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Extended Abstract

Apert Syndrome Due to Mutation of FGFR2 Gene (Fibroblast Growth Factor Receptor 2) – a Disorder of Advanced Paternal Age- a Case Report

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Abstract

The effects of advanced maternal age on off springs have been well studied and the best documented example is Down Syndrome. A small group of congenital disorders, called paternal age effect (PAE) disorders include Apert Syndrome, Crouzon Syndrome, Achondroplasia and Thanatophoric Dysplasia. They are associated with increased paternal age, relative to the general population. One such case of Apert Syndrome has been discussed in this article.

Introduction

Paternal age effect (PAE) disorders, which include Achondroplasia, Apert Syndrome and Costello Syndrome are due to for certain monogenic conditions. These disorders occur due to specific mutations exclusively originating from the male germline, in genes encoding components of the tyrosine kinase receptor/RAS/MAPK signaling pathway. The children, affected with these disorders, have fathers with advanced age.

Case Report

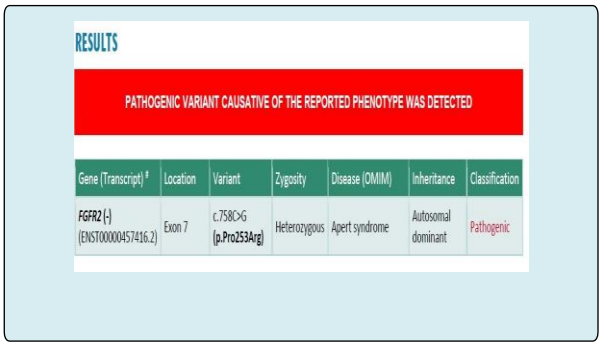
An 8yr. old boy presented with progressively increasing and misshapen head, dysmorphic face, short stature and malformed hands and feet. His father was of advanced age (45yrs). The parents of the child gave a history of global developmental delay, delayed speech and failure to grow in their child.. On examination, the child had moderate intellectual disability and hypernasal monosyllabic speech, dysmorphic facies with turricephaly (tall, tower shaped skull), brachycephaly (transverse diameter > antero- posterior diameter) and tall, broad forehead, prominent supra orbital ridges, shallow orbits, proptosis, hypertelorism, depressed nasal bridge, high arched cleft palate. There were bilateral “mitten hands” - second to fifth digits of both hands showed syndactyli (complete fusion of fingers), contiguous nail beds (synonychia) and cup-shaped palms. The

thumbs were proximally placed, broad, and radially deviated (hitchhiker's thumb). Bilateral "sock feet" deformity – syndactyli and synonychia of the second to the fifth toe was seen with broad halluces. Bilateral genu valgum was also observed.

X-ray skull revealed bony bridging along coronal sutures (bicoronal synostosis). Further, hand and foot radiography showed cutaneous and osseos syndactyli. The clinical diagnosis was that of Apert syndrome, through phenotypic and radiological findings. Genetic testing was

advised for skeletal dysplasia gene panel by next generation sequencing. Report indicated heterogeneous missense mutation in the FGFR2 gene (c.758C>G p.Pro253Arg). [*fig 1*]

Fig 1: Molecular genetic report of proband


RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
FGFR2 (-) (ENST00000457416.2)	Exon 7	c.758C>G (p.Pro253Arg)	Heterozygous	Apert syndrome	Autosomal dominant	Pathogenic

Genetic counseling - Apert syndrome is an autosomal dominant disorder. In 98% of cases, there is de novo mutation. Thus, the risk of recurrence in siblings of proband is minimal (<1%). Usually these patients have decreased reproductive fitness. The de novo mutations are commonly associated with advanced paternal age.

Discussion

Apert syndrome is one of the commonest examples of paternal age effect (PAE) disorders caused by specific missense mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene. Apert Syndrome belongs to the FGFR-related craniosynostosis syndromes. In craniosynostosis, there is premature closure of cranial sutures, with a birth incidence of 1 in 3000. In Apert Syndrome, bicoronal synostosis occurs in infancy. The molecular basis of the Apert Syndrome is remarkably constant – one of the 2 missense mutations caused by substitution of nucleotides resulting in amino acid substitutions – serine252tryptophan or proline253arginine.[1]

The paternal age effect (PAE) in Apert Syndrome - PAE disorders are caused by dominant heterozygous mutations, with a triad comprising paternal origin

of mutations, an advanced paternal age effect and a high germline mutation rate.

Spermatogenesis requires regular mitotic divisions of spermatogonial stem cells (SSCs) from puberty onward, at a rate of 23 divisions per year to produce mature sperm cells. Spermatogenesis involves recurrent rounds of DNA replications, so there is a high possibility of random mutational events arising in the male germline.

The traditional explanation for paternal age effects was age-dependent accumulation of recurrent mutations taking place within localized hypermutable DNA hotspots (the copy- error hypothesis. In Apert syndrome, the associated mutations due to increased age are very pronounced. Probably other age-dependent factors, such as erroneous DNA replication, inefficient DNA repair mechanisms, or repeated mutagenic exposures may contribute to the accumulation of mutations

The major determinant of the paternal age effect is expression of mutant protein in Seminiferous Stem Cells (SSC). The mutant SSCs are selected in preference to normal SSCs, and undergoes localized clonal expansion. This mechanism is named *protein-driven selfish selection.* The sperm of all men develop PAE mutations as they age and selfish selection of mutant SSCs is likely to be a universal process.

Conclusion

With advancing age, the sperm of all men show PAE mutations.a Prenatal screening via cell - free fetal DNA from maternal blood can be offered to couples with advanced age in the male partner, to screen for PAE disorders like Apert's syndrome, and achondroplasia