

Mini Review

Is Genetics of Craniosynostoses Investment in the Craniofacial Medicine?

Erika Nagle*

Department of Biology and Microbiology, Riga Stradins University, Latvia

*Corresponding author

Erika Nagle, LV 1007, Dzirciema str. 16, Riga, Latvia, Tel: 371 29194750; Email: Erika.Nagle@rsu.lv / erikanagle@gmail.com

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- genotype/phenotype correlation

Abstract

Craniosynostoses are very severe genetic conditions, they compromise not only the physical functions but also mental well-being of an affected person, because this abnormality cannot be masked - it is on patient's cranium and face. Research in the field of craniofacial genetics opens new horizons in craniofacial medicine. DNA testing allows connecting a specific mutation with a particular phenotype, and this can help in predicting the development of craniofacial complex, as well as in planning surgery, post-operative treatment, and genetic counselling of the patient.

ABBREVIATIONS

FGFR: Fibroblast Growth Factor Receptors; P.Ser252Trp: Protein Serine252Tryptophane; BP: Base Pair

INTRODUCTION

Craniosynostoses could be characterized by odd shaped skull due to premature fusion of a single or several cranial sutures. It is genetically and phenotypically a heterogeneous group of diseases and several sub-categories exist. The two main categories of craniosynostoses are primary (single suture involved, craniosynostosis is a single event) and secondary (several sutures involved, craniosynostosis is one feature of a syndrome) craniosynostoses. In addition, craniosynostosis is a feature seen in more than 100 genetic syndromes.

Genetics of craniosynostoses has been widely studied for years due to high occurrence rates (between 1 in 2100 to 1 in 2500 [1]). Over the two past decades DNA sequencing has provided a new approach in understanding molecular bases of craniosynostoses; consequently this knowledge has been used for predicting the phenotypic outcomes of a patient. Identification of mutations can lead to improvement in genetic counselling; it can have implication on diagnostic testing as well as secure more effective treatment of a patient.

Phenotypic characteristics of craniosynostoses

Crouzon syndrome (OMIM 123500) is characterized by premature fusion of coronal and sagittal suture. This results in midface hypoplasia, maxilla hypoplasia, shallow orbits, exophthalmos, beaked nose, and clinically normal hands and feet [2-4]. Apert syndrome (OMIM 101200) is characterized by premature fusion most commonly of coronal suture, mid face hypoplasia, dilated cerebral ventricles, and bilateral syndactyly

of the hands and feet [2,3,5]. Pfeiffer syndrome (OMIM 101600) is characterized by multi suture premature fusion, broad thumbs and broad and medially deviated halluces; in severe cases it can result in cloverleaf skull, brain anomalies, tracheal sleeve, and fused elbows [2,3]. Three subtypes of Pfeiffer syndrome are known. Type 1 Pfeiffer syndrome patients have mild brachycephaly, mid face hypoplasia, normal intelligence, and good outcome [5]. Type 2 and type 3 have poor outcome with death in infancy [5].

Genetic aetiology of craniosynostoses

Among different genes involved in craniosynostoses, fibroblast growth factor receptors (FGFR) are of utmost importance in the aetiology of many secondary craniosynostoses and they are involved in aetiology of primary craniosynostoses also. It is well known that FGFR play an important role in undifferentiated cells to become bone cells in the head, hands, and feet. Fibroblast growth factors (FGF) and fibroblast growth factor receptors (FGFR), and especially FGFR 2, regulate the balance between proliferation and differentiation of progenitor osteogenic cells on the neural crest [6]. FGFR is a huge gene family and three of them FGFR 1, FGFR 2, FGFR 3 are well known for causing secondary craniosynostoses. Mutations in FGFR 1-3 genes account for the majority of secondary craniosynostosis such as Crouzon syndrome, Apert syndrome and Pfeiffer syndrome, and from these 90% of the syndromic craniosynostoses are due to mutations in FGFR 2 [7,8]. The majority of FGFR 2 mutations are missense mutations resulting in ligand-independent constituted receptor activation [7]. Constitutive activation of the receptor results in advanced undifferentiated mesenchymal cells (immature cells) differentiation into bone cells which results in premature closure of the skull sutures. Many mutations are known and specific genotype/phenotype correlation is established.

Genotype /phenotype correlation in case of craniosynostoses

Genotype /phenotype correlation is best known and well documented in Apert syndrome. Almost all Apert syndrome cases are due to two missense mutations p. Ser252Trp and p. Pro253Arg. It is known that there is a strong link between two mutations and the severity of the symptoms. Both mutations change receptor's affinity for the ligand [9] and the phenotypes of patients are quite different (Table 1).

The different mutations can also influence post-operative outcome in patients. In case of p.Ser252Trp mutation patients showed a profound mid-face protrusion and severe malocclusion, but in patients with identified mutation p. Pro253Arg patients showed a mild mid-face retrusion and good dental occlusion [12].

Two Apert syndrome cases that show strong genotype/phenotype correlation have been reported also in case of *Alu* insertion mutations [12]. Phenotypic analysis of two patients showed that outcome of mutation with similar origin is different, depending on the mutation site (Table 2).

