Conclusions: The present results suggest that atypical serrated lesions in UC patients may develop from a novel neoplastic pathway that is dependent on KRAS mutations, but independent of BRAF mutations, being distinct from the canonical inflammatory dysplasia pathway or pathways associated with sporadic serrated polypos.

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Aberrant lipid metabolism in patients with DGAT1 deficiency
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Background: Congenital diarrheal disorders (CDD), which includes early-onset inflammatory bowel disease (EO-IBD), are rare disorders of the gastrointestinal system that can be attributed to numerous monogenic aetiologies. Recently, mutations in DGAT1 have been identified in patients a form of CDD which involved early-onset protein-losing enteropathy (EO-PLE), but the underlying molecular pathomechanism of DGAT1 deficiency has remained largely elusive. Methods: In our cohort of EO-IBD and EO-PLE patients, we studied 9 patients from 6 unrelated pedigrees suffering from early onset severe diarrhea, hypoalbuminemia, and sometimes fatal PLE that segregates perfectly with the disease in an autosomal recessive fashion. We performed whole exome sequencing to identify genetic disease aetiologies. We confirmed the phenotype through rescue by exogenous expression of DGAT1 in patients’ fibroblasts and intestinal organoids. We identified 5 novel bi-allelic loss-of-function mutations in the gene DGAT1 encoding diacylglycerol-acyltransferase 1. DGAT1 catalyses the formation of triglyceride from diacylglycerol and acyl-CoA. The mutations led to severely reduced or absent protein expression, resulting in lack of lipid droplet formation after treatment with oleic acid in patient derived fibroblasts and intestinal organoids. Using lipid chromatography, we show that DGAT1 deficiency specifically altered triglyceride metabolism. Exogenous DGAT1 reconstitution, and intriguingly exogenous DGAT2 expression rescued lipid droplet formation in fibroblasts. Conclusions: We here identified the largest cohort of DGAT1 deficient patients thus far, linking DGAT1 deficiency to altered lipid metabolism and fat intolerance. For the first time, we show the importance of DGAT1 in gut epithelium, and that exogenous DGAT1 and DGAT2 expression could rescue aberrant lipid metabolism in patient cells. We highlight the importance of potentially identifying known CDD-causing monogenic defects in sequencing of early-onset IBD patients for correct genetic diagnosis.

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Upadacitinib-induced endoscopic improvement is associated with modulation of pathways involved in Crohn’s disease pathogenesis
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Background: Upadacitinib (UPA; ABT-494) is an oral JAK1 selective inhibitor being investigated to treat Crohn’s disease (CD). In a phase 2 study (NCT02365649), UPA showed significant benefits compared with placebo in CD patients who had inadequate response/intolerance to an immunosuppressant or a TNFα antagonist. Methods: To understand the mechanisms underlying endoscopic improvement (defined as SES-CD ≤ 4 in either the ileum or colonic segment) in patients receiving UPA induction treatment for 16 weeks, a sub-study analysed total RNA from intestinal biopsies using genome-wide RNA-seq transcriptional profiling. Samples from colon and/or ileum were obtained at Screening and week 12 or 16 in 60 CD patients receiving either placebo, or UPA at 3, 6, 12, 24 mg BID or 24 mg QD. An average of 50 M read-pairs/sample was obtained using an Illumina HiSeq 3000 sequencing system. Gene expression levels were calculated and differentially expressed genes (DEGs) in UPA-receiving patients (all doses combined) were statistically identified using the limma R package. Pathway analysis was performed on IPA.

Results: Endoscopic improvement was achieved in 20/30 colonic and 10/28 ileal segments in patients receiving UPA (n = 50 patients). In subjects with endoscopic improvement, we observed a significant (nominal p value < 0.05) regulation of 1433 genes in the colon (411 genes; adjusted p value <0.05) and 1256 genes in the ileum (adjusted p value < 0.35). Of those, 473 UPA-induced DEGs were shared in both intestinal locations. Pathways significantly down-regulated by UPA were related to cell adhesion and migration (ICAM-1, IL1A, CXCL1, CXCL5, CXCL8, MMP3, MMP8, etc), TREM1 signalling (TREM1, NLRP3, IL1B, CSF2, NLRP14, TLR8, ITGA5, IL6, CCL3, TLR9, FGR2B, TLR2, NOD2, CCL7, ITGAX, etc), IFN signalling (IFITM3, IFNG, IF6, IFITM2), IL-17 response (S100A8/S100A9), cytokine communication in immune cells (IL24, IL53, IL26, IL22A, IL13RA2, IL18RAP, IL1RA, IL31RA, IL7R, IL1RN, IL23A, IFNG, CSF2, CSF3, etc), pattern recognition receptor response