Craniosynostosis as a clinical and diagnostic problem: molecular pathology and genetic counseling

Abstract

Craniosynostosis (occurrence: 1/2500 live births) is a result of premature fusion of cranial sutures, leading to alterations of the pattern of cranial growth, resulting in abnormal shape of the head and dysmorphic facial features. In approximately 85% of cases, the disease is isolated and nonsyndromic and mainly involves only one suture. Syndromic craniosynostoses such as Crouzon, Apert, Pfeiffer, Muenke, and Saethre-Chotzen syndromes not only affect multiple sutures, but are also associated with the presence of additional clinical symptoms, including hand and feet malformations, skeletal and cardiac defects, developmental delay, and others. The etiology of craniosynostoses may involve genetic (also somatic mosaicism and regulatory mutations) and epigenetic factors, as well as environmental factors. According to the published data, chromosomal aberrations, mostly submicroscopic ones, account for about 6.7-40% of cases of syndromic craniosynostoses presenting with premature fusion of metopic or sagittal sutures. The best characterized is the deletion or translocation of the 7p21 region containing the TWIST1 gene. The deletions of 9p22 or 11q23-qter (Jacobsen syndrome) are both associated with trigonocephaly. The genes related to the pathogenesis of the craniosynostoses itself are those encoding transcription factors, e.g., TWIST1, MSX2, EN1, and ZIC1, and proteins involved in osteogenic proliferation, differentiation, and homeostasis, such as FGFR1, FGFR2, RUNX2, POR, and many others. In this review, we present the clinical and molecular features of selected craniosynostosis syndromes, genotype-phenotype

correlation, family genetic counseling, and propose the most appropriate diagnostic algorithm.

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