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IDENTIFICATION OF NOVEL MISSENSE PATHOGENIC VARIANT IN FGFR3 GENE CAUSING ACHONDROPLASIA (ACH) IN PAKISTANI PATIENTS

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Abstract

Achondroplasia (ACH; OMIM# 100800) is a genetic disease, an autosomal dominant skeletal dysplasia with associated phenotype of disproponate short-limbed dwarfism. The only causative gene responsible for disorder is Fibroblast growth factor receptor 3 (FGFR3, OMIM# 134934), located on chromosome 4p16.3 with 19 exons. Along with this ,FGFR3 also described for certain other genetic abnormalities like lacrimo-auriculo-dento-digital (LADD) syndrome, Muenke syndrome, Crouzon syndrome with acanthosis nigricans, epidermal nevi , SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans), thanatophoric dysplasia, camptodactyly, tall stature, hearing loss syndrome (CATSHL syndrome). The current study designed for investigation of a Pakistani family with short stature disproponate skeletal dysplasia without cousin marriage history. Affected girl was 2.5years old born from short height parents indicated severe clinical and radiological phenotypes including severe short-limbed short stature with marked ossification abnormalities and significant delay in speech. Our affected members reported with very short upper and lower limbs with large head circumference which differentiated from other disorders. Genomic DNA was extracted from the proband and proceeded for whole-exome sequencing. A novel missense mutation (c.1144 G>A, p.Gly382Arg) in FGFR3 gene was identified and confirmed its cosegregation within family by Sanger sequencing which is predicted to cause damaging effects and likely to lead nonsense mediated abnormality. This confirm the fact that pathogenic variant in FGFR3 is the major cause of achondroplasia and may be for other related phenotypes. The novel missense variant in FGFR3 gene is responsible for the unique phenotype of skeletal dysplasia (achondroplasia)

Keywords: Achondroplasia, FGFR3, Muenke syndrome, Megaloencephalopathy, skeletal dysplasia

1. INTRODUCTION

One of the skeletal dominant autosomal disorders is achondroplasia, it is clinically characterized by disproportionate short stature, midface hypoplasia, lordotic lumbarspine, and a trident hand configuration [1]. Phenotypically achondroplasia (ACH) and hypochondroplasia (HCH) do not have major differences, they observe from mild to severe phenotypic variations reported with same genetic basis [2].

The exact frequency of achondroplasia in different populations is still unknown. The occurrence rate is almost same as observed in case of hypochondroplasia, which recorded in 1 in 25,000 to 30,000 live newborn births [3]. World widely varying ratio related to prevalence rate of achondroplasia births was recorded as 1 in 10,000 to 40,000

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individuals [4]. Both inherited phenotypes ACH and HCH had identified with abnormal short stature including short arms and legs, genu varum, lumbar lordosis, and abnormal head circumference. Proper molecular investigation along with phenotypic and clinical data is imperative for differentiation between two disorders as ACH and HCH [5]. Prominent clinical presentations included macrocephaly, frontal bossing, broad and stubby hands and feet as well as mild generalized joint laxity reported as unique phenotypic characterizations. Defective long bones with wide-appearing diaphysis, mild flaring of metaphyseal-epiphyseal junction, and slight shortening of ulna relative to radius, elongated ulnar styloid, elongated distal fibula, short and broad femoral neck and rectangular proximal tibial epiphyses are frequent radiological abnormal demonstrations of disorder. However, in hypochondroplasia these features tend to be milder, and some are often subtle or absent in different patients from same family [6], [7]. Advanced parental age (father >40) recorded as critical factor for appearance of disorder in children as 90% cases reported with older age father than youngers [8].

ACH is caused by alteration in FGFR3 (fibroblast growth factor recptor3) gene localized on chromosome 4p16.3. Tyrosine kinase receptor family that contained 4 members (FGFR 1–4) also included FGFR3. It is composed of 1 extracellular, ligand-binding domain including 3 immunoglobulin-like loops (Ig I–III), 1 hydrophobic transmembrane (TM) domain, and 2 cytoplasmic TK sub-domains TK1 and TK2. It is expressed during skeletal growth and endochondral ossification and plays an important role in the regulation, proliferation, differentiation, as well as other processes involved in growth and development [9].

A specific protein which acts as cell surface receptor for fibroblast growth factor is encoded by FGFR3 .It plays significant role in body as regulation of chondrocyte differentiation, cell proliferation, and development of normal body skeleton [10]. More than 90% reported cases of ACH link to common point mutation, G380R, affected transmembrane domain of FGFR3 protein [1], which identified as gain of function mutation of FGFR3 gene [11].

FGFR3 plays significant role in normal development of skeleton and dysregulation leads to skeletal dysplasia proved by several ACH mice models presented in previous studies [1].

Currently, at least 77 mutations have been reported in FGFR3 gene from which 11 mutations are related to achondroplasia (ACH) according to the Human Gene Mutation Database (HGMD, http://www.hgmd.org/), PubMed, Embase, and Web of science. However, mutational screening of the FGFR3 gene is still needed more work. Identification of more novel findings will provide more insights in order to discover the molecular basis for the pathogenesis of ACH.

In present study, Pakistani family has investigated for search of genetic cause of skeletal disorder. Phenotypic and radiological examinations suggested initial diagnosis of genetic disease as Achondroplasia (ACH) , and the molecular investigation revealed a novel missense mutation (c.1144 G>A; p.Gly382Arg) in exon-9 of FGFR3 gene.

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2. MATERIALS AND METHODS

A Pakistani family with history of non-related union and with unique phenotypic appearance of skeletal dysplasia in three affected members identified from urban area of province Punjab, Pakistan.

2.1 Recruitment of affected members for blood and DNA sampling

The affected Pakistani family included three patients (IV-6, IV-9, and IV-12) (**Figure 1**) with clear sign and symptoms of abnormal short stature disorder. The available affected members were referred to Jinnah Hospital, Lahore, for a genetic consultation over skeletal deformities and intellectual disability. Written informed consent was obtained from all the participants of the study. A pedigree construction followed detailed family history. A physical examination with particular emphasis on orthopedic findings, anthropometric measurements were done. The skeletal surveys and relevant laboratory investigations were performed.

Peripheral blood sampling was followed by DNA extraction using the QIAamp DNA Blood Mini kit in three family members, including (III-3, III-4 and IV-1). The current study was approved under letter number (UCP/Regr /Notification /2329) by Ethical Review Committee (ERC) of University of Central Punjab (UCP) Lahore, Pakistan.

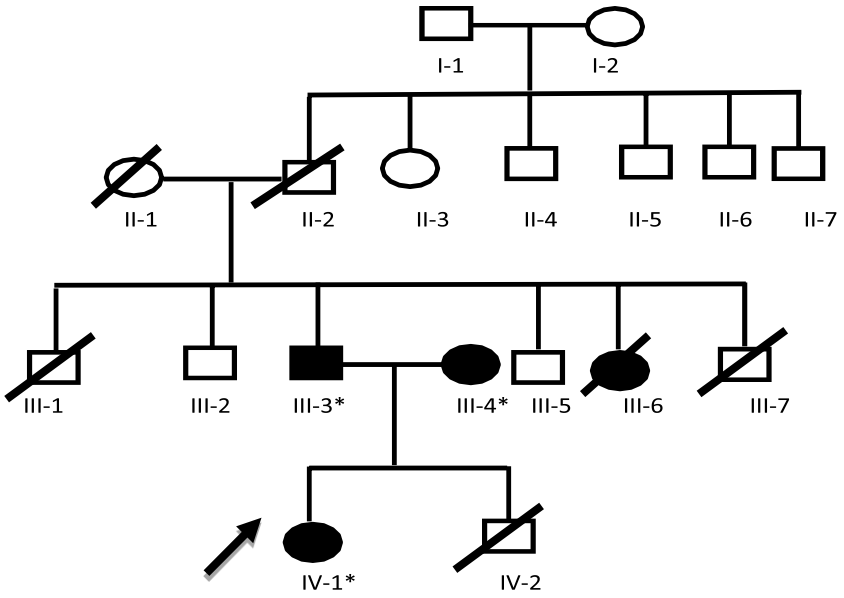

Figure 1

Pedigree of the Achondroplasia (ACH) family in which novel missense variant (c.1144 G>A, p.Gly382Arg) identified in FGFR3 gene. A symbol of asterisk indicated availability of DNA samples for study. The arrow highlighted the patient under molecular

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investigations for disease investigations. The numbers in the symbols show the unaffected male and female relatives of IV-1.

2. 2 DNA Sequencing

The sequence for reference of FGFR3 (NM_000142.5) was collected from a well-known genome browser data base "UCSC" (http://genome.ucsc.edu/cgi-bin/hgGateway). An updated software "AmplifX v1.5.4" was used for primers designing, applied for amplification of all 19 coding exons of FGFR3 gene. An optimized pair of primers for amplification of FGFR3 gene (FGFR3-F: 5′-ccctctagactcactggcgtta-3′, T_m 60.8°C), (FGFR3-R: 5′-tctacatggtgagcagagacga -3, T_m 60.1°C) used for segregation analysis. Sanger sequencing was performed for confirmation of cosegregation within family. The regions of interest were amplified by PCR. Exo-Sap protocol was followed for cleanup of PCR products. ABI3730 genetic analyzer was used for DNA sequencing followed by preparation of sequencing reaction. A sequence alignment tool "BioEdit version 6.0.7" was applied for alignment of sequencing results against the reference genome (http://www.mbio.ncsu.edu/BioEdit/bioedit.html). The minor allele frequency (MAF) of the pathogenic variant was verified from genome aggregation database (gnomAD, http://gnomad-old.broadinstitute.org/). In order to exclude possibility of Polymorphism in local population a panel including more than 90 healthy samples from ethnically same population were also sequenced. The possible alterations on structural stability of related protein was predicted by certain bioinformatics tool including Mutation Taster (http://www.mutationtaster.org/) and PROVEAN (http://provean.jcvi.org/index.php).

3. RESULTS

3.1 Phenotypic and radiological investigations

3.1.1 Patient-I (III-3)

The first enrolled patient (III-3) was a 42 year old male ,confirmed with the presence of clear sign and symptoms of skeletal abnormality including, distorted short stature with shorten limbs, narrowing of interpediculate distance in lumber spine large head size and asymmetric genu valgum. He born to normal healthy parents with normal delivery process.

The conditions of deafness, night blindness, colour blindness and renal impairments were excluded. Normal facial appearance except large head circumference was noted. The status of ectodermal appendages including nail, hair, teeth and sweat glands recorded healthy with good IQ and confidence level. The patients was quite social with friendly behavior. He had short stature with height of 126 cm and weight 41kg with BMI as 28.

Radiological findings of patient skeleton indicated rhizomelic shortening of the limbs and mild genu valgum deformity in both upper and lower limbs with short neck of femoral bone. Wrists showed relatively shorter ulnae bilaterally with asymmetric distal radioulnarjoints. Lower limbs joints showed relatively decreased acetabular angles. Left hemi pelvisshow an oval radiopacity may be a calculus. The thorax did not show any anomalies by

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inspection; cardiac and lung texture were reported normal. Ultrasonography of abdominal organs and the heart yielded normal results **(Figure 2)**.

