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REVIEW ARTICLE

Pfeiffer type 2 syndrome: review with updates on its genetics and molecular biology

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Abstract

Introduction Pfeiffer syndrome is a rare autosomal dominant inherited disorder associated with craniosynostosis, midfacial hypoplasia, and broad thumbs and toes. The syndrome has been divided into three clinical subtypes based on clinical findings.
Methods This review will specifically examine the most severe type, Pfeiffer syndrome type 2, focusing on its genetics and molecular biology.
Conclusion This subtype of the syndrome is caused by de novo sporadic mutations, the majority of which occur in the fibroblast growth factor receptor type 1 and 2 (*FGFR1/2*) genes. There is not one specific mutation, however. This disorder is genetically heterogeneous and may have varying phenotypic expressions that in various cases have overlapped with other similar craniosynostoses. A specific missense mutation of *FGFR2* causing both Pfeiffer and Crouzon syndromes has been identified, with findings suggesting that gene expression may be affected by polymorphism within the same gene. Compared to other craniosynostosis-related disorders, Pfeiffer syndrome is the most extreme phenotype, as the underlying mutations cause wider effects on the secondary and tertiary protein structures and exhibit harsher clinical findings.

Keywords Pfeiffer syndrome · Acrocephalosyndactyly · Craniosynostosis · Cloverleaf skull · Fibroblast growth factor receptor (FGFR)

Introduction

Pfeiffer syndrome, also known as acrocephalosyndactyly, most commonly involves craniosynostosis (mostly coronal), midfacial hypoplasia, broad thumbs and great toes, brachydactyly, and variable soft tissue syndactyly [4, 7, 9, 23]. The incidence of Pfeiffer syndrome is estimated to 1 in 100,000 births [9]. Due to clinical variability, Cohen [7] divided Pfeiffer syndrome into three clinical subtypes based on the severity of phenotype: type 1 is genetically inherited as an autosomal dominant trait [1] and refers to the "classic" Pfeiffer syndrome, noted as the mildest form, characterized as mild midfacial hypoplasia and skull malformations, little to no ocular proptosis, and with slight broadened and minimally deviated thumbs and great toes [1, 2, 9]; type 2 is the most severe form, with a cloverleaf skull (or kleeblattschædel) (Figs. 1, 2, and 3), severe midfacial hypoplasia, ocular proptosis, broad thumbs and great toes, and skeletal deformations of the extremities [1, 2, 4]; type 3 is intermediate, where affected individuals have facial and skeletal deformities similar to type 2, yet lacking cloverleaf skull [2]. The subtypes of Pfeiffer syndrome vary in their prognosis, ranging from relatively benign neurological and developmental manifestations, to high mortality rates. Types 2 and 3 are characterized as having severe neurological compromise with harsh clinical outcomes. Type 2 is the most problematic, often associated with early postpartum death, primarily due to neurological and respiratory complications. The prognosis for type 3 is similar in outcome to type 2, but with milder to moderate intellectual and physical developmental delays [1], despite death almost inevitably occurring within the first 2 years of life [2]. Type 2 not only risks neurological compromise due to premature fusion of the skull, but also

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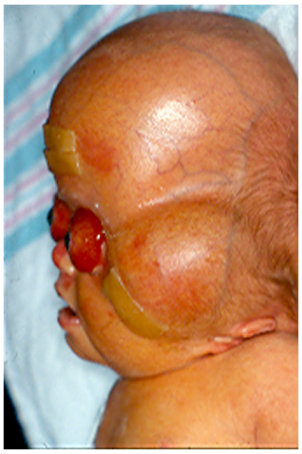

Fig. 1 Lateral view of a clinical case of Pfeiffer syndrome type 2. Note the severe cloverleaf deformity of the skull and proptosis of the eyeballs

can have ankylosis of the elbow joint (less occasional in type 1), immobilizing the distal upper appendages [7]. Given the poor prognostic outcomes of type 2, the occurrences of these syndromes are most often sporadic in nature [25].

