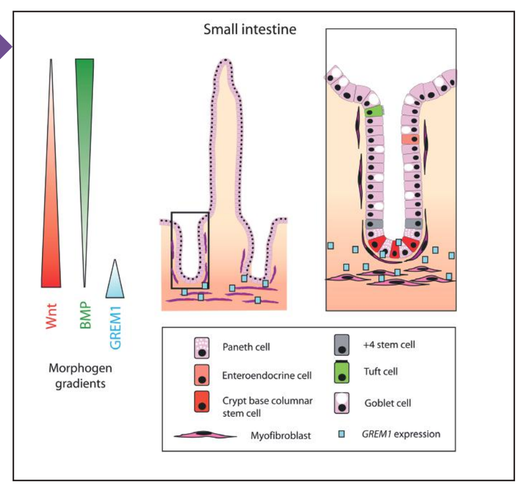
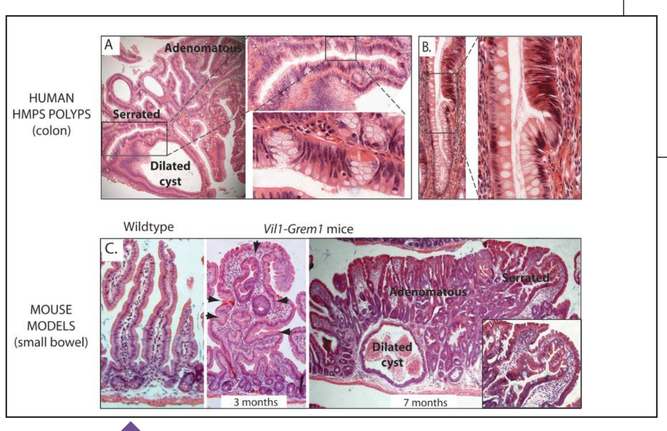
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

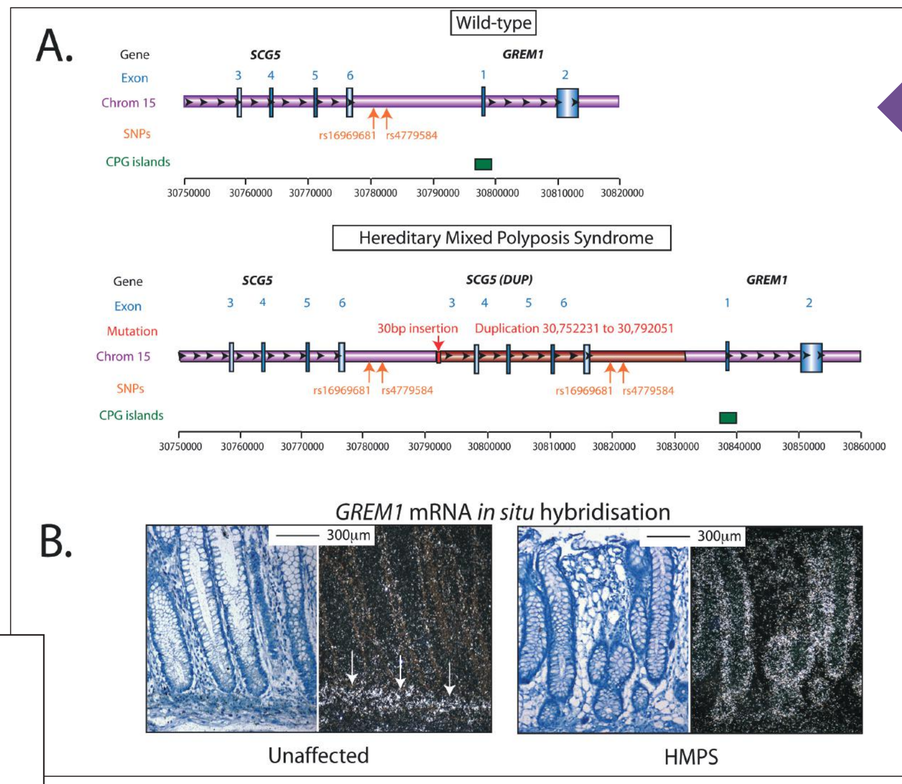
Colorectal cancer can arise from cells situated outside the crypt base stem cell niche