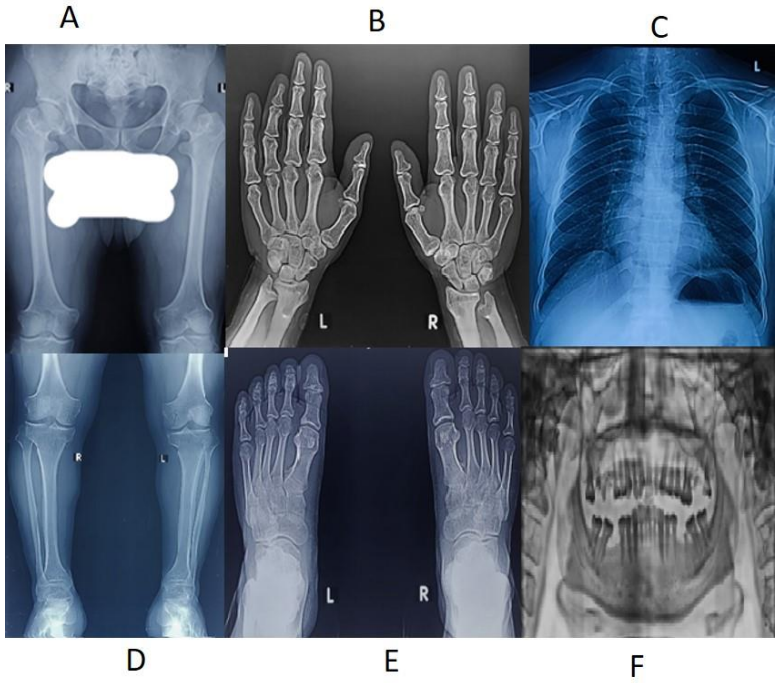

Figure 2

(A) Radiographic findings of the lower abdominal region of 42 years old patient in indicating narrow pelvis with sciatic notch (D) Radiographic findings of lower digits showing flaring of the distal femoral with broadening of proximal tibia metaphyses (B, E) Radiographic findings of upper and lower digits depicting mild shortening of the metacarpals and phalanges,(C) Radiological findings of chest indicating Normal ribs morphology (F) OPG image clear mild disproponate teeth appearance

3. 1. 2 Patient-II (IV-1)

The second affected member was 2.5year old affected female (IV-1) observed with same phenotypic characters of skeletal dysplasia as in first affected male member (III-3). She was born to non-related parents after full term uncomplicated delivery.

Clinical characterization indicated with short stature and prominent frontal bossing of head with large head size. Limbs indicated no signs of polydactyly with relatively smaller phalanges and metacarpals bones **(Figure 3).** She had normal nails, teeth and facial appearance with proper hair texture, good mental health. Her immunity was of average level as frequent infections episodes since her birth were reported by her mother. She was observed with meningitis at age of 4 months. She had weak bones appearance and could not walk till age of 2.5 years. She also observed with some speech issues. Her birth parameters of height and weight were reported to be 50 cm (25^{th}-50^{th} pencentile) and 3000 g (25^{th}-50^{th} pencentile), respectively. She had a height of 83.5 cm and weight (7.4

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kg). BMI of patient was recorded as 10.54. She was a disproportionate dwarf with short-limbs, brachydactyly and slight genu varum.

Radiological investigations of chest revealed normal appearance of rib cage and cardiac size within normal range. Both upper /lower limbs radiology showed shortening of long bones with decreased bone density and flaring of distal metaphyses. Knee joints appeared with genu valgum. Metacarpals showed distally irregularities bilaterally. Her clinical and radiologic findings were consistent with clinic-radiologic criteria for ACH.

