Fibroblast Growth Factor Receptor 3

Alternative Names
FGFR3

Record Category
Gene locus

WHO-ICD
N.B.: Classification not applicable to gene loci.

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
134934

Mode of Inheritance
Autosomal dominant

Gene Map Locus
4p16.3

Description
The fibroblast growth factors are a family of polypeptide growth factors involved in a variety of activities, including mitogenesis, angiogenesis, and wound healing. They contain an extracellular domain with either 2 or 3 immunoglobulin (Ig)-like domains, a transmembrane domain, and a cytoplasmic tyrosine kinase domain. Expression analysis for the fibroblast growth factor receptor 3 gene demonstrated a relative expression mainly in the skeleton and central nervous system especially during skeletal growth and endochondral ossification. Fibroblast growth factor receptor 3 (FGFR3) is a major negative regulator of linear bone growth, acting to inhibit growth plate chondrocyte proliferation and terminal differentiation. FGFR3 is normally activated by ligand-induced dimerization that activates the intrinsic tyrosine kinase activity of the receptor. This leads to transphosphorylation of key tyrosine residues in the cytoplasmic domain of the receptor that serve as docking sites for adaptor proteins and effectors that propagate FGFR3 signals.

Molecular Genetics
Mutations in the transmembrane domains of the fibroblast growth factor receptor 3 gene, located on the short arm of chromosome 4 (4p16.3) cause thanatophoric dysplasia. Thanatophoric dysplasia Type II cases have a single recurrent mutation (A-G) in the tyrosine kinase domain of FGFR3, but thanatophoric dysplasia type I cases have different mutations affecting either the extracellular or intracellular domains of FGFR3. The most common mutation encountered in thanatophoric dysplasia type I is a C-T transition, resulting in a change of arginine to cysteine (R248C) in the extracellular domain of FGFR3.

Epidemiology in the Arab World
Algeria
[See: Palestine > Falik-Zaccai et al., 2000].

Egypt
Pusch et al. (2004) reported the screening of ancient bone samples for diagnostic achondroplasia mutations. The diagnostic G-A transition in the FGFR3 gene at cDNA position 1138 was detected in cloned polymerase chain reaction (PCR) products obtained from the dry mummy of the Semerchet tomb, Egypt (first dynasty, approximately 4,890-5,050 BP [before present]). The mummy had short stature. However, these mutations were also reproducibly observed in four ancient control samples from phenotypically healthy individuals (false-positives), rendering the reliable molecular typing of ancient bones for achondroplasia impossible. Pusch et al. (2004) spiked contemporary human template DNA from a phenotypically healthy individual with an ancient DNA extract from a cave bear. Again, sequences with the diagnostic G-A transition in the FGFR3 gene were observed. Pusch et al. (2004) suggested that false-positive G-A transitions likely result from errors introduced during the PCR reaction. Amplifications in the presence of MnCl(2) indicate that position 1138 of the FGFR3 gene is particularly sensitive for mutations.

Iraq

[See: Palestine > Falik-Zaccai et al., 2000].

Morocco
[See: Palestine > Falik-Zaccai et al., 2000].

Palestine
Falik-Zaccai et al. (2000) analyzed the FGRF3 gene for the occurrence of the G380R mutation (G>A and G>C transition) and the mutation G375C (G>T transition at codon 375) in 31 unrelated sporadic patients and in one family (with an affected father and son) diagnosed clinically to have achondroplasia. The studied patients were mostly Jewish (24 of the 32, 75%); 11 were of Sephardic origin (Morocco, Iran, Iraq, Tunisia, Yemen and Algeria), and 8 were of Ashkenazi background (Eastern Europe). The non-Jewish patients included one Druze, three Christian Arabs, two Moslem Arabs and three Bedouins. Falik-Zaccai et al. (2000) found the G>A transition at codon 380 in 29 sporadic patients with achondroplasia and in the familial case as well (father and son). All patients were found to be heterozygous to this mutation. The G>C transition at codon 380 was found in one patient. Falik-Zaccai et al. (2000) were not able to detect any of the three mutations in two patients, including one of the Christian Arabs patients, with an atypical form of achondroplasia. Falik-Zaccai et al. (2000) concluded that the results of this study further supports the unusual observation that nucleotide 1138 of the FGFR3 gene is the most mutable nucleotide discovered to date across different populations.

Tunisia
[See: Palestine > Falik-Zaccai et al., 2000].

United Arab Emirates
Simsek et al. (2003) described Emirati patient(s) with type I Thanatophoric Dysplasia with a c.742C>T (p.R248C) mutation in the FGFR3 gene.

Bekdache et al. (2010) performed a postnatal examination using direct DNA sequencing of FGFR3 gene for a female infant with suspected thanatophoric dysplasia. A c.742C>T heterozygous mutation was identified, resulting in arginine to cysteine amino acid change at position 248 (p.R248C).

Yemen
[See: Palestine > Falik-Zaccai et al., 2000].

References

Bekdache GN, Begum M, Al-Gazali L, Ali BR, Akawi NA, Mirghani H. Prenatal diagnosis of thanatophoric dysplasia and obstetrical challenges. J Obstet Gynaecol. 2010; 30(6):628-30. PMID: 20701518

Falik-Zaccai TC, Shachak E, Abeliovitch D, Lerer I, Shefer R, Carmi R, Ries L, Friedman M, Shohat M, Borochowitz Z. Achondroplasia in diverse Jewish and Arab populations in Israel: clinical and molecular characterization. Isr Med Assoc J. 2000; 2(8):601-4. PMID: 10979354

Pusch CM, Broghammer M, Nicholson GJ, Nerlich AG, Zink A, Kennerknecht I, Bachmann L, Blin N. PCR-induced sequence alterations hamper the typing of prehistoric bone samples for diagnostic achondroplasia mutations. Mol Biol Evol. 2004; 21(11):2005-11. PMID: 15254256

Simsek M, Al-Gazali L, Al-Mjeni R, Bayoumi R. Improved diagnosis of a common mutation (R248C) in the human growth factor receptor 3 (FGFR3) gene that causes type I Thanatophoric dysplasia. Clin Biochem. 2003; 36(2):151-3. PMID: 12633765

Related CTGA Records

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Hypochondroplasia
Saethre-Chotzen Syndrome
Thanatophoric Dysplasia

External Links

http://www.achondroplasia.co.uk/
http://www.genetests.org/profiles/hypochondroplasia
http://www.genetests.org/profiles/td
http://www.marchofdimes.com/professionals/681_1204.asp
http://www.medicinenet.com/achondroplasia/article.htm
http://www.orpha.net/data/patho/GB/uk-Thanatophoric-dysplasia.pdf
http://www.orpha.net/static/GB/achondroplasia.html

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