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Review Article

ACHONDROPLASIA: GENETICS AND SKELETAL SURVEY REVIEW

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A R T I C L E I N F O

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A B S T R A C T

Achondroplasia (ACH) (OMIM 100800) considered as most common short limbed dwarfism, caused by point mutation in gene coding for transmembrane portion of FGFR 3 receptors. One suspected of achondroplasia referred to genetic clinic with classical phenotype and X-ray findings. Instead of doing extensive molecular testing, point mutation in FGFR3 gene done and confirmed diagnosis. Pedigree showed multiple termination of pregnancies due to fear of recurrence and lack of knowledge. Being clinician it's our responsibility to identify clinical condition and counsel about prognosis and recurrence risk. Since it has a high prevalence in community discussed in detail here.

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INTRODUCTION

Skeletal dysplasia (Osteochondrodysplasia) defined as heterogenous group of genetic disorders causing abnormal bone and cartilage development, resulting in abnormal size, shape and proportions of skeletal system. Some are non-survivable ex-utero called lethal dysplasia and non-lethal types present in neonatal period as short stature. Achondroplasia known for many centuries in literature considered as most common type of non-lethal skeletal dysplasia, with a prevalence estimated1:15000 in population. 80% cases are denovo mutations (parents unaffected) and 95% cases have point mutation in FGFR3 gene. A suspected case of ACH referred to our genetic clinic for evaluation, since FGFR3 variants have diverse phenotype expression explained in detail here.

Case

5-year-old male born out of non-consanguineous marriage referred from ortho for evaluation of skeletal dysplasia. 3 generation pedigree showed multiple termination of pregnancies in view of recurrence risk (Fig:1). O/E short limb (rhizomelic) short stature child with normal head circumference and IQ. Facial profile showed mild frontal bossing, midface hypoplasia, depressed nasal bridge with normal trunk (sitting height), exaggerated lumbar lordosis with protuberant abdomen. Limbs showed rhizomelia, brachydactyly with "trident hand" configuration (Fig 1).

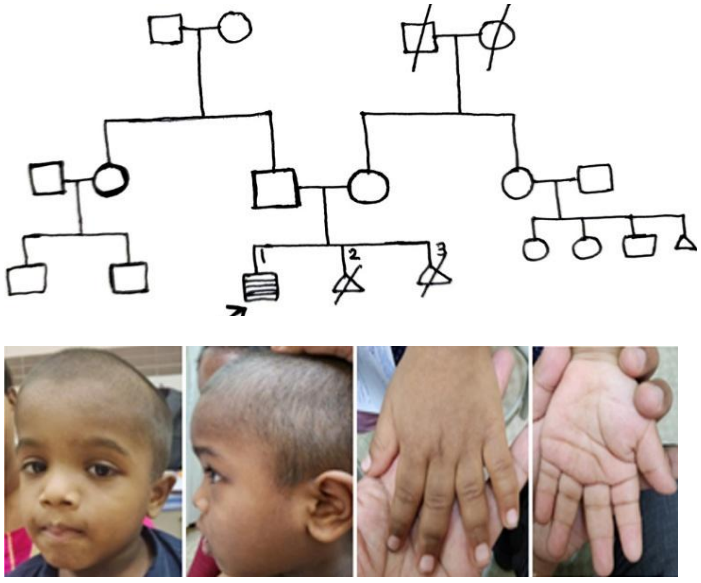

Fig 1: 3G pedigree with multiple terminations and facial profile showing frontal bossing, flat mid face, depressed nasal bridge, trident hand, brachydactyly.

Skeletal survey showed metaphyseal dysplasia-splaying and flaring with preserved epiphysis. (Fig 5). CT evaluation showed no FMS or atlanto-axial instability. Molecular testing by sanger sequencing confirmed diagnosis. Pre-test and post-test counselling done and multidisciplinary management started. Counselled about clinical condition, target height, under trial treatments, recurrence risk and prenatal options.

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DISCUSSION

Dwarfism/short staure exist in all living populations- humans, birds and animals and has been described in ancient scriptures, models and paintings.[1] Though considered as an abnormal variant in nature, dwarfs held many important positions in human history for their intellect/humour/fancy attire/decortive values, when compared to other species. Excavated statues, paintings, scriptures-Babylon, Mesopotamia, Egypt, Indiaillustrated the high profile life they led in ancient world-even potraited as gods.(Fig 2) Various illustrative papers been published in literature about skeletal dysplasia and dwarf in human history.[1,2,3]Achondroplasia existed among humans dated long backand potraited, accounts for its non lethality, normal lifespan and normal intellect, compared to other skeletal dysplasias.

