****

**Genetic variation at 11q23.1 confers colorectal cancer risk by dysregulation of a colonic tuft cell transcriptional activator**

**Rajasekaran V, Harris B, Osborn R, *et al.* Genetic variation at 11q23.1 confers colorectal cancer risk by dysregulation of colonic tuft cell transcriptional activator POU2AF2. *Gut* 2025; 74(5): 787-803. doi: 10.1136/gutjnl-2024-332121.**

Variation of chromosome 11q23.1 has previously been associated with colorectal cancer (CRC), with risk hypothesised to be exerted through local expression quantitative trait locus (cis-eQTL) effects on specific genes, including *POU2AF2* (POU Class 2 Homeobox Associating Factor 2). However, the significance of these genes, and mechanism of conferring risk, has been challenging to elucidate.

This group employed a suit of techniques – RNA sequencing, single-cell RNA sequencing, chromatin immunoprecipitation sequencing and single-cell ATAC (Assay for Transposase-Accessible Chromatin) sequencing – to first identify and characterise relative gene contribution to CRC risk, before validating these findings through concurrent human tissue and mouse model work.

They concluded a number of trans-genes to be newly implicated as both colonic tuft cell markers and CRC risk genes, and rs3087967 specifically was shown to be a prime eQTL variant at 11q23.1, colocalising with CRC risk. Further, this risk genotype was demonstrated to essentially act as a trans-eQTL hub for a gene-set highly enriched markers of tuft cells.

Subsequent immunofluorescent studies in human tissue confirmed rs3087967 to be associated with tuft cell deficit, and epigenomic analysis implicated POU2AF2 as controlling tuft cell-specific trans-genes. This study went on to suggest genetic variation at 11q23.1 exerted its colorectal cancer risk through specific dysregulation of the colonic tuft cell transcriptional activator POU2AF2. Even in mouse models (where POU2AF2 is the main transcriptional activator of tuft cells with a tumour suppressive role), this hypothesis held, with CRISPR (clustered regularly interspaced short palindromic repeats)-mediated deletion of 11q23.1 risk locus in germline seemingly exacerbating ApcMin/+ mouse phenotype on nullification of POU2AF2.

In conclusion, although the precise role of tuft cells in the colon remains somewhat unclear, they would appear to have a key tumour-protective role within the epithelium, and genetic variation at 11q23.1 would seem to confer CRC risk through dysregulation of colonic tuft cell transcriptional activator POU2AF2. This potentially paves the way for new novel biomarker or chemopreventive work.