Landmark study gives clearest picture of genetic causes of bowel cancer

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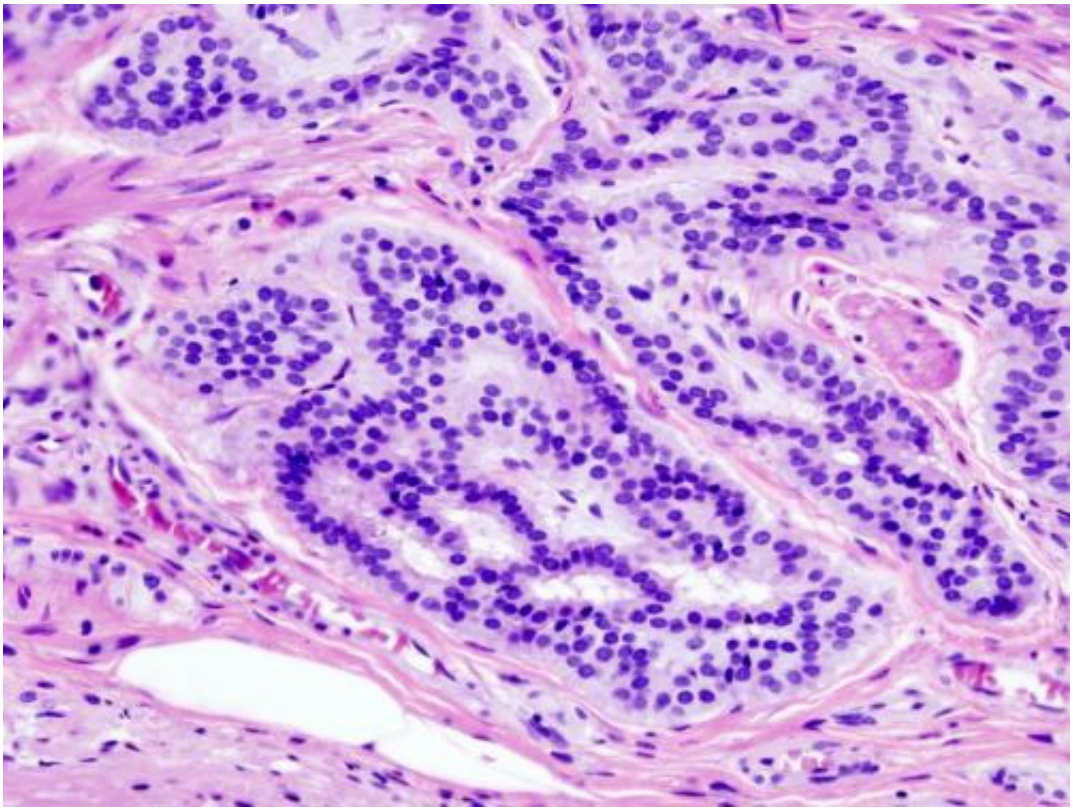

Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

A landmark study has given the most detailed picture yet of the genetics of bowel cancer - the UK's fourth most common cancer.

The study examined all the genes from more than 1,000 people with

bowel cancer and is the largest of its type ever conducted.

A team led by scientists at The Institute of Cancer Research, London, uncovered five new potential genes which, when mutated, appeared to cause bowel cancer in a very low proportion of cases.

Further research is needed to confirm these links as the mutations were very rare - each being linked to only a handful of cases in the 1,000-strong patient cohort.

The study, largely funded by Cancer Research UK, also concluded that the major genes that greatly increase the risk of bowel cancer have now almost certainly been found. The research is published in *Nature Communications* today.

Researchers found that added together, all the discovered variants in the known bowel cancer genes accounted for less than a third of familial cases of bowel cancer - those occurring in people whose close relatives had already developed it.

The rest of the familial cases must therefore be caused largely by minor DNA variations that in combination add up to increase risk, the study found, with environmental factors also contributing.

For an individual person, the risk of developing bowel cancer comes from a mix of inherited risk through their genes and environmental risk, which is caused by non-genetic factors such as lifestyle.

Around 12 per cent of cases occur in people with a family history of bowel cancer, with inherited mutations in known cancer-causing genes such as APC and MLH1 often playing a major role.

The researchers explored the genetics of bowel cancer further by

sequencing all the DNA used to produce protein - the exome - from 1,000 patients who developed the disease at a relatively young age and had a strong family history.

These patients - with a strong inherited component to their cancer risk - were selected from a repository of more than 25,000 cases held at The Institute of Cancer Research (ICR).

The ICR researchers concluded that beyond the five potential new genes identified there were unlikely to be any further major bowel cancer genes - pinning down the total number to around 12, excluding the five potential new ones.

Mutations in those genes accounted for 15-31 per cent of the 1,000 familial cases, meaning that much of the remaining risk must come from common variations in DNA, each with only a small individual impact on risk.

This suggests that these minor variations - around 30 of which have been discovered so far - are more important to inherited risk than previously thought.

Many more of these are yet to be discovered, meaning that more research is required in order to identify them.

The discovery of these variants could lead to essential new understandings of the biology of bowel cancer and potentially new ways to prevent it.

Study leader Professor Richard Houlston, Professor of Molecular and Population Genetics at The Institute of Cancer Research, London, said:

"Our study is the largest ever conducted of the genetics of bowel cancer,

and sets out a detailed map of the disease that could lead us to new ways of treating or preventing it.

"The research closes one chapter in the study of bowel cancer, by concluding that all the major risk genes have now been found. But it opens another by underlining the importance of tracking down the many missing genetic variations which each have a very small effect alone, but together make the biggest impact on inherited risk.

"Each cancer gene that has been discovered, or common genetic variant that we will continue to uncover, provides us with new insights into the underlying biology of the disease, and increases our ability to assess people for their risk."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"This study represents an important contribution to our understanding of the genetics of bowel cancer. It provides a marker of the dramatic progress we have made so far in decoding the inherited risk of the disease, and gives us confidence that the most important risk genes have now been found."

Dr Emma Smith, Cancer Research UK's science information manager, said:

"Understanding the faulty genes that play a role in the development of bowel cancer in people who have a strong family history of the disease could shed light on the biology underpinning it, and lead to new ways to prevent and treat the disease in future."

More information: *Nature Communications*, DOI: 10.1038/ncomms11883

Provided by Institute of Cancer Research