Fig 2: a) Lord Kubera depicted as dwarf[1] b) Achondroplasia figure portraited on sarcophagus c) God Bes, Egypt d) skeletal dysplasia from Benin kingdom-Africa[3]

Dwarfing presents as short limb, short trunk or propotionate (short limb with short trunk). Short limb dwarfism include Achondroplasia, Hypochondroplasia, Metaphyseal OCD's, where sitting height (trunk) will be normal range. Further short limb divided to rhizomelic (proximal), mesomelic (middle) and acromelic (distal) type. Achondroplasia (prevelance1:20000) considered as most common non lethal skelethal dysplasia. Though a misnomer (A-absence, Chrondroplasia-caritage formation) coined by Parrot in 1878,[4]actually includes abnormal enchondral ossification. 80% cases are sporadic and 20% have an affected parent. Caused by point mutation in FGFR3 gene coding for transmembrane domain of receptor- two type of base substituition seen with 100% penetrance-transition of c.1138G>A (98% of affected individuals) and a transversion of c.1138G>C (1% of affected individuals) making it easy to do targeted gene testing rather doing an extended gene panel also cost effective (10 times less)[5]Our case sanger sequencing showed c.1138G>A and confirmed ACH.(Fig 3)

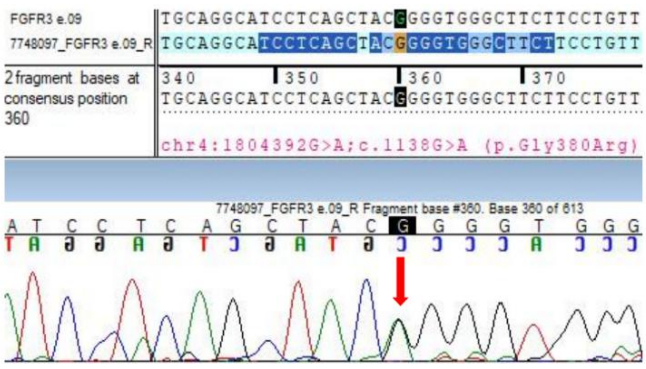


Fig 3: Sequence chromatogram showing variant in exon 9 of FGFR3 [chr4:1804392G>A; c.1138G>A; p.Gly380Arg] in heterozygous condition.

ACH and many other skeletal dysplasia and craniosynostosis syndromes are related with FGFR mutations. FGFR are secreted protein ligands of transmembrane receptors that bind to FGF class of proteins, which are involved in various cell signalling, proliferation, differentiation, migration and selective apoptosis in embryogenesis. It includes 4 members (FGFR 1/2/3/4) coded by different genes in different chromosomes, yet they share a high homology (56-71%).[6] Structurally they have a "canonical RTK architecture" consisting of an extracellular domain, transmembrane domain and an intracellular split tyrosine kinase domain. (Fig 4) Mutations are mainly gain of function and clinically associated with 2 groups of development disorder: Achondroplasia family of skeletal dysplasia and Craniosynostosis.[7]Increased paternal age implicated in all FGFR3 mutations including ACH.[8]

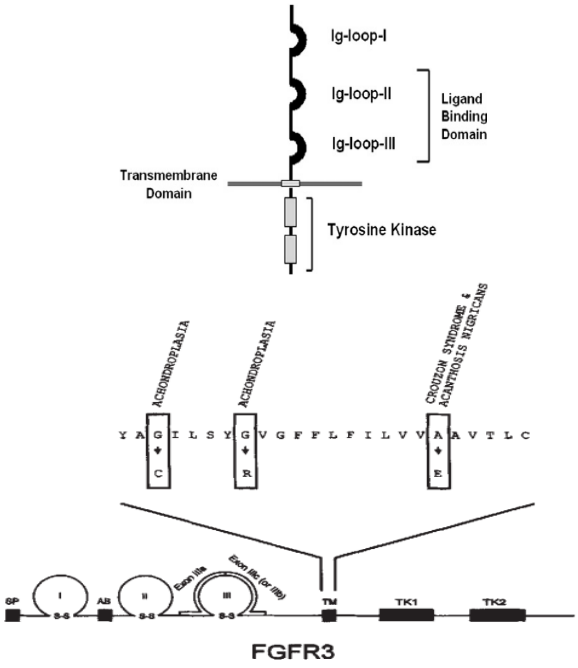


Fig 4: FGFR receptor with extracellular three Ig like domain (D1,D2,D3), single transmembrane domain and intracellular split tyrosine kinase domain and locus proximity of ACH and CAN causing phenotype overlap[7]

