Genetic Syndromes Associated with Craniosynostosis

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Craniosynostosis is defined as the premature fusion of one or more of the cranial sutures. It leads not only to secondary distortion of skull shape but to various complications including neurologic, ophthalmic and respiratory dysfunction. Craniosynostosis is very heterogeneous in terms of its causes, presentation, and management. Both environmental factors and genetic factors are associated with development of craniosynostosis. Nonsyndromic craniosynostosis accounts for more than 70% of all cases. Syndromic craniosynostosis with a certain genetic cause is more likely to involve multiple sutures or bilateral coronal sutures. FGFR2, FGFR3, FGFR1, TWIST1 and EFNB1 genes are major causative genes of genetic syndromes associated with craniosynostosis. Although most of syndromic craniosynostosis show autosomal dominant inheritance, approximately half of patients are de novo cases. Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, and Antley-Bixler syndrome are related to mutations in FGFR family (especially in FGFR2), and mutations in FGFRs can be overlapped between different syndromes. Saethre-Chotzen syndrome, Muenke syndrome, and craniofrontonasal syndrome are representative disorders showing isolated coronal suture involvement. Compared to the other types of craniosynostosis, single gene mutations can be more frequently detected, in one-third of coronal synostosis patients. Molecular diagnosis can be helpful to provide adequate genetic counseling and guidance for patients with syndromic craniosynostosis.

Key Words: Craniosynostosis · Apert syndrome · Pfeiffer syndrome · Crouzon syndrome · Antley-Bixler syndrome · Saethre-Chotzen syndrome.

INTRODUCTION

Craniosynostosis describes partial or complete premature fusion of cranial sutures. Ocular hypertelorism, proptosis, beaking of the nose and midface hypoplasia are the common facial features of the craniosynostosis. The prevalence of craniosynostosis is estimated to be 1 in 2100 to 2500 live births. The sagittal suture (40–55%) is the most commonly affected, followed by the coronal (20–25%), metopic (5–15%), and lambdoid (<5%) sutures. The syndromic craniosynostosis is the hereditary form of craniosynostosis, which is associated with extracranial phenotypes such as limb, cardiac, central nervous system and tracheal malformations. Syndromic craniosynostosis comprises 15–30% of the total, and specific single gene mutations or chromosome abnormalities could be identified in at least 20% of all cases. Mutations of several genes including FGFR1, FGFR2, FGFR3, TWIST1, and EFNB1 genes have been frequently reported to be associated with syndromic craniosynostosis (Table 1). Among identified genetic causes, mutations of the FGFR2 gene are critically involved in various syndromic craniosynostosis showing multiple suture involvement. However, FGFR2 mutations show variable clinical expressivity, and patients with the same FGFR2 mutation can exhibit diverse clinical manifestations. Therefore, FGFR2-related craniosynostosis syndromes are usually named according to the accompanying extra-cranial manifestations. Particularly in isolated coronal synostosis, single gene mutations can be detected in one-third of patients. This higher detection rate of mutations may indicate a stronger genetic background for coronal synostosis than other forms of craniosynostosis. Here, common genetic syndromes associated with craniosynostosis are introduced with a brief review of their respective genetic backgrounds.

GENETIC SYNDROMES WITH CRANIOSYNOSTOSIS INVOLVING MULTIPLE SUTURES

Among the various causative genes for craniosynostosis syndromes, FGFR2, FGFR3, and FGFR1 comprise the FGFR family related to craniosynostosis and FGFR2 is the main gene of the family. FGFRs play a central role in the growth and differentiation of mesenchymal and neuroectodermal cells by binding to FGF and initiation of signal transduction. Also, FGFRs regulate cranial suture fusion on a macroscopic level. Animal studies suggest that defective FGF signal transduction due to mutations on...
FGFRs leads to growth arrest of the cranium and the midface\(^{20}\). Mutations in FGFRs have been linked to various clinical craniosynostosis syndromes including Apert (OMIM\#101200), Pfeiffer (OMIM\#101600), Crouzon (OMIM\#123500), Antley-Bixler (OMIM\#207410), Muenke (OMIM\#602849), and Jackson-Weiss (OMIM\#123150) syndromes. These FGFR-related craniosynostosis syndromes are autosomal-dominantly inherited, and share several craniofacial features including premature closure of multiple cranial sutures. On the other hand, a wide phenotypic range has been shown even in patients with identical FGFR2 mutations\(^{17}\). Therefore, differential diagnosis is usually based on presence or absence of distinct limb and dermatological features\(^{18}\).

**Apert syndrome**

Apert syndrome (AS) is characterized by craniofacial malformations including bicornal synostosis and severe symmetrical syndactyly of fingers and toes (Fig. 1A). Syndactyly is a characteristic feature of AS that permits distinction from the other FGFR2-related syndromes, and shows a complex fusion leading to ‘mitten hand’ deformity in both hands and feet. It occurs in 6–15 out of 1000000 live births\(^{3}\). This syndrome is caused by a genetic mutation in the FGFR2 gene, and approximately 98% of all patients have specific missense mutations of FGFR2 located in the linker between the IgII and IgIII domains, either p.Ser252Trp (66%) or p.Pro253Arg (32%)\(^{24}\). Facial manifestations include a flat forehead and retracted midface, proptosis, hypertelorism, and low-set ears. Narrow pharynx and retracted midface frequently result in airway compromise. The other associated anomalies are skeletal malformations, poor joint mobility, eye and ear problems, cleft palate, and orthodontic and other dental problems. Learning disability requiring special education is also

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**Table 1. Common genetic syndromes associated with craniosynostosis**

<table>
<thead>
<tr>
<th>Genetic syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Inheritance</th>
<th>Involved sutures</th>
<th>Hand/foot anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apert syndrome</strong></td>
<td>FGFR2</td>
<td>10q26</td>
<td>Autosomal-dominant</td>
<td>Multiple</td>
<td>Syndactyly of hands and feet</td>
</tr>
<tr>
<td><strong>Pfeiffer syndrome</strong></td>
<td>FGFR2</td>
<td>10q26</td>
<td>Autosomal-dominant</td>
<td>Multiple</td>
<td>Broad and medially deviated thumbs and big toes, brachydactyly</td>
</tr>
<tr>
<td><strong>Crouzon syndrome</strong></td>
<td>FGFR2, FGFR3</td>
<td>10q26, 4p16.3</td>
<td>Autosomal-dominant</td>
<td>Multiple</td>
<td>Normal hands and feet, normal intelligence</td>
</tr>
<tr>
<td><strong>Antley-Bixler syndrome</strong></td>
<td>FGFR2, POR</td>
<td>10q26, 4p16.3</td>
<td>FGFR2; autosomal-dominant, POR; autosomal-recessive</td>
<td>Multiple</td>
<td>Radio-humeral or radio-ulnar synostosis, congenital adrenal hyperplasia (POR)</td>
</tr>
<tr>
<td><strong>Saethre-Chotzen syndrome</strong></td>
<td>TWIST1</td>
<td>7p21</td>
<td>Autosomal-dominant</td>
<td>Coronal</td>
<td>Ptosis, syndactyly, hearing loss</td>
</tr>
<tr>
<td><strong>Muenke syndrome</strong></td>
<td>FGFR3 (p.Pro250Arg)</td>
<td>4p16.3</td>
<td>Autosomal-dominant</td>
<td>Coronal</td>
<td>Normal hands and feet</td>
</tr>
<tr>
<td><strong>Craniofrontonasal syndrome</strong></td>
<td>EFNB1</td>
<td>Xq12</td>
<td>X-linked dominant</td>
<td>Coronal</td>
<td>Bifid nasal tip, cleft lip and/or palate, syndactyly, grooved nails</td>
</tr>
</tbody>
</table>

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**Fig. 1.** A: Pre-operative 3D CT images show brachycephaly with premature fusion of bilateral coronal and lambdoid sutures, and skeletal radiographs show complex syndactyly of the hands and feet in Apert syndrome. B: Skeletal radiographs of the hands and feet show cutaneous syndactyly, broad radially-deviated thumbs, and broad big toes in Pfeiffer syndrome. C: Bilateral radio-humeral synostosis of the elbows joints was noted in Antley-Bixler syndrome.
commonly accompanied (40–70%)\(^2\). Most of patients with AS arise from de novo mutations, which are mainly originated from sperms of their father\(^3\).

**Pfeiffer syndrome**

Distinctive and characteristic features of Pfeiffer syndrome (PS) are broad, radially deviated thumbs and/or big toes along with craniosynostosis. Partial syndactyly on hands and feet can be accompanied in some patients (Fig. 1B). This syndrome affects about 1 in 100000 live births\(^6\). Other manifestations including hydrocephalus, proptosis, ankylosed elbows, visceral anomalies, and delayed neuropsychological development may be found. The craniofacial severity is variable among PS patients, and PS can be classified into three clinical subtypes based on the severity of clinical phenotypes. Type 1 has the 'classic' phenotypes with brachycephaly, midface hypoplasia, finger and toe abnormalities, and normal intelligence with generally good outcome. Type 2 and 3 show more severe phenotypes including cloverleaf skull (only shown in Type 3), severe proptosis, elbow ankylosis or synostosis, developmental delay with neurological complications\(^11,26\).

Mutations in both \(FGFR2\) and \(FGFR1\) cause PS, and \(FGFR2\) mutations found in PS overlap those in Crouzon syndrome. Differentiation between PS and Crouzon syndrome rely on the presence or absence of hands and feet anomalies\(^23,26\).

**Crouzon syndrome**

Crouzon syndrome (CS) is the representative craniofacial dysostosis syndrome, showing a prevalence of 16 in 1000000 live births\(^7\). Craniofacial characteristics of CS are a tall and flat forehead, proptosis, and midface hypoplasia. However, the severity of facial deformity is milder than that of AS, and cleft palate is rarely associated with CS. In opposition to AS or PS, CS has normal intelligence, hands and feet\(^1\). Most (94%) of CS is caused by mutations in \(FGFR2\)\(^1\), although a specific mutation in \(FGFR3\) (p.Ala391Glu) has been identified in patients with CS and acanthosis nigricans on the skin\(^1\). Advanced paternal age linked to de novo development of CS in the offspring has also been demonstrated\(^2\).

**Antley-Bixler syndrome**

Antley-Bixler syndrome (ABS) is a rare form of syndromic craniosynostosis with additional systemic synostosis, including radio-humeral or radio-ulnar synostosis (Fig. 1C). ABS also shows mid-facial hypoplasia, which leads to airway narrowing in most patients. Some patients have congenital heart diseases and renal anomalies. To date, two genes (\(FGFR2\) and \(POR\)) have been identified to cause ABS\(^13\). Patients with \(FGFR2\) shows severe skeletal manifestations and associated complications without endocrinological or genital abnormalities. However, patients with \(POR\) mutations present skeletal manifestations and congenital adrenal hyperplasia with ambiguous genitalia\(^29\). In contrast to the inheritance pattern of \(FGFR2\) mutation (autosomal-dominant), \(POR\) mutations are inherited in an autosomal recessive fashion. The \(POR\) gene encodes P450 oxidoreductase (POR), which transfers electrons to microsomal enzymes, including three other steroidogenic enzymes. Therefore, \(POR\)-deficient patients show not only impaired sexual development and steroidogenesis but also skeletal malformations, the mechanism of which is presumed to involve the role of cholesterol biosynthesis in bone formation\(^7\).

**GENETIC SYNDROMES ASSOCIATED ISOLATED CORONAL SYNOSTOSIS**

The coronal synostosis, the second most common form of craniosynostosis, accounts for 20–25% of all patients with craniosynostosis. Single gene mutations can be more frequently detected in one-third of patients with coronal synostosis (bicoronal, 37.5%; unicoronal, 17.5%) than other types of isolated suture synostosis\(^13,28\). Among causative genes, the \(TWIST1\), \(FGFR3\), and \(EFNB1\) genes are known to be associated with coronal synostosis, particularly in syndromic patients\(^13\).

