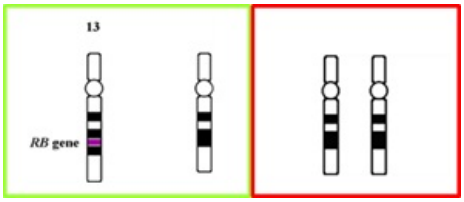
Hereditary cancer, cancer in families

Cancer is nowadays common diagnosis at clinics so it can surely happen that more members of one family are affected. It can be a random occasion, or it can be a result of common exposure to environmental mutagens, or it can be genetic problem. There are genes, mainly tumor suppressors, that could run in the family and cause higher chance for their carriers to have cancer (inherited gene defects account for about 5-10% of all cancers). Tumor suppressors keep the cells under control by slowing down cell division, repair DNA mistakes, or send the cells to apoptosis.

Cancer syndromes affect the same organs as sporadic cancers but typically come at younger age and bilaterally. Some family pedigrees show higher presence of affected members with one cancer type while others present with different tissue/organ cancers. For clinicians this means to focus on hereditary cancer syndrome in differential diagnostics.

Retinoblastoma (historicaly first documented example) affects the eye retina. Sporadic cases appear at children age in one eye whereas familial cases with inherited mutation in RB1 gene come sooner and are present in both eyes and tumors can develop in other organs as well.



In green box, you see inherited RB1 gene deletion on the 13th chromosome - a predisposition for retinoblastoma.

In the red box, you see situation on the somatic level, both chromosomes miss the RB1 gene, retinoblastoma.

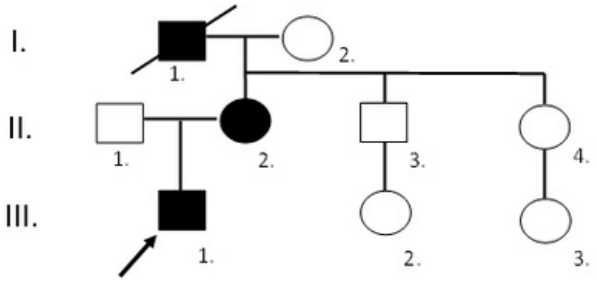
Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome caused by germline mutations of the APC (adenomatous polyposis coli) gene. FAP has a frequency of 1 in 5000 to 10,000 live births and affects males and females equally. It accounts for 1% of all colorectal cancers (CRC). FAP is the result of an inactivating mutation in APC and clinical manifestation may be heterogeneous even within the same family.

Lynch syndrome is an autosomal dominant condition caused by a mutation in one of several DNA mismatch repair genes (MMR). Defective MMR proteins lead to the so-called mutator or replication error phenotype and thus increase rate of mutation and increase the potential for malignancy. The average age of CRC diagnosis in Lynch syndrome is around 44 years, versus 64 years in sporadic cancer. The lifetime risk for developing CRC is 80%. Lynch syndrome accounts for about 3% to 5% of all CRC and 2% of endometrial cancer. It is the commonest inherited colon cancer syndrome.

Li-Fraumeni syndrome is a rare disorder that increases the risk of developing several types of cancers (breast cancer, soft tissue sarcoma, leukemias, and more), particularly in children and young adults. More than half of Li-Fraumeni syndrome families have inherited mutations in the TP53 gene. Minority of cases present mutation in CHEK2 gene.

Breast cancer, about 5–10% of cases are due to inherited genes, including BRCA1 and BRCA2. BRCA1 gene product has a role in DNA double strand break repairs. The lifetime risk for a carrier of BRCA1 gene mutation to have breast cancer is 80%.

A typical hereditary cancer pedigree looks like this:



LEGEND: I/1 died CRC, 55yrs; II/2 CRC at 48 yrs, III/1 polyposis, 35yrs

Explanation: CRC runs in a family in autosomal dominant manner (both females and males are affected, vertical transmission). Gene that was inherited was most probably tumor suppressor gene APC. One of his alleles carries mutation. The other mutation happened on the somatic level and caused polyposis in colon (Knudson 2-hit hypothesis) that eventually became a tumor (in I/1 and II/2). Individuals II/3 and II/4 were not tested for the presence of mutation in APC gene, although they could also be carriers. The age of manifestation of the disease depends on many factors (personal genetic background, environmental factors like smoking, dietary habits, obesity, radiation, etc.). Person III/2 could also be a carrier if his father II/3 (although healthy) is a carrier. Some individuals do not manifest the disease even if they are carriers of mutation, again, due to factors of personal

genetic background or environmental factors. Carriers have a high predisposition for the cancer throughout their life, APC mutation is a highly penetrant allele in familial adenomatosis polyposis (almost 100%). Hereditary cancer syndromes helped to identify major tumor suppressor genes in human genome. Molecular diagnostic departments apply nowadays NGS methods to identify the exact genetic cause of hereditary syndrome by screening selected gene panels (for example, 200 genes can be sequenced at one time).