Differentials: Hypochondroplasia (HCH) allelic variant with a milder phenotype, where FGFR3 mutation (Asn540Lys) proximal TK domain seen, 10% cases will have intellectual disability. Pseudoachondroplasia (PSACH) mutation in COMP gene (19p13.1). Absence of facial gestalt (normal facial features and preserved head circumference) and "trident hand" helps in clinical differentiation and presence of epimetaphyseal changes, normal interpedicular distance wideningwith"central vertebral anterior tongue"/platyspondyly helps in radiological differentiation.[9]Severe phenotype, developmental delay and acanthosis nigricans need to consider SADDAN syndrome[missense mutation (p.Lys650Met) FGFR3 gene].Skeletal features SADDAN will resemble both ACH and TD features with "reverse bowing" of tibia and fibula.[10]Doubtful cases always demandmolecular testing.

Skeletal findings of ACH are classically described in literature, a few findings noted in our case described here (Fig 5).

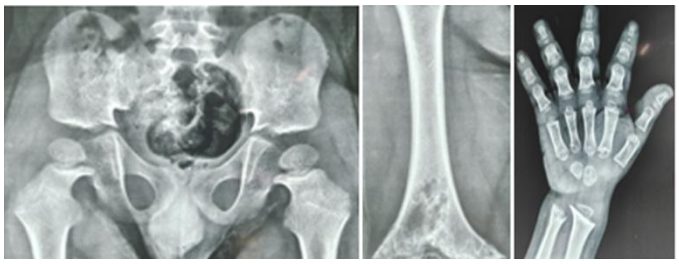
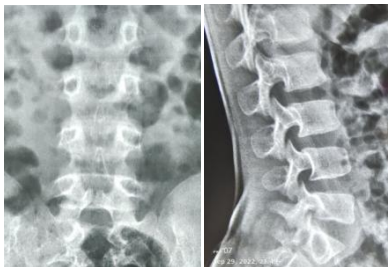


Fig 5: Our case skeletal survey showing a) round iliac wings, flat acetabular roof, genu varum. b) metaphyseal dysplasia and flaring with mild "chevron deformity" c) trident hand" with separation between F3-F4 also note wide short tubular bones and mild metaphyseal widening at wrist (red) d) thick pedicle, interpedicular narrowing and posterior vertebral scalloping.



10% cases association with acanthosis nigricans seen, but these are not indicators of underlying hyperinsulinemia, thyroid issues or malignancy. Many other FGFR3 variants [Hypochondroplasia, Crouzon with Acanthosis(CAN), SADDAN, Thanatophoric Dysplasia (TD)] show similar acanthosis, postulated due to FGFR3 activation on keratinocytes. No specific investigation or treatment recommended. Parents should be counselled these are not dirt and will not wash away with heavy scrubbing. (Fig 6)

Fig 6: Acanthosis in our FGFR3 variants a) Achondroplasia b&c) Crouzon syndrome with Acanthosis (CAN)

ACH need special growth chart for evaluation and target height is about 125-130 cm in males and 120-125 in females. Clinically hypotonia, brisk reflexes and sleep apnoea may be an early indicator for FMS/AAI need imaging. Our case noted severe OSA, evaluation showed 90% adenoid hypertrophy and adenotonsillectomy done. Regular follow up recommended for premature and severe spinal canal stenosis.

Till now no drugs marketed for height gain in India, Vosoritide [C-type Natriuretic Peptide (CNP) analogue] under phase III trial have shown some promising results in height gain by stimulating chondrocytes and growth of long bones.[11] Previous limb lengthening surgeries- Ilizarov surgeries were done, now not usually discussed in counseling sessions. History of successful ACH individuals can be pointed out in counseling session to boost up parental confidence. Recurrence risk in denovo cases is<1%, parents should be reassured and prenatal options should be provided to avoid unnecessary terminations.

Conclusion

Clinicians should be aware of recurrence risk and differentials of ACH more than diagnosis. Targeted sanger sequencing helps to confirm diagnosis and also lessen the cost burden to parents especially in resource limited settings. Hypotonia and brisk reflexes need CT evaluation to rule out FMS. Vosoritide is a promising drug in literature.

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