically characterize potential immune defects. We will also be using knock out cell models to understand the effect of loss of function of DOK4 in different cell types.

Results: Preliminary data shows variation in expression of the protein within patient peripheral blood mononuclear cells (PBMCs) compared to a healthy donor. Overexpression in HEK293T cells shows changes in MAPK and NFkB signaling.
Conclusions: With this study, we hope to identify new therapeutic targets for patients with *DOK4* mutations.

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