In health, balanced signalling gradients control cell fate. Stem cell division at the base of the crypt results in daughter cells that divide, differentiate and die within the 5–7 days that it takes for cells to pass along the crypt-villus escalator. Wnt signal at the crypt base provokes cell division whilst bone morphogenetic protein (BMP) at the luminal surface induces differentiation and apoptosis. BMP antagonists such as GREM1 *are expressed exclusively from the fibroblast cells below the crypt and act on the stem cell niche to maintain stem cell function*





Aberrant epithelial expression of GREM1 *upsets the homeostatic signalling balance in the gut and results in the expansion of a proliferating population of progenitor cells. These cells form ectopic crypts, divide, acquire somatic mutations and are capable of initiating carcinogenic change*



A. The rare autosomal dominant Hereditary Mixed Polyposis Syndrome (HMPS) is caused by a 40KB duplication of chromosome 15 including the upstream gene regulation region of the GREM1 *gene. B. The duplication causes a massive increase in* GREM1 *production and switches expression from the intestinal fibroblasts underneath the crypt to the epithelium (mRNA in situ expression)*

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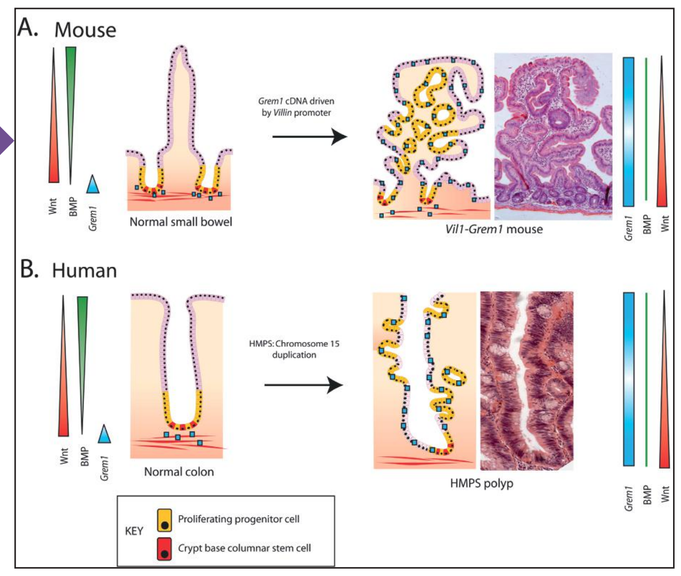

WHAT WAS KNOWN

- Intestinal stem cells are located at the base of the intestinal crypt, marked by *Lgr5* gene expression
- Interacting signalling pathways such as the Wnt and bone morphogenetic protein (BMP) pathway normally regulate cell division, maturation and death as intestinal cells migrate
- Secreted BMP antagonists expressed exclusively from stromal cells maintain the stem cell niche
- Crypt base stem cells were thought to be the sole cell of origin of colorectal cancer

WHAT WE DID

- Mapped and defined a genetic defect in the rare condition Human Hereditary Mixed Polyposis syndrome (HMPS)
- Developed an animal model to test cancer pathogenesis in these patients by overexpressing *Grem1* throughout the mouse intestinal epithelium (*Vil1-Grem1* mouse)

WHAT THIS ADDS

- HMPS is caused by a germline duplication of the gene regulatory regions upstream of the BMP antagonist *GREM1*
- This mutation changes *GREM1* tissue expression from stromal cells to the epithelium itself, disrupting the signalling pathway balance
- Aberrant epithelial *GREM1* expression causes an expansion in the progenitor cell population of the intestinal crypt
- The expanded population of progenitor cells divide, form ectopic crypt structures and acquire somatic mutations leading to carcinogenic change
- A subtype of sporadic human polyps called traditional serrated adenomas (TSAs) with hitherto unknown pathogenesis, share the same carcinogenic pathway
- First studies to show that a subtype of human colorectal cancer arises from cells outside the crypt base stem cell niche, suggesting a basis for tumour resistance to chemotherapy and potential new drug targets

REFERENCES

Hereditary mixed polyposis syndrome (HMPS) is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist *GREM1*.

E Jaeger*, S Leedham*, A Lewis, S Segditsas, M Becker, P R Cuadrado, H Davis, K Kaur, K Heinimann, K Howarth, J East, J Taylor, H Thomas & I Tomlinson.

Nature Genetics 2012 May 6; 44(6):699–703.

Aberrant epithelial *GREM1* expression initiates colonic tumorigenesis from cells outside the stem cell niche.

H Davis, S Irshad, [21 further authors], I Tomlinson, & S J Leedham.

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