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Case Report

Apert syndrome with S252W FGFR2 mutation and characterization using Phenomizer: An Indian case report

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ABSTRACT

Human genetic disease needs differential diagnosis to optimize clinical management, enable prenatal detection, and genetic counselling. The current methods of robust DNA sequencing also require next generation phenotyping to match with for better interpretation of genotypic and phenotypic heterogeneity commonly observed. We report use of human ontology based phenotypic characterization with Phenomizer that gives statistical score for possible diagnoses based on which, the gene mutation was studied.

A case of craniosynostosis which refers to a group of syndromes characterized by a premature fusion of skull was studied. The phenotypic features viz, dental crowding and dental malocclusion, bulbous nose, downslanted palpebral fissures, radial deviation of thumb, syndactyly of fingers, macrocephaly, and oxycephaly were entered to query the web-based tool *Phenomizer* which indicated high probability of mutation in FGFR2 gene. The proband, a 13-year-old male born to non-consanguineous parents showed mutation on FGFR2 gene at c.755C>G indicative of Apert syndrome. Apert syndrome is one of the most severe craniosynostosis syndromes with two possible mutations in the exon IIIa of FGFR2 gene reported in majority of the cases. This case study shows the importance of Phenomizer and molecular genetic analysis in differential diagnosis of genetic diseases.

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1. Introduction

The human genetic diseases require team of clinician, geneticist, and laboratory personnel in addition to proband and family. The important part in clinical examination of genetic diseases is description of phenotype which can be subjective and superfluous to specific and harmonized based on the expertise of the person involved. The current whole genome sequencing approaches are highly informative due to increased sensitivity and thus give more scope of finding causative genetic changes, provided phenotyping is also next generation to match with. The Phenomizer serves to carry out phenotypic analysis using standard and globally harmonized terminology for each trait, offering computation advantage for similarity searches.[1] Phenomizer is freely available web based tool which employs semantic similarity in an ontology to rank candidate diseases (the differential diagnosis) based on the query terms and *p* value that indicates whether the similarity scores of best-matching candidate diseases are significant than would be expected by chance.[1] The Phenomizer itself does not make diagnoses instead provides ranked list of possibilities that can be used as a part of the diagnostic workup and thus narrow down the diagnosis process.

Craniosynostosis is a heterogeneous group of syndromes characterized by a premature sutural fusion as a sole or with other anomalies.[2] It exhibits considerable phenotypic and genetic heterogeneity with incidence of 1 in 2500 live births.[3] There are more than 180 syndromes included in the category of craniosynostosis; out of which around eight types are linked with mutations in fibroblast growth factor receptor (FGFR2) gene i.e. isolated coronal synostosis, Pfeiffer syndrome, Crouzon syndrome, Apert syndrome, Beare–Stevenson syndrome, Jackson–Weiss syndrome, Crouzon syndrome with acanthosis nigricans, and Muenke syndrome.[4]

Inspite of recent advances in laboratory medicine, in the majority of cases, diagnosis remains a challenge unless that requires use of strategies developed and validated over the last 30 years.[5] The molecular genetics rearrangement is vital to get accurate diagnosis and thus customized treatment, disease

Abbreviations: FGFR, fibroblast growth factor receptor; BKT, Binet Kamat intelligence test; ADHD, attention deficit hyperactivity disorder.

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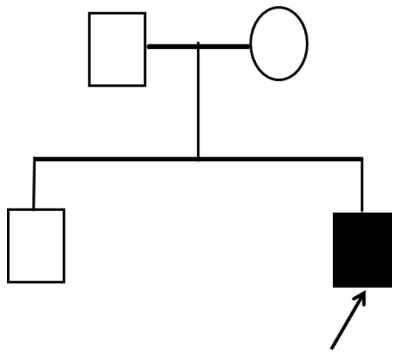

Fig. 1. Pedigree of proband.

management, and genetic counselling. The molecular diagnosis helps clinician to persuade the family for acceptance of the disability, and connect with other parents and support groups.

1.1. Case report

We describe here a 13-year-old male with intellectual disability and major dysmorphisms. The proband is second child born to non-consanguineous, healthy parents when the mother was 24-year-old with a normal male child of 4 years (Fig. 1). At age of 2 months plain CT scan of brain showed prominent cisterna magna, fused coronal sutures, hypoplastic appearance of frontal and sphenoid bones and sagittal and lambdoid sutures appeared open. The X-ray report of chest at age of 5 months showed a prominent broncho-vascular markings at both hilar and parahilar zones. The global developmental delay was noticed from early infancy, he started sitting at 1 year, unclear speech at 1.5 years and walking at 2 years. Clinical history revealed that at the age of 3 the proband had low haemoglobin, low plasma electrolytes namely sodium, chlorides, bicarbonates with anionic gap. The C-reactive protein test was positive (24 mg/L). At the age of 12 years the proband was tested for thyroid function test including T3, T4 and TSH (thyroid stimulating hormone) which was normal.