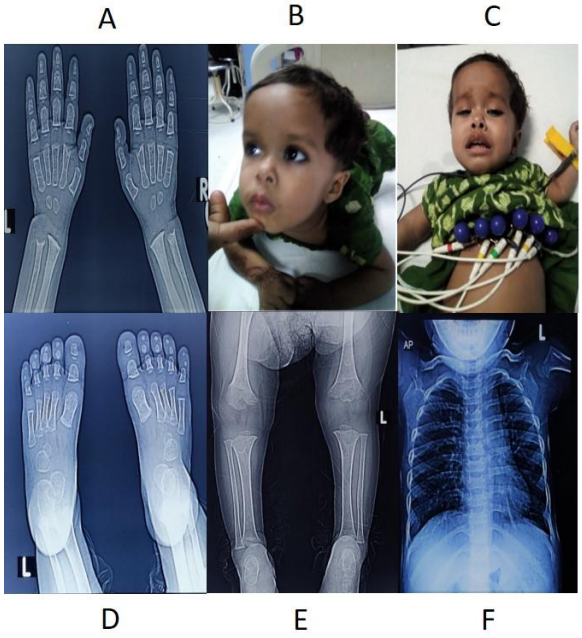

Figure 3

Phenotypic and radiological characterization of Patient-2 (IV-1) are showing clinical and radiological characterization of 2.5 years old patient showing frontal bossing, flattened nasal bridge with short limbs. (A,D, E-F) Radiological findings give appearances of the thorax, pelvis, and tubular bones deformities like brachydactyly and brachymetacarpia. As observed in patients with achondroplasia (ACH)

3.2 Biochemical examinations

Biochemical parameters investigations including complete blood count, blood glucose level, lipid profile, liver functioning test and erythrocyte sedimentation rate (ESR) appeared normal with reference values, in the three affected members (III-3, III-4 and IV-1). High values of certain lipid profile parameters like TG (triglycerides), total lipid, LDL led to obesity or may be cardiac diseases in future. As current findings of echocardiogram (ECG) and abdominal ultrasound were unremarkable. Findings of abdominal ultrasound (USG) in patient (III-3) declared normal status of all organs like size and texture of heart, liver,

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kidneys and bladder. Scrotal USG reported normal testis measurements and structure of epididymis.

3.3 Mutational analysis

DNA samples of all three affected members (III-3, III-4, and IV-1) were proceeded for all nineteen coding exons of FGFR3 gene PCR amplification. Sanger sequencing identified a novel missense pathogenic variant (c.1144 G>A; p.Gly382Arg) in exon-9 of FGFR3 gene **(Figure 4)**. The affected father (III-3) presented this mutation in heterogyous status **(Figure 4 Panel B)**, absent in mother (III-4) **(Figure 4 Panel A)**., while in homozygous state presented in affected child (IV-1) **(Figure 4 Panel C)**., thus confirming its segregation within the family. Previously a pathogenic variant (c.1145 G>A; p.Gly382Arg) at other site in same exon with same alteration of amino acid sequence reported [12]. The minor allelic frequency of this variant is not present in gnomAD data base. This pathogenic variant located in the transmembrane domain at position 382 (Gly382Arg) .Confirmation of highly conserved nature of Gly382 within various species by Clustal W tool and pathogenicity by different bioinformatics tools as PolyPhen and Mutation Taster performed in a previous study [12]. This missense alteration in FGFR3 is predicted to cause a gain-of-function effect where uncontrolled FGFR3 activation leading to defects in long bone growth. Father and daughter showed positive status for current variant. While affected mother showed no variant in this gene as she was investigated later on for other genetic variant on basis of her specific phenotypic characterization. She was identified with compound heterozygous mutation in EVC2 gene.