Strong genotype/phenotype correlation is observed in Crouzon syndrome also. Unusual clinical feature such as scaphocephaly are observed in case of missense mutation p.Tyr105Cys [9,15]. Missense mutation p.Ala391Glu in FGFR 3 gene can result in Crouzon syndrome with *Acanthosis nigricans*

Table 1: Genotype/phenotype correlation in Apert syndrome; two missense mutation cases.

Abnormality	p.Ser252Trp	p.Pro253Arg
Visual impairment	More severe [10]	Less severe [10]
Amblyopia	More frequent [10]	Less frequent [10]
Strabismus	More frequent [10]	Less frequent [10]
Pale optic disk	Less frequent [10]	More frequent [10]
Cleft palate	More frequently [11,9,12,13,]	Less frequently or absent[11,9, 12,13,]
Syndactyly/limb anomalies	Less severe [11,9,14]	More severe [11,9,14]

Table 2: Genotype/phenotype correlation in Apert syndrome; two *Alu* insertion cases [11].

Structure characterized	368 bp insertion within intron 8	~ 350 bp insertion within exon 9
Cranium	Brachycephaly	Turribrachycephaly
Midface	Hypoplasia	Hypoplasia
Eyes	Hypertelorisms, ocular proptosis	Hypertelorisms, ocular proptosis, strabismus with amblyopia
Palate	High arched	High arched
Vertebral column	Scoliosis	Scoliosis
Limbs	Complete syndactyly	Complete syndactyly, bilateral contracture of the elbows with rhizomelia
Mental development	Good	Delay was apparent, nospech

[16]. This pathology in addition to typical Crouzon syndrome craniofacial appearance have a velvety hyper-pigmented skin usually seen in body folds as neck, axillae, eyelids, perioral, inguinal, and perianal regions [16]. Pfeiffer syndrome could serve as an example of genotype/phenotype correlation as well. Type 1 Pfeiffer syndrome is caused by mutations in FGFR 1 gene or FGFR 2 gene, whereas type 2 and type 3 Pfeiffer syndromes are caused by mutations in FGFR 2 gene only [17]. Severe case of Pfeiffer syndrome type 2 with anterior ocular chamber defects has been reported; molecular analysis identified missense mutation p.Ser351Cys [18].

Prediction of the phenotype depending on genotype could help in determining precise diagnosis, surgery planning, dental treatment, and for counselling patients suffering from craniosynostoses.

DISCUSSION & CONCLUSION

Molecular diagnosis provides a powerful tool in prenatal diagnosis. For example, prenatal diagnosis of craniosynostoses associated with digital abnormalities should include a differential diagnosis of Apert syndrome and Pfeiffer syndrome, both of which can be caused by FGFR 2 mutations [17]. Nevertheless Apert syndrome in 98% is associated with 2 missense mutations of p.Ser252Trp and p. Pro253Arg [12,19], but Pfeiffer syndrome is associated with p.Trp290Cys, p.Ttyr340Cys, p.Cys342Arg, and p.Ser351Cys missense mutations [1]. Depending on the mutation, it is possible to predict the phenotype of the unborn child. Palatal anomalies including cleft palate and high arched palate have been reported in the most common secondary craniosynostoses [20]. Several reports [11,9,12,13,16] have documented that Apert syndrome patients with the p.Ser252Trp mutation present more frequently a cleft palate, whereas patients with the p.Pro253Arg mutations exhibit a more severe syndactyly. Prenatal diagnosis for at-risk fetuses requires identification of the possible mutations in the family members for several reasons. Due to variable expressivity of the condition, molecular diagnosis is important for asymptomatic parents and sibs for recurrence risk prognosis. If child is born with craniofacial abnormalities molecular diagnosis could be done before surgery, usually at infancy.

Most of common secondary craniosynostoses are caused by mutations in FGFR 2 gene and show typical phenotypes. Nevertheless, it should be considered that specific features could be observed in case of specific mutation. For example, if prenatal scans show brachicephaly, hypertelorisms, exophthalmus, beaked nose, with no hand and foot anomalies these would give indication for a Crouzon syndrome. But if foetal DNA was analysed for mutations in FGFR 2 gene (mutated in case of classic Crouzon syndrome) and DNA analysis showed negative results for FGFR 2 mutations, but positive results for p. Ala391Glu mutation in FGFR 3 gene, you can predict that the patient will have not only the typical craniofacial appearance that characterize Crouzon syndrome, but also will have additional features such as dark skin in body folds and diagnosis is Crouzon syndrome with *Acanthosis nigricans*.

Knowledge of specific mutation can help health professionals in providing explanations to patient's parents and the patient why

children with the same diagnosis could have different outcome in the phenotype. For example, one child with Apert syndrome can be severe mentally retarded, but another one can attend normal school (Table 2).

Information about genotype/phenotype correlation can be useful in predicting more precise prognosis of the disease, outcome of surgery, and it can influence algorithm of genetic counselling. Research in the field of genetic background of craniosynostoses brings new approach in treatment and management of the patients with craniosynostoses. Any genetic research in the field is an investment at interest to improve the patients' with this genetic pathologies well-being.

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