Chromosomal instability syndromes

Diseases associated with impaired DNA repair, more commonly called **chromosomal instability syndromes** or **syndromes associated with increased fragility of chromosomes** show some common features. These are autosomal recessive syndromes associated with increased sensitivity to UV radiation and other mutagens. They are often associated with **hyper or hypopigmentation**, **short stature** and an **immune defect**. The high sensitivity of patients to mutagens is associated with an increased level **of chromatid and chromosome breaks** and chromosome exchanges in their cells. In some diseases, these changes are specific (e.g. increased level of sister chromatid exchanges and exchanges between homologous chromosomes in Bloom syndrome, specific breaks on chromosome 7 and 14 in ataxia telangiectasia and Nijmegen breakage syndrome). The level of acquired chromosomal aberrations is increased spontaneously, or the patient's cells are more sensitive to the *in vitro* induction of aberrations by mutagens. Because this is a repair or replication disorder, patients have **a multifold increased risk of developing cancer**.

Fragile syndromes – chromosomal instability syndromes				
Title/Abbreviation	**Clinical manifestations**	**Cytogenetic findings; increased level**	**Disorder**	**Genes**
Ataxia telangiectasia (Luis-Bar sy; AT)	Cerebellar ataxia, telangiectasia, growth retardation, hypogonadism, combined immunodeficiency, predisposition to malignancies	chromosome breaks and exchanges, especially in chromosomes 7, 14, ev. 2 and 22 (immunoglobulin gene and T-cell receptor gene regions)	Defect in signal recognition for repair (double-stranded DNA breaks=DSBs)	ATM
Bloom syndrome (BS)	Dwarfism, hyperpigmentation, butterfly rash on the face, immunodeficiency, predisposition to tumors	chromosome breaks, exchanges between homologous chromosomes, sister chromatid exchanges (SCEs)	DNA helicase — DNA replication and repair	BLM
Fanconi anemia (FA)	Growth retardation, pancytopenia, skeletal abnormalities, brown skin, no immunodeficiency, predisposition to leukemia and other malignancies	Chromosome breaks and exchanges	Excision repair, repair of UV damage	**Heterogenous:** *7 complementation group (A-G) genes:* FANCA, FANCC, FANCD2, FANCE, FANCG *Non-localized genes:* FANCB, FANCD1
Xeroderma pigmentosum (XP)	Extreme sensitivity to sunlight, skin changes, neurological dysfunctions, mental retardation, predisposition to tumors, especially of the skin	Spontaneous level not increased, chromosome breaks, sister chromatid exchanges after induction (especially UV radiation)	Nucleotide excision repair (NER) except XPV form — DNA polymerase H	**Heterogenous:** *7 complementation groups (A-G) + variant form genes:* XPA, XPB (ERCC3), XPC, XPD (ERCC2), XPE, XPF (ERCC4), XPG (ERCC5), XPV (Pol eta)
Nijmegen breakage syndrome (NBS)	Growth, mental retardation, microcephalic, dysmorphia, immunodeficiency, predisposition especially to lymphoid malignancies	Breaks and changes, especially of chromosomes 7,14 (*regions of immunoglobulin genes and genes for T lymphocyte receptors*)	Repair of DNA double-strand breaks	NBS1 – nibrin

A cytogenetic affect (increased chromosomal instability) and an increased risk of tumors are also shown by **syndromes associated with premature aging** such as **Werner's syndrome** (cataract, subcutaneous calcification, skin changes, premature graying, premature arteriolosclerosis – **WRN gene** – DNA helicase/exonuclease RECQL2) a **Cockayne syndrome** (dwarfism, mental retardation, deafness, premature senility – genes CSA (ERCC8), CSB (ERCC6)), in patients also expressing symptoms of **xeroderma pigmentosum** (XP/CS) genes XPB (ERCC3), XPD (ERCC2), XPG (ERCC5).

Links

Related articles

- Chromosomal abnormality
- Mutation and Mutagenesis
- DNA repair
- Ataxia telangiectasia
- Bloom syndrome
- Fanconi anemia

Recommended literature

- HURET, J. L. *Atlas of Genetics and Cytogenetics in Oncology and Haematology* [online]. [cit.

2010]. <http://atlasgeneticsoncology.org/>.