Individual types of colorectal cancer revealed through mutation patterns

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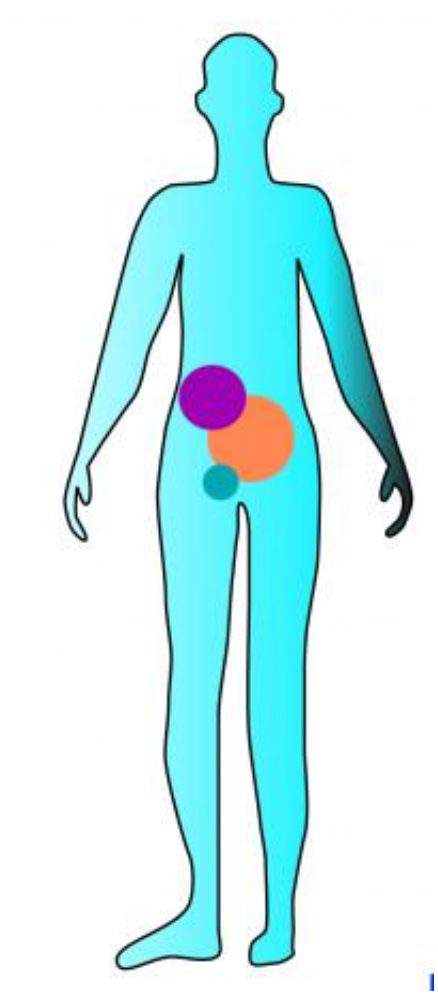

Diagnosis of colon cancer with new sequencing technologies. Credit: Monica Shevack, Scientific Illustrations

(PhysOrg.com) -- The fight against colorectal cancer, the third most common form of cancer with one million cases worldwide, is always a race against the clock. Early diagnosis and the identification of the particular type of the disease involved are crucial to the prospects of a successful cure. Because there are different molecular pathways to colorectal cancer, it has become increasingly clear in recent years that information about the type of cancer in question can be found in the patient's genetic pattern. However, the variety of the changes or mutations in the genome is extensive and the methods available up to now often only enabled a limited interpretation.

Scientists from the Max Planck Institute for Molecular Genetics in Berlin have now developed an efficient analytical strategy: with the help of targeted DNA sequencing and bioinformatics, they can identify the mutation patterns behind a colorectal cancer case in a single step (*PLoS ONE*, December 22th, 2010).

The instability of so-called microsatellites, small sequences of DNA that frequently repeat themselves, is a characteristic attribute that enables the differentiation of varying types of colorectal cancer. As soon as the DNA repair system fails to function correctly, these microsatellites become unstable. In current cancer diagnosis, the first step involves the examination of the patient's genome for instable microsatellites. If these are found, it may be assumed that the repair mechanisms are defective; in the next step, an attempt is made to analyse the repair gene and establish which mutations have triggered the disease.

"This step-by-step diagnosis is tedious and expensive, and its application was limited up to now," explains Michal-Ruth Schweiger, head of the study at the MPI for Molecular Genetics. Her team succeeded in transferring the tools for the diagnosis of colorectal cancer research to the new sequencing technologies and thereby combining several steps in the diagnostic process. The targeted sequencing of the building blocks of

the informative tumour genome (exome) makes it possible to ascertain, in a single step, whether the microsatellites are unstable, and which mutations promote the development of the disease. The scientists used next generation sequencing with the highest throughput - the very latest gene sequencing method - along with bioinformatics analysis methods. The latter examine the functional relevance of the tumour mutations using special computer programs - the software uses and collates the extensive information about genes and their functions available on publicly accessible databases. A combination of two classification algorithms (PolyPhen and MutationTaster) is used. If both algorithms classify a mutation as "dangerous", it is included in the list of candidates for subsequent analysis by oncologists.

In the recently published study, the Berlin-based scientists examined the tumour tissue of colorectal cancer patients with different microsatellite statuses. They sequenced a total of six cancer tumour genomes. Around 50,000 small nucleotide mutations could be identified for each tissue. Rigorous bioinformatics analysis enabled the researchers to filter out the functionally significant mutations: 358 mutations in tumours with unstable microsatellites and 45 in tumours with stable microsatellites. Hence, it became clear that tumours with unstable microsatellites have approximately eight times more functionally relevant mutations than tumours with stable microsatellites.

At the same time, the scientists were able to identify several mutations in already known tumour-relevant genes, the BRAF and KRAS genes, including the damaged repair gene, and TP53, a gene known as the "guardian of the genome" as it can usually prevent the growth of a tumour. In addition to the known mutations, changes in the BMPR1A gene in two patients were also demonstrated and functionally characterised. This gene is already known to play a role in juvenile polyposis syndrome, a disease of childhood and young adulthood accompanied by extensive polyp formation in the gastrointestinal tract,

which can form a preliminary stage of colorectal cancer. The mutations of the gene described in the study show effects on signal transmission within the cancer cell.

The scientists firmly believe that their new analytical strategy not only helps to win time in the fight against the cancer, but also represents an important step in the direction of personalised medicine. Among other things, their analyses provided information about genes that respond to certain drugs and about the mutated target genes of drugs. "Because we identify the molecular causes in addition to the raised mutation rate, we also establish the basis for individually tailored treatments," explains Schweiger. "Our combination of gene sequencing and bioinformatics analysis could become the gold standard for individualized cancer treatments in the future."

More information: Bernd Timmermann, et al. "Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis." *PLoS ONE*, December 22th, 2010, doi:10.1371/journal.pone.0015661

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