Molecular biology

Molecular genetics of congenital skull malformations are of great interest due to the various comorbidities that may arise such as arteriovenous malformations, systemic angiomas, cavernous hemangiomas, and sinus pericranii [3, 15, 32]. Regarding Pfeiffer type syndromes, the molecular genetics are similar to other craniosynostosis abnormalities, such as Crouzon, Apert, and Jackson Weiss syndromes, which all may be a result of hypermorphic fibroblast growth factors (FGFR) 1/2/3 (located on chromosomes 8p, 10q, and 4p respectively), *MSX2*, or *TWIST* mutations [30]. Very often, these autosomal dominant syndromes are known to have existing overlaps associated with *FGFR1* and *FGFR2* mutations.

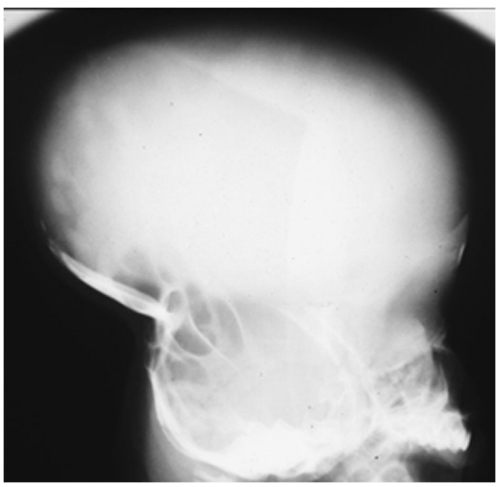

Fig. 2 Lateral radiograph of the patient seen in Fig. 1

Pfeiffer syndrome is genetically heterogeneous with over 25 mutations detected on *FGFR1* and *FGFR2*, accounting for 60–70% of mutations of Pfeiffer syndrome [2, 8, 9]. The majority of affected individuals express a mutation of *FGFR2*, with approximately 5% associated with an additional *FGFR1* mutation. Normally, affected individuals with *FGFR1* mutation have only been associated with Pfeiffer syndrome type 1, the less severe phenotype; however, comorbidity of *FGFR1* and *FGFR2* may represent isolated cases of clinical and molecular genetic interest [9, 19]. Clinical subtypes are not mutually exclusive to specific mutations on *FGFR*; rather, similar mutations can give rise to different clinical phenotypes. Plomp and colleagues [19] investigated five cases of Pfeiffer syndrome type 2, in which two patient's (Patient 1 and Patient 5) DNA analysis indicated a 1036 T➔C de novo mutation in *FGFR2*. Patient 1 died 4 h following birth and presented with cloverleaf skull, hypertelorism, proptosis, severe midfacial hypoplasia, broad nose, protruding tongue, large ears, broad thumbs, single palmar crease, and broad halluces medially deviated. Patient 5 presented with mild cloverleaf skull deformation, proptosis with exphoria, severe choanal narrowing, beaked nose, low set ears, large thumbs, and large medially deviated halluces. Patient 5 underwent surgery for choanal stenosis and skull deformity and was still alive at 5 years and 8 months. The differences between these two cases very clearly demonstrate the range of phenotypic expression and severity that may be observed in individuals with Pfeiffer type 2 [19]. Similar craniosynostosis type disorders have mutations that overlap, which rightfully points toward an interesting characteristic of disorders that involve mutation of the *FGFR* genes. The same missense mutation identified in Pfeiffer type 2 syndrome, 1036 T➔C, has also been reported in classic Crouzon syndrome. A possible explanation is that the expression of *FGFR2* is affected by a polymorphism sequence in another part of the same gene [19, 24].

