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CHROMOSOMAL MUTATIONS AND ASSOCIATED HEREDITARY DISEASES: ETIOLOGY AND PATHOGENESIS

Doliyev Ahmadjon Ulugbek ogli

E-mail: ahmadjondoliyev@gmail.com

1st-year student, Faculty of Medicine, Asia International University

Scientific Supervisor: Shukurova Shokhina Tuygunovna

Senior Lecturer, Department of General Sciences, Asia International University

E-mail: shukurovashoxinatuygunovna@oxu.uz

Abstract. This article provides a comprehensive analysis of the etiology and pathogenesis of hereditary diseases caused by chromosomal mutations. Changes in chromosome number and structure — aneuploidy (trisomy, monosomy), polyploidy, deletion, duplication, translocation, inversion, and complex "de novo" structural variants (dnSVs) — lead to severe developmental defects in early embryogenesis, pregnancy loss, and congenital multisystem disorders. The article thoroughly examines etiological aspects such as meiotic nondisjunction, premature sister chromatid separation (PSSC), reverse segregation, weakening of cohesin and spindle apparatus, the effect of advanced maternal age, environmental mutagens, and genetic factors (including the high frequency of consanguineous marriages in Central Asia). It also proposes strategies for prenatal screening, genetic counseling, and disease prevention.

Keywords: chromosomal mutations, aneuploidy, gene dosage imbalance, meiotic nondisjunction, PSSC, reverse segregation, Down syndrome, Turner syndrome, Klinefelter syndrome, cri-du-chat syndrome, DYRK1A, chromosomal microarray analysis (CMA), prenatal diagnostics.

Introduction. The human genome consists of 46 chromosomes (22 pairs of autosomes and 2 sex chromosomes), which play a central role in storing, replicating, and expressing hereditary information. Chromosomal mutations — alterations in number or structure — constitute a major group of hereditary diseases. Such anomalies occur in 0.4–0.9% of live births and are responsible for 50–67% of embryonic losses during pregnancy. Most of these mutations arise "de novo" in healthy parents, although they can be inherited through balanced translocation carriers. The development of

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cytogenetic analysis, FISH, CMA, and NGS technologies has dramatically improved the detection of micro-anomalies, complex "de novo" structural variants (dnSVs), and submicroscopic changes. Chromosomal mutations contribute not only to intellectual disability, skeletal and visceral anomalies, but also to cardiovascular diseases, infertility, immunodeficiency, and increased oncological risk. This article focuses on etiology and pathogenesis, as their deep understanding is crucial for effective family genetic counseling, prenatal screening, and preventive measures.

Main Part. Chromosomal mutations are divided into numerical changes (genome mutations) and structural changes. Numerical abnormalities include aneuploidy (gain or loss of one or more chromosomes) and polyploidy (multiplication of the complete chromosome set). Aneuploidy is the most common and results from meiotic nondisjunction (failure of chromosomes to separate), premature sister chromatid separation (PSSC), and reverse segregation. These errors predominantly occur in maternal meiosis I and increase sharply with advancing maternal age. Polyploidy (e.g., triploidy) arises from fertilization errors — diploid gametes or dispermy — and usually leads to early pregnancy loss. Structural mutations include deletion (loss of a segment), duplication (extra copy), translocation (exchange between chromosomes), inversion, and complex "de novo" structural variants (dnSVs). Deletions and duplications cause gene dosage imbalance: haploinsufficient genes become insufficient with one copy, while extra copies disrupt cellular function. Carriers of balanced translocations are phenotypically normal, but meiotic recombination can produce unbalanced variants in offspring. Inversions and dnSVs alter gene sequences, disrupting transcriptional regulation and epigenetic control. Recent studies indicate that dnSVs rank third among causes of rare disorders after simple deletions and duplications. Etiologically, chromosomal mutations arise from internal (genetic) and external (environmental) factors. Internal factors include natural errors in meiosis and mitosis, particularly impaired recombination in oocytes, weakening of the cohesin complex, spindle apparatus and kinetochore dysfunction, telomere shortening, DNA damage, and mitochondrial dysfunction. Advanced maternal age is the primary risk factor: after age 35, the frequency of trisomy 21 increases exponentially due to weakened cohesin and spindle assembly checkpoint (SAC) signaling. In younger women, meiosis I nondisjunction predominates, while PSSC and reverse segregation increase with age. External factors include ionizing radiation, chemical mutagens (pesticides, certain drugs), viral infections (rubella), folate deficiency, obesity, smoking, and metabolic disorders. "De novo" mutations account for ~80% of cases, but the risk rises to 10–15% in families with balanced translocation carriers. In Central Asia, including Uzbekistan, the high prevalence of consanguineous marriages