**Saethre-Chotzen syndrome**

Saethre-Chotzen syndrome (SCS), also known as acrocephalosyndactyly type III, usually involves unilateral or bilateral coronal synostosis and mild limb deformities (Fig. 2A). It is autosomal-dominantly inherited and is induced by loss-of-function mutations of \(TWIST1\), detected in 60–80% of SCS patients\(^2\). \(TWIST1\) encodes for a transcription factor that is responsible for mesenchymal cell development of cranium. \(TWIST1\) also has been thought to be interacted with \(FGFR2\) during fetal developmental\(^8\). The estimated prevalence of SCS is 1 in 25000–50000 live births\(^8\). The clinical phenotypes of SCS vary profoundly, ranging from isolated unicoronal craniosynostosis to the most extreme manifestation of multiple suture involvement. Other clinical features of this syndrome include ptosis, low-set ears, hearing loss, hypertelorism, broad great toes, clinodactyly, and partial syndactyly. Most patients have normal intelligence\(^21\).

**Muenke syndrome**

Muenke syndrome (MS) is also characterized by unilateral or bilateral coronal synostosis with autosomal dominant inheritance. The other features shown in MS are proptosis, down-slaunting palpebral fissures, hearing loss, developmental delay, and specific bone anomalies of the hands and feet\(^4\). Significant phenotypic overlap has been detected between SCS and MS, as coronal suture involvement is the major clinical finding. A single mutation of p.Pro250.Arg in \(FGFR3\) is the defining molecular characteristic of Muenke syndrome\(^2\). However, the mutation, p.Pro250.Arg in \(FGFR3\), is also known to be the single largest etiology and it can be found in nonsyndromic cases besides MS\(^2\). The birth prevalence harboring this mutation is approximately 1 in 10000 live births, accounting for 8–10% of patients with coronal synostosis\(^4\). Considering that MS shows variable expressivity in craniosynostosis and is known as a relatively common diag-
nosis in patients with craniosynostosis syndromes, testing for p.Pro250Arg in FGFR3 can be recommended as the first-line genetic study to perform in nonsyndromic craniosynostosis patients\(^\text{11}\) .

**Craniofrontonasal syndrome**

Craniofrontonasal syndrome (CFNS) is a rare form of syndromic craniosynostosis affecting bilateral coronal sutures. Unique facial dysmorphism on the midline structures including hypertelorism, frontal bossing, grooved or bifid nasal tip, cleft lip and/or palate, high arched palate can be the important clues to clinical diagnosis of CFNS (Fig. 2B)\(^\text{1}\) . Clavicle pseudoarthrosis, syndactyly, clinodactyly, broad thumbs with grooved nails, wiry hair, and dental anomalies are also frequently accompanied. Most patients have normal intelligence\(^\text{10}\) . The causative gene EFNB1 on chromosome Xq12, encodes for a membrane-anchored ligand which can bind to an ephrin tyrosine-kinase receptor. This receptor is responsible for the regulation of embryonic tissue-border formation, and is important for skeletal and craniofacial development\(^\text{4}\) . CFNS shows a paradoxical X-linked inherited pattern. Contrary to most X-linked disorders, females are more severely affected in CFNS, whereas males are asymptomatic or show milder facial phenotypes\(^\text{27}\) . This phenomenon is associated with the process of random X-inactivation in females. X-inactivation in females is a process by which one of the two copies of the X chromosome present is inactivated to balance genetic material of the X chromosome with males. The choice of which X chromosome will be inactivated is random. So, mosaic pattern of cells in females may interfere with normal cell-cell interactions and result in the severe clinical phenotypes shown in females\(^\text{25}\) .

**CONCLUSION**

Great progress in the detection and analysis of craniosynostosis-causative genes has been made in recent years, but craniosynostosis remains a heterogeneous and challenging disorder. Even though specific genetic alterations including single gene mutations or chromosome abnormalities could be identified only in approximately 20% of patients with craniosynostosis, molecular diagnoses can prove helpful in providing adequate genetic counseling to their family members and anticipating associated complications in later life, for these mutation-identified patients.

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