Mutator genes, stability of the cell genome

This article has been translated from WikiSkripta; ready for the **editor's review**.

Mutator Genes

DNA repair genes control the stability of the cell's genome. They are responsible for repair of damage (error correction) DNA.

- Mutation or inactivation of these genes leads to the accumulation and maintenance of mutations in the cell and genome instability.
- Increased frequency and accumulation of mutations in the cell is one of the causes of malignant transformation.
- The products of these genes are used in the repair mechanisms of damaged DNA.
- Mutator genes, unlike oncogenes and tumor suppressor genes, do not provide the cell with the ability to proliferate uncontrollably by themselves. Thus, the mutation of mutator genes leads to an increased frequency (100–1000 times) of mutated oncogenes and tumor suppressor genes

Genes enabling the excision repair process

These include genes whose products ensure the cutting out of a damaged section of DNA (excision). Their recessive mutation causes diseases called xeroderma pigmentosum and Cockayne syndrome, which are pre-cancers with increased susceptibility to skin cancers induced by UV-radiation exposure.

“Mismatch” repair genes - mutation of genes for repairing faulty base pairing (Mismatch Repair genes)

Another group of mutator genes. Encoded proteins correct base misplacement during DNA replication (but not complementary).

- A manifestation of mutations of these genes is instability at the nucleotide level, instability of the length of microsatellite loci (MIN) - microsatellite instability (incorrect base pairing causes changes in the length of microsatellite sequences - their lengthening or shortening).
- Length instability of microsatellite sequences leads to replication errors.
- Mutations are recessive in nature.
- Microsatellite sequences are distributed throughout the genome, their length is heritable. They are repetitive sequences of dinucleotides or trinucleotides, 50,000–100,000 (CA)n repeats occur in the human genome.

Germline mutations in particular hMSH2 (human MutS homolog 2), hMLH1, hPMSI and hPMS2 genes underlie **hereditary nonpolyposis colorectal cancer (HNPCC)** - inherited autosomal dominant, it is considered a familial occurrence affected 3 or more family members with a affinity coefficient of 0.5 and with the occurrence of the disease before the age of 50.

- Familial occurrence of HNPCC accompanied only by the finding of colon or rectal cancer so-called **Lynch syndrome I**.
- About 30% of HNPCC patients also develop cancers in other organs (endometrium, pancreas, stomach, urinary tract). This is the so-called *Lynch syndrome II*.
- HMSH2 (chrom. 2p15-p22), hMLH1 (chrom. 3p21.3), hPMSI (2q31–33) and hPMS2 (chrom. 7p22) genes are responsible for base mismatch repair (MMR). Their mutations predispose to Lynch syndrome.

Instability of microsatellites has been described as a characteristic phenotypic manifestation in other tumors - breast cancer and lung, GIT tumors, endometrium, meningiomas. Defects in the DNA-repair mechanism contribute to the accumulation of genetic defects, promote the progression of malignantly transformed cells.

Examples of mutator genes explored

hMSH2	HNPCC, type 1, ovarian tumors, glioblastomas, T-cell lymphomas
hMSH6	HNPCC, type 5, ovarian tumors, endometrial carcinoma
hMLH	HNPCC, type 2, Turcott syndrome accompanied by the occurrence of glioblastomas and leukemia
hPMS1	the protein encoded by this gene forms heterodimers with the protein encoded by the hMLH1 gene, it has been detected in a mutated form in some HNPCC
hPMS2	HNPCC, type 4, Turcott syndrome accompanied by the occurrence of glioblastomas

Turcott syndrome is clinically characterized as the coincidence of the hereditary occurrence of primary colon tumors (FAP or HNPCC) with tumors of the central nervous system, or with leukemia

· **defects in the DNA-repair mechanism** contribute to the accumulation of genetic defects, promote the **progression** of malignantly transformed cells

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Source

- ŠTEFÁNEK, Jiří. *Medicine, diseases, studies at the 1st Faculty of Medicine, UK* [online]. [cit. 2010-02-11]. <http://www.stefajir.cz>.