The pattern of severity of different syndromes based on phenotype may also be explained by the severity of the affected protein structure during mutation. The *FGFR2* gene is an extracellular ligand-binding structure comprised of three immunoglobulin loops, a single transmembrane domain, and an intracellular tyrosine kinase. Most mutations resulting in craniosynostosis syndrome (Alpert, Crouzon, Pfeiffer syndrome, and Jackson Weiss syndrome) are missense mutations in exon 9 of immunoglobulin loop of *FGFR2*. Most often, mutations resulting in Pfeiffer syndrome phenotypes involve substitutions of cysteine residues that dramatically alter the secondary and tertiary structures of the receptor by misplaced or loss of disulfide linkages, and mutative nucleophilic activity with neighboring residues (see Table 1) [12, 18, 20, 22, 24]. Codon 342 of *FGFR2* is well known as a hotspot for gene alteration where the elimination of cysteine, which maintains the third immunoglobulin loop structure, becomes replaced with Arg, Ser, Try, Trp, and Phe in various syndromes [25].

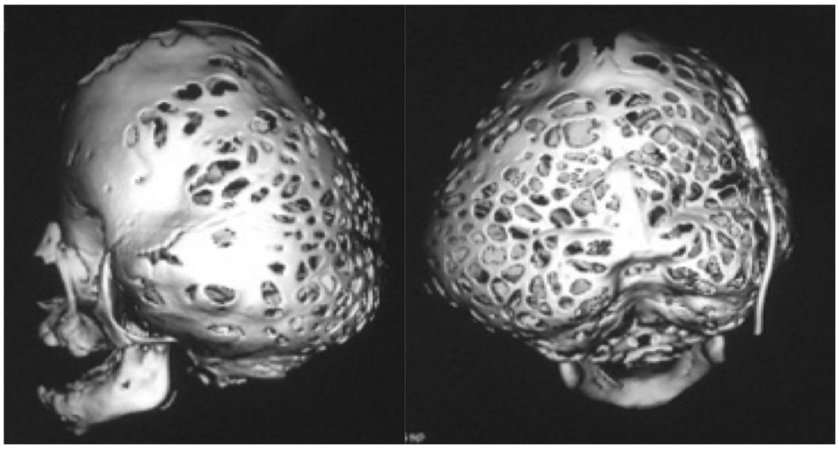

Fig. 3 3D reconstructed CT of a child with Pfeiffer syndrome type 2. Note the significant craniolacunia

However, novel mutations at codon 290 exon 7 (IIIa) noted a missense mutation of TGG (Trp) to TGT (Cys). The result was an additional cysteine leading to the formation of mutant disulfide bridge; in a Trp ➔ Arg mutation, Crouzon syndrome results in its classic form; Trp ➔ Gly substitutions precipitate mild Crouzon phenotypes. It was noted that the severity of phenotypic appearance was correlated to hierarchical protein substitution in the order Cys>Arg>Gly, with addition of Cys resulting in the most severe clinical features due to disruption of the conformation of the global protein structure [25, 29].

Because of the de novo nature of mutation that causes Pfeiffer syndrome, various mutations continue to be discovered. A study conducted by Blaumeiser et al. [4] prenatally diagnosed a 30-week gestation with Pfeiffer syndrome type 2 via 3D sonography. DNA analysis was acquired via cordocentesis, which identified a *FGFR2* (Y340C residue) mutation. Based on parental DNA, this was a de novo mutation, resulting from an unpaired cysteine interfering with receptor dimerization. Pfeiffer syndrome type 2 may also exhibit phenotypic expression without mutation of *FGFR1/2* and does not rule out diagnosis. In a case presented by Bernstein et al. [2], a 27-week gestation with ultrasound findings of cloverleaf skull, hypertelorism, flattened bridge of the nose, and varus deformity of the great toe resulted in a presumptive diagnosis of Pfeiffer syndrome type 2 based on clinical features. Following the termination of pregnancy, a DNA analysis showed no identifiable mutation in *FGFR1/2*. During investigations by Plomp et al. [19], three out of five patients with Pfeiffer syndrome type 2 were unable to identify a mutation on *FGFR 1/2* despite clinical presentation. An implication of this study is that an identified mutation in *FGFR 1/2* may not be necessary for diagnosis when clinical features of Pfeiffer syndrome are phenotypically expressed.