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increases genetic load — according to official data, nearly 10% of children born with disabilities result from such unions. These factors collectively amplify meiotic errors, leading to aneuploidy and structural changes. Pathogenesis is illustrated through gene dosage imbalance, altered signaling pathways, epigenetic dysregulation, and disrupted cell differentiation, using the most common syndromes: Down (trisomy 21), Shereshevsky-Turner (45,X), Klinefelter (47,XXY), cri-du-chat (5p deletion), as well as Patau (trisomy 13) and Edwards (trisomy 18) syndromes. The primary pathogenic mechanism is gene dosage imbalance. In trisomies, excess genes increase protein and ncRNA synthesis by 1.5-fold, disrupting cell cycle, apoptosis, signaling (e.g., IGF, DYRK1A pathways), and tissue differentiation. In monosomies, haploinsufficiency of critical genes halts developmental processes. In structural mutations, loss or disruption of specific genes impairs neuronal migration, cardiac formation, immune system, and skeletal development. The gene dosage imbalance and amplified developmental instability hypotheses are fundamental. The Down syndrome critical region (DSCR, 21q22.1–q22.3) highlights the combined effects of several genes (DYRK1A, APP, RCAN1, SOD1). Overexpression of "DYRK1A" (21q22.13) contributes to neurodegeneration, cardiac defects, and progeroid features by increasing DNA damage and reducing Lamin B1 levels. Recent studies show variable inter-individual expression of Hsa21 genes, linked to epigenetic control and cell-type specificity. Mosaicism mitigates clinical severity but complicates diagnosis. Pathogenesis begins in early embryogenesis, resulting in multisystem defects. Somatic chromosomal changes also participate in carcinogenesis (e.g., t(9;22) Philadelphia chromosome).

Research Results. Modern research precisely demonstrates the frequency, mechanisms, and clinical outcomes of chromosomal mutations. Aneuploidy occurs in 50–67% of miscarriages and is the leading cause of embryonic demise. Down syndrome (trisomy 21) is the most common, affecting 1:700–1:800 live births. In 95% of cases it is free trisomy (meiotic nondisjunction), 3–4% Robertsonian translocation, and 1–2% mosaic. Pathogenesis involves overexpression of DSCR genes, particularly "DYRK1A", leading to neurodegeneration, cardiac defects (45–50%), immunodeficiency, and early-onset Alzheimer's disease. Maternal age-related nondisjunction mainly occurs in meiosis I; recent data confirm the age-dependent rise in PSSC and reverse segregation. Shereshevsky-Turner syndrome (45,X or mosaic) occurs in 1:2000–1:2500 females and causes ovarian dysgenesis, short stature, aortic coarctation, and cardiac defects due to haploinsufficiency of the SHOX gene. Klinefelter syndrome (47,XXY) affects 1:500–1:1000 males, leading to testicular atrophy, infertility, and gynecomastia; X-inactivation partially mitigates severity. Cri-du-chat syndrome (5p deletion) has an incidence of 1:15,000–1:50,000. Loss of genes

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in 5p15.2–15.3 (including CTNND2) causes microcephaly, intellectual disability, cat-like cry, and growth delay; deletions are often *de novo* and paternal in origin. Trisomy 13 (Patau) and trisomy 18 (Edwards) present with severe brain and cardiac anomalies and frequently result in pregnancy loss. Array-CGH and NGS detect 10–20% more micro-anomalies and complex rearrangements than conventional methods. CMA identifies additional 6–10% clinically significant CNVs in cases with normal karyotype, especially in fetuses with ultrasound anomalies (up to 12% in cardiovascular defects). In pregnancy losses, mosaicism is often higher in extra-embryonic mesoderm. In Central Asia, consanguineous marriages elevate the frequency of chromosomal mutations. Overall, mutations occurring early in embryogenesis cause severe phenotypes, while later events result in milder or mosaic forms. CMA and NIPT significantly enhance early diagnosis.

Conclusion: The etiology of hereditary diseases associated with chromosomal mutations primarily involves meiotic errors (nondisjunction, PSSC, reverse segregation), advanced maternal age, weakening of cohesin and spindle apparatus, as well as environmental and genetic factors (including consanguineous marriages). Pathogenesis depends on gene dosage imbalance (particularly “DYRK1A”), altered signaling pathways, epigenetic regulation, and disruption of developmental processes, leading to multisystem defects. These disorders impose a serious burden on family and public health. Modern research confirms the high efficacy of prenatal screening, CMA, NGS, and genetic counseling. In the future, technologies such as CRISPR gene editing, folate supplementation, control of age-related risks, and prevention of consanguineous marriages can substantially reduce disease incidence. In-depth study of this topic will contribute significantly to the advancement of medical genetics and reproductive medicine.

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