Current medical history includes mild mental retardation with IQ (intelligence quotient) 60% based on BKT (Binet Kamat intelligence test) and ADHD (attention deficit hyperactivity disorder). The phenotypic features of proband are depicted in Fig. 2. The X-ray reports of skull and mandibular region showed deformities (Fig. 3). The variations in size of body parts with respect to standards were recorded.[6] Minor changes and dysmorphism are depicted in Tables 1–3.

2. Materials and methods

2.1. Karyotyping

The GTG banded karyotyping was done following standard protocol.[7] Peripheral blood was collected in heparinised vial aseptically after obtaining written informed consent from parents. Short term culture of whole blood with PHA as mitogen was carried out. Air dried slides were used for GTG banding and karyotype was done as per the International System for Human Cytogenetic Nomenclature 2013[8] using digital image analysis system and IKAROS karyotyping software (Metasystems, Germany).

2.2. Phenomizer query

The phenotypic features of the proband were added to the Phenomizer viz, 3–4 finger syndactyly, dental crowding,

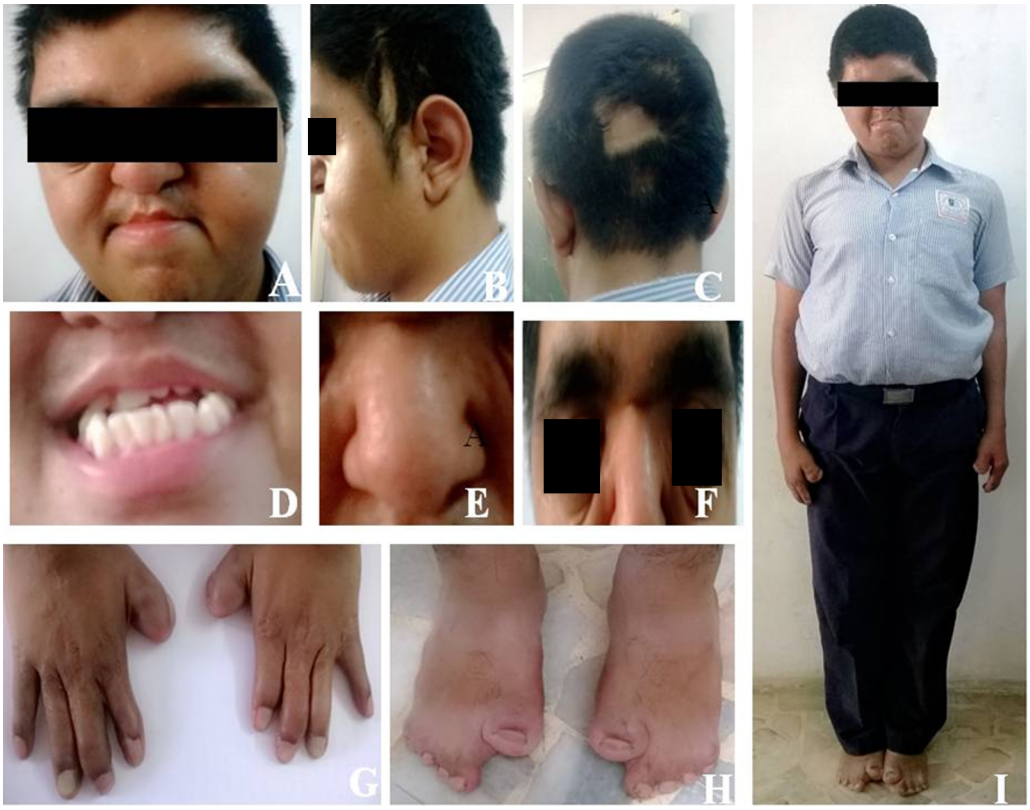

Fig. 2. Figure depicts major phenotypic anomalies of the patient viz. (A and B) Flat facial features, (C) craniosynostosis, (D) dental crowding and dental-malocclusion, (E) bulbous nose, (F) downslanted palpebral fissures, (G and H) radial deviation of thumb, 1–2 finger syndactyly, 2–3 finger syndactyly and 3–4 finger syndactyly and (I) macrocephaly and oxycephaly (corrective surgeries performed).

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