Achondroplasia

Alternative Names
ACH

Record Category
Disease phenotype

WHO-ICD
Congenital malformations, deformations and chromosomal abnormalities > Congenital malformations and deformations of the musculoskeletal system

Incidence per 100,000 Live Births
101- ~

OMIM Number
100800

Mode of Inheritance
Autosomal dominant

Gene Map Locus
4p16.3

Description
Achondroplasia is the most common form of human dwarfism with characteristically rhizomelic shortening of extremities and relative macrocephaly. It follows an autