FGFR2 GENE MUTATIONS IN MALAYSIAN PATIENTS WITH ASSOCIATED CLINICAL FEATURES OF APERT SYNDROME AND CROUZON SYNDROME

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INTRODUCTION

- The *FGFR2* gene encodes for fibroblast growth factor receptor 2 (*FGFR2*) protein, involves in important processes such as cell growth and division, cell maturation, bone development, formation of blood vessels, wound healing, and embryonic development. [1]
- The *FGFR2* gene (NM_000141.4), consists of 17 coding DNA located on chromosome 10q26.13.[2] The *FGFR2* gene is one of the most extensively studied gene in various craniosynostotic syndrome including Crouzon syndrome, Pfeiffer syndrome, Apert syndrome, Jackson-Weiss syndrome and few others with Apert syndrome and Crouzon syndrome being the most commonly referred to our laboratory for molecular investigation.
- Apert syndrome presented with craniosynostosis (premature fusion of one or more cranial sutures) and acrocephaly, including brachycephaly, midface hypoplasia and syndactyly of hands and feet.[3]
- Crouzon syndrome typically characterized by craniosynostosis, exorbitism, hypertelorism, midface hypoplasia, hooked nose, thin vermilion of the upper lip and mandibularprognathism.[4]
- Most of *FGFR2* associated diseases are inherited in autosomal dominant trait.

OBJECTIVE

- The objective of this study was to identify mutations in *FGFR2* gene in patients with craniosynostosis syndrome to determine disease phenotype.

METHODOLOGY

- Eight patient samples (from 2019-2020) age range from 6 months to 3 years old, suspected for Craniosynostosis syndrome, Crouzon syndrome and Apert Syndrome (AS) were analysed.
- DNA was extracted from EDTA-blood samples using magnetic bead based method and quantified by using Nanodrop spectrophotometer before subjected to PCR with specific primers.
- A total of 17 PCR amplicons for each patient were then purified before proceeded to cycle sequencing and final detection by DNA sequencing using 3500 ABI Genetic Analyzer.
- Raw data were analysed using SeqScape software and variants found were reviewed with Human Gene Mutation Database (HGMD) for previously reported cases. The pathogenicity of mutation was predicted using MutationTaster software.

RESULT & DISCUSSION

Table 1 : Patients' demographic and mutations finding.

Patient	Age	Sex	Ethnic	Nucleotide changes	Protein changes	Exon	Reported in HGMD
1	10m	F	M	c.755C>G	p.(Ser252Trp)	7	Apert Syndrome[5]
2	1y	F	M	c.755C>G	p.(Ser252Trp)	7	Apert Syndrome[5]
3	3m	F	M	c.758C>G	p.(Pro253Arg)	7	Apert Syndrome[5]
4	3y	M	M	c.758C>G	p.(Pro253Arg)	7	Apert Syndrome[5]
5	6m	M	M	c.755C>G	p.(Ser252Trp)	7	Apert Syndrome[5]
6	1y	F	M	c.1040C>G	p.(Ser347Cys)	8	Crouzon Syndrome[6]

Abbreviation: y=year, m=month, M=male and F=female

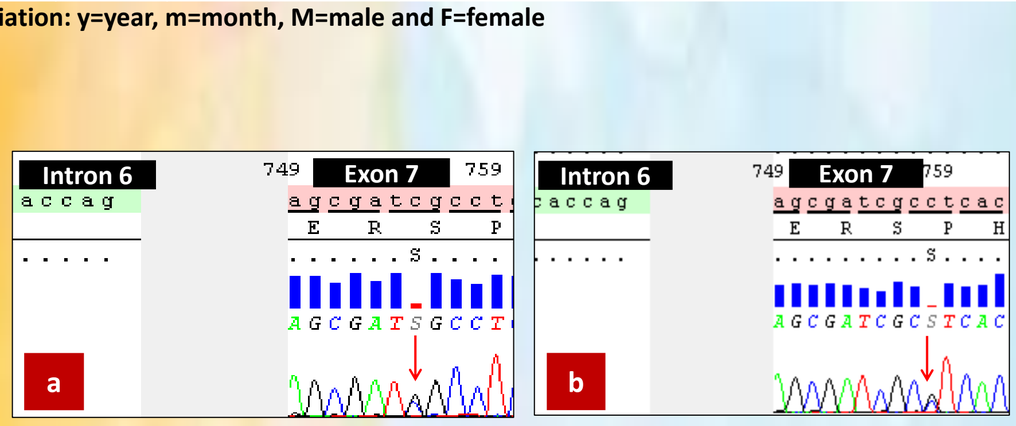

Fig. 1: Two mutations most detected in Apert Syndrome; c.755C>G (fig. a) and c.758C>G (fig. b).

- Six out of eight patient samples have mutation in *FGFR2* gene as described in Table 1. Five patients have reported mutation associated with Apert Syndrome while remaining one patient has mutation related with Crouzon syndrome.
- Mutation at c.755C>G p.(Ser252Trp) and c.758C>G p.(Pro253Arg) in exon 7 were detected in three and two of Apert Syndrome patients, respectively (Fig. 1). These two mutations are the most frequently mutations detected approximately 85% and 15% in Apert Syndrome.[2]
- In patient with Crouzon syndrome, mutation c.1040C>G p.(Ser347Cys) was detected in exon 8. Consistently with study by Gorry, M. C. et. al., approximately 95% of Crouzon syndrome have mutation in either exon 8 or exon 10, which encode the extracellular immunoglobulin-like III (IgIII) domain of the receptor.
- Molecular genetic testing should be performed as early diagnosis is important for early intervention, both medically and surgically with multiple interdisciplinary teams are crucial for the management of this disorder. For example, craniectomy is often performed before 6 months of age to treat craniosynostosis and this may improve intelligence.

CONCLUSION

We have identified two distinct mutations in *FGFR2* gene in patient with Apert Syndrome from unrelated families, consistent with other studies. Since Apert Syndrome and Crouzon syndrome are relatively rare syndrome and difficult to diagnose, molecular diagnosis will provide useful information for the disease diagnosis and genetic counseling.

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