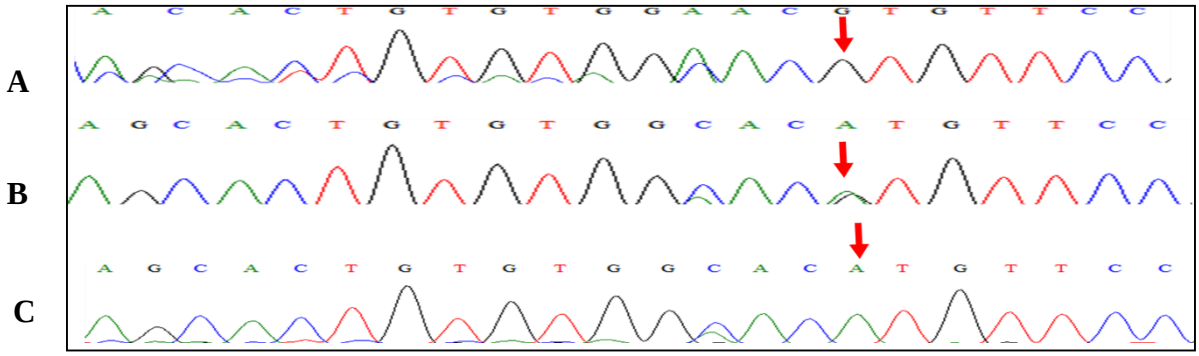

Figure 4

Nucleotide sequence of exon-9 of FGFR3 gene showing a novel missense variant (c.1144 G>A, p.Gly382Arg) in FGFR3 gene, where panel (A) indicating wild type nucleotide sequence, while panel (B) is depicting the DNA sequence of a heterozygous father (III-3). Panel (C) presenting DNA sequence in an affected member (IV-1). Arrow pointing the position of nucleotide variant.

4. DISCUSSION

Our study includes three related ACH patients (III-3, III-4 and IV-1). ACH initially diagnosed by various phenotypic appearances like short stature, disproportion of long

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bones, and certain neurological disabilities. Additional features of ACH are macrocephaly, coarse facial feature, rhizomelia, and bone deformities.

Radiological findings correlated with the physical phenotypic characterization. Normal recordings of clinical parameters in newborn male member (IV-2) at time of birth indicated him as healthy but unluckily could not survive. Sanger sequencing indicated a novel missense mutation (c.1144 G>A; p.Gly382Arg) in FGFR3 which co-segregates with father in family, while mother was not identified with it. This genetic alteration is responsible for achondroplasia (ACH) skeletal dysplasial condition.

ACH is characterized by a number of clinical manifestations which also overlap with other genetic disorder HCH. Both share clinically and radiologically many common characters like larger head size, shortening of extremities, metaphyseal flaring, reduced the interpediculate distance in the lumbar spine, square iliae, and short fish mouth like structure development in femoral bone, although severity of phenotypic conditions is more in ACH as compared to HCH [13]. The radiological findings of our patients were coincided with reported data of ACH affected members [14].

In current study, both affected members have typical features of the ACH as presence of a trident hand and dysmorphic facial appearance, differentiated them from HCH. The average height of our male patient was reported as 126 cm which is in coincidence with previously publish data, where average height in male in range of (120-127) males [15], while in case of HCH, affected males were observed with 146.1 cm in height [16]. Human FGFR3 (OMIM# 134934) gene is responsible for achondroplasia skeletal disorder, which translates into fibroblast growth factor receptor 3 protein. By following ligand-receptors binding principle, various acidic and basic fibroblast growth hormone combine with receptors and play an important role in the development and maintenance of bone structure [10].

The FGFR3 polypeptide structurally is composed of three main domains, including an extracellular domain, a transmembrane domain, and an intracellular domain [17]. In the present study a missense homozygous mutation was detected in the transmembrane domain of FGFR3 at position 382. The identified position of amino acid in polypeptide is highly conserved among various species. Previous data reported many pathogenic missense mutations in the transmembrane domain of FGFR3, which are leaded to achondroplasia (ACH) or hypochondroplasia (HCH) disorders in affected individuals [18], [19], [12].