Table 1 Pfeiffer syndrome FGFR2 gene missense mutations

Locus	Mutation	Codon	Position	Reference
exon IIIa	Ser267Pro	*T*CC → *C*CC	799	[12]
	Phe276Val	*T*TT → *G*TT	826	[12]
	Cys278Phe	T*G*C → T*T*C	833	[15]
	Trp290Cys	TGG → TGC	870	[19]
	Trp290Cys	TGG → TGT	870	[7]
	Cys342Gly	*T*GC → *G*GC	1024	[12]
exon IIIc	Tyr340Cys	TAT → T*G*T	1019	[12]
	Cys342Ser	T*G*C → T*C*T	1024	[12]
	Cys342Ser	*T*GC → *A*GC	1024	[16]
	Cys342Trp	TGC → TG*G*	1026	[17]
	Cys342Arg	*T*GC → *C*GC	1024	[13, 14, 17]
	Ser351Cys	TCC → T*G*C	1052	[18]

Clinical and surgical aspects

Relevant for the clinician and surgeon are (but are not limited to) ultrasonographic diagnoses of Pfeiffer type 2, as well as the various latent manifestations of congenital skull defects such as hydrocephalus and Chiari type malformations [30]. Ultrasonographic screening of Pfeiffer type 2 at the second trimester has been well demonstrated by Bernstein [2]. In certain cases, the craniofacial signature of Pfeiffer type 2 may be absent altogether, while the defects involving the hands and feet are observed, thus the traditional means by which Pfeiffer (and other craniosynostoses) is diagnosed (2D ultrasonography, MRI) may not be sufficient for conclusive prenatal diagnosis alone [11]. Ultrasonic diagnosis of type 2 Pfeiffer syndrome may be obtained via observation of "mitten hands" (complex syndactyly) and confirmation of *FGFR 1/2* mutation as early as the second trimester, as demonstrated by Gorincour and colleagues [10]. At least 40% of individuals affected by Pfeiffer syndrome will express ventricular dilatation and, fewer, ventriculomegaly due to increased intracranial pressure from premature sutural closure. Pre- and postoperative monitoring ventricular size and intracranial pressure are of utmost importance in order to prevent hindbrain herniation, which is corrected most effectively via posterior cranial vault

expansion [30]. Due to the increase in intracranial pressure throughout the prenatal interval, neurodevelopmental delays and or permanent cognitive deficiencies are likely in cases of craniosynostoses that involve multiple sutural closures and increased skull thickness. Surgical correction of skull deformities can also give rise to hydrocephalus [31]. Cinalli [6] reported 5 of 18 cases (28%) of Pfeiffer syndrome requiring surgical intervention for hydrocephalus.

Of the many comorbidities of Pfeiffer type 2, Chiari type I malformations occur in up to 50% of patients [5]. Hydrocephalus may also exacerbate existing Chiari type I malformations [5, 26–28, 31]. Chiari type I malformations appear to arise post-partum, typically between 6 weeks to 4 months after birth [5, 21]. Surgical correction of Chiari type I malformations in craniosynostosis may show improvement after extreme cranial vault remodeling and hindbrain decompression; however, more complicated cases may involve remodeling or craniectomy at the base of the occiput [21].

Conclusions

Although mutations on *FGFR2* accounts for the majority of Pfeiffer syndrome type 2 cases, a lack of mutation on *FGFR* cannot exclude a Pfeiffer syndrome type 2 diagnosis when clinical findings are present, thus further investigation is necessary in order to conclude an exact genotypic and phenotypic correlation. A better understanding of the genetics and molecular biology of the various craniofacial anomalies such as Pfeiffer syndrome is important for the clinician and researcher alike.

Compliance with ethical standards

The authors have nothing to disclose.

Conflict of interest The authors declare that they have no conflict of interest.

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