Abnormalities in chromosome structure, their causes and clinical presentation in man

Definitions

1. **Balanced aberrations** – phenotypically harmless; no loss and no gain of unique genetic material
   - translocation
   - inversion
   - insertion
2. **Unbalanced aberrations** – usually phenotypically harmful; with loss or gain of genetic material
   - deletion
   - duplication
   - isochromosome
   - ring chromosome

Origin of structural aberrations

chromosome breaks – on one or more chromosomes, in one or more breakpoints

- stable products (with centromere and two telomeres) – regular segregation in mitotic cycles, rearrangement present in all cells of organism
- unstable products – irregular segregation in mitotic cycles
  - acentric fragments - usually lost at anaphase
  - dicentric fragments - dragged to both poles of spindle, randomly broken or lost in some cells (resulting in secondary rearrangement formation, mosaicism or monosomy)

Translocation

Exchange or transfer of chromosomal segments from one chromosome to another. Change in gene localization, but no gain or loss of DNA → balanced rearrangement.

Types:

- **reciprocal translocations** – breakage and exchange of chromosomal material between at least two nonhomologous chromosomes – may result in changes in size and arm ratio; no phenotype effect for carriers except semisterility (altered gametes with imbalanced chromosome complement may be formed due to unbalanced segregation of the involved chromosomes)
- **Robertsonian translocations** – breakage of two acrocentric chromosomes (13, 14, 15, 21 or 22) and their subsequent centric fusion of the long arms of two acrocentric chromosomes – results in change of total chromosome number (46 → 45);

short arms are lost without clinical importance as containing genes for rRNA (multiple copies on the other acrocentric chromosomes); no phenotype effect for carriers except semisterility; risk for having a baby with Down syndrome if chromosome 21 is involved in translocation segregation of trivalent structure in Robertsonian translocations (see Figure No. 1)

Inversion

180° change of direction of a chromosomal segment (two breaks on one chromosome, rotation of the middle segment and rejoining) Change in gene order, but no gain or loss of DNA → balanced rearrangement Normal phenotype except position effect variegation

- break within a gene may disrupt gene function
- breaks within 2 genes may cause gene fusion

(more details in question No. 114 – Chromosomal aberrations in cancer cells)

Inversion loop formed at meiosis I – crossover within the loop may cause chromosome recombination and imbalanced gametes formation with reduced total number of viable gametes. Risk for offspring – fetal abnormalities or reduced fertility (recurrent miscarriages).

Types:

- **pericentric inversion** – inversion spans centromere, can be detected microscopically by altered arm ratio and change in bands order
- **paracentric inversion** – centromere outside inversion, no change of arm ratio, can be detected only by change in bands order

Deletion

Loss of segment of DNA → unbalanced rearrangement. Origin: breakage and loss of acentric segment, unequal crossover, ring chromosome,...

Types:

- terminal – one break on one chromosome, distal acentric segment lost
- interstitial – two breaks on one chromosome arm, middle segment lost, the segments left rejoined

Microdeletion syndromes (contiguous genes syndromes)

- variable phenotype (mental retardation, congenital anomalies, craniofacial dysmorphy, growth retardation)
- mostly submicroscopic deletion < 4 Mb
- loss of gene block, variable phenotype consequences depending on size of deleted segment and genes involved
- Clinical presentations:
  - Phenotypic effects depend on particular genetic content (locus and size of lost and/or amplified genomic segment) involved in rearrangement.

Clinically important syndromes with structural aberrations in man

1. **Down syndrome** – translocation form, 4-5% of all Down sy cases in population – unbalanced Robertsonian translocation; karyotype e.g. 46,XY,rob(14;21),+21
   - one of parents could be balanced carrier of Robertsonian translocation with karyotype e.g. 45,XY,rob(14;21)
   - the recurrence risk of having Down sy baby in balanced carriers is theoretically 1/3, in practice is lower (male carriers: 1-3%, female carriers: 5-10%), except transl. 21;21
   - in case of translocation 21;21 is risk of recurrence 100% for any balanced carrier parent
   - Symptoms of Down syndrome (see question No. 38 – Autosomal aneuploidy in man)
2. **Turner syndrome** – deletion form, deletion on the short arm of chromosome X; karyotype 46,X,del(Xp)
   - symptoms very similar to monosomy X variant of Turner syndrome but modified by amount of deleted genes; critical deleted region is pseudoautosomal region 1 (PAR1) on Xp, incl. gene SHOX (causing short stature and dysproportions in extremities lenght)
   - phenotype is usually variable and milder, in some cases fertility could be preserved
   - Symptoms of Turner syndrome (see question No. 39 – Gonosomal aneuploidy in man)
3. **Cri du chat** (cat cry syndrome) – terminal deletion on the short arm of chromosome 5
   - Phenotype:
     - microcephaly, severe somatic and mental retardation, round „moon-shaped“ face, hypoplastic larynx in early months of childhood – high shrill cry (like a mewing cat)
4. **Prader-Willi sy** – interstitial microdeletion on the short arm of paternal chromosome 15
   - Etiology: microdeletion is detected approx. in 70% of children with Prader-Willi sy, others are caused by uniparental (maternal) disomy with genomic imprinting effect, rarely by point mutations of genes in critical region for Prader-Willi/Angelman syndromes or imprinting regulating genes
   - Phenotype:
     - Newborn, early infants - severe hypotonia, developmental delay
     - Later – mild to moderate mental retardation, overeating – extreme obesity with possible letal complications (diabetes mellitus, cardiovascular disorders,...), hypogenitalism, behavioral disorders (sleeplessness, anger, annoyance,...)
5. **Angelman sy** – interstitial microdeletion on the short arm of maternal chromosome 15
   - Etiology: microdeletion is detected approx. in 70% of children with Angelman sy, others are caused by uniparental (paternal) disomy with genomic imprinting effect or point mutations of genes in critical region for Prader-Willi/Angelman syndromes
   - Phenotype:
     - severe mental retardation, absent speech, jerky movements, ataxia, stiff-legged gait, epileptic seizures, behavioral disorders (stereotypic movements, paroxysms of easily provoked laughter), „happy puppet“ syndrome
     - Genomic imprinting mechanisms (see question No. 52 – Epigenetics, genetic imprinting)
6. **Other microdeletion syndromes**:
   - DiGeorge/VCFS/CATCH 22 sy (deletion on chromosome 22)
   - Wolf-Hirschhorn sy (deletion on chromosome 4)
   - Williams-Beuren sy (deletion on chromosome 7)