In this scenario, Gly380Arg is most common mutation which is responsible for unregulated, stable dimerization of FGFR3, independent of ligand receptor binding mechanism. The formation of hydrogen bonds between side chains of two arginine amino acids plays significant role for stability of this important protein. This indicating the significance of this functional domain for polypeptide. Mutation Gly382Asp is located in near about two other mutations, the Val381Glu HCH mutation and the Gly380Arg ACH mutation. A brief gradient of severity of disease establishes for these mutations, as follows: Gly380Arg homozygote > Gly380Arg compound heterozygote > Val381Glu

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heterozygote > our case. > 90% of the ACH cases are caused by Gly380Arg mutation in exon 10 of FGFR3 gene [20], [21], [12]. A sporadic case of ACH with (c.T1142A p.Val381Glu) mutation was also reported in literature which is confused phenotypically with HCH [19]. According to different data repositories (HGMD, Pubmed, Embase, and Web of Science) at least (11) mutations have been reported related to ACH. Although mutations were detected in all three domains of FGFR3 gene but about 60% reported cases of HCH are related to intracellular FGFR3-tyrosine kinase domain, such as (Asn540Lys), (Ile538Val) [10].

The comparative study of achondroplasia (ACH) affected individuals with hypochondroplasia (HCH) patients demonstrated that more sever clinical sign and symptoms observed in ACH patients, which suggests that residues 381 and 382 are also critical for receptor activation as in case of residue 380, or that the hydrogen bonding strength is disturbed by nucleotide alterations[10].

5. CONCLUSION

The current study solved the case of genetic disorder where phenotypic clinical and radiological findings demonstrated the presence of inherited condition of achondroplasia (ACH) which confirmed by molecular techniques linked to FGFR3 gene. Our results will expand the genetic mutational spectrum of FGFR3 gene causing ACH phenotype.

References

1) Lee YC, Song IW, Pai YJ, Chen SD, Chen YT. Knock-in human FGFR3 achondroplasia mutation as a mouse model for human skeletal dysplasia. Scientific reports. 2017 Feb 23; 7(1):1-0.
2) Yuan H, Huang L, Hu X, Li Q, Sun X, Xie Y, Kong S, Wang X. FGFR3 gene mutation plus GRB10 gene duplication in a patient with achondroplasia plus growth delay with prenatal onset. Orphanet Journal of Rare Diseases. 2016 Dec; 11(1):1-9.
3) Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet journal of rare diseases. 2019 Dec; 14(1):1-49.
4) Foreman PK, van Kessel F, van Hoorn R, van den Bosch J, Shediac R, Landis S. Birth prevalence of achondroplasia: A systematic literature review and meta-analysis. American journal of medical genetics Part A. 2020 Oct; 182 (10):2297-316.
5) Gomes ME, Kanazawa TY, Riba FR, Pereira NG, Zuma MC, Rabelo NC, Sanseverino MT, Horovitz DD, Llerena Jr JC, Cavalcanti DP, Gonzalez S. Novel and recurrent mutations in the FGFR3 gene and double heterozygosity cases in a cohort of Brazilian patients with skeletal dysplasia. Molecular Syndromology. 2018; 9(2):92-9.
6) Bellus GA, Hefferon TW, de Luna RO, Hecht JT, Horton WA, Machado M, Kaitila I, McIntosh I, Francomano CA. Achondroplasia is defined by recurrent G380R mutations of FGFR3. American journal of human genetics. 1995 Feb; 56(2):368.
7) Kaissi AA, Farr S, Ganger R, Hofstaetter JG, Klaushofer K, Grill F. Treatment of varus deformities of the lower limbs in patients with achondroplasia and hypochondroplasia. The Open Orthopaedics Journal. 2013 Feb 8; 7(1).

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E-Publication: Online Open Access
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DOI 10.17605/OSF.IO/BR8E3

8) Coi A, Santoro M, Garne E, Pierini A, Addor MC, Alessandri JL, Bergman JE, Bianchi F, Boban L, Braz P, Cavero-Carbonell C. Epidemiology of achondroplasia: A population-based study in Europe. American journal of medical genetics Part A. 2019 Sep; 179(9):1791-8.
9) Yao G, Wang G, Wang D, Su G. Identification of a novel mutation of FGFR3 gene in a large Chinese pedigree with hypochondroplasia by next-generation sequencing: A case report and brief literature review. Medicine. 2019 Jan; 98(4).
10) Gonçalves D, Rignol G, Dellugat P, Hartmann G, Sarrazy Garcia S, Stavenhagen J, Santarelli L, Gouze E, Czech C. In vitro and in vivo characterization of Recifercept, a soluble fibroblast growth factor receptor 3, as treatment for achondroplasia. PLoS One. 2020 Dec 28; 15(12):e0244368.
11) Kitoh H, Matsushita M, Mishima K, Kamiya Y, Sawamura K. Disease-specific complications and multidisciplinary interventions in achondroplasia. Journal of Bone and Mineral Metabolism. 2022 Jan 14:1-7.
12) Chen J, Yang J, Zhao S, Ying H, Li G, Xu C. Identification of a novel mutation in the FGFR3 gene in a Chinese family with Hypochondroplasia. Gene. 2018 Jan 30; 641:355-60.
13) Xue Y, Sun A, Mekikian PB, Martin J, Rimoin DL, Lachman RS, Wilcox WR. FGFR3 mutation frequency in 324 cases from the International Skeletal Dysplasia Registry. Molecular genetics & genomic medicine. 2014 Nov; 2(6):497-503.
14) Song SH, Agashe MV, Huh YJ, Hwang SY, Song HR. Physeal growth arrest after tibial lengthening in achondroplasia: 23 children followed to skeletal maturity. Acta orthopaedica. 2012 Jun 1; 83(3):282-7.
15) Trotter TL, Hall JG, Committee on Genetics. Health supervision for children with achondroplasia. Pediatrics. 2005 Sep;116(3):771-83.
16) Romeo A, Lodi M, Viri M, Parente E, Baldi M, Righini A, Milani D. Does the co-occurrence of FGFR3 gene mutation in hypochondroplasia, medial temporal lobe dysgenesis, and focal epilepsy suggest a syndrome?. Pediatric neurology. 2014 Apr 1;50(4):427-30.
17) He X, Xie F, Ren ZR. Rapid detection of G1138A and G1138C mutations of the FGFR3 gene in patients with achondroplasia using high-resolution melting analysis. Genetic testing and molecular biomarkers. 2012 Apr 1; 16(4):297-301.
18) Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, Bocian M, Winokur ST, Wasmuth JJ. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell. 1994 Jul 29;78(2):335-42.
19) Heuertz S, Le Merrer M, Zabel B, Wright M, Legeai-Mallet L, Cormier-Daire V, Gibbs L, Bonaventure J. Novel FGFR3 mutations creating cysteine residues in the extracellular domain of the receptor cause achondroplasia or severe forms of hypochondroplasia. European Journal of Human Genetics. 2006 Dec; 14(12):1240-7.
20) Satiroglu-Tufan NL, Tufan AC, Semerci CN, Bagci H. Accurate diagnosis of a homozygous G1138A mutation in the fibroblast growth factor receptor 3 gene responsible for achondroplasia. The Tohoku Journal of Experimental Medicine. 2006; 208(2):103-7.
21) Placone J, Hristova K .Direct Assessment of the Effect of the Gly380Arg Achondroplasia Mutation on FGFR3 Dimerization Using Quantitative Imaging FRET. PLoS ONE. 2012 Oct. 7(10): e46678. https://doi.org/10.1371/journal.pone.0046678

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Declarations

Ethics approval and consent to participate

Informed written consent was taken from affected and unaffected family members. The work was approved by the Human research and Ethical Review committee of University of Central Punjab (UCP), Lahore, Pakistan under the letter number (UCP/Regr/Note/2329).

Availability of data

All the clinical and molecular data is available for the reader, please contact the corresponding authors.

Competing interests

The authors have no conflict of interest.

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Author has self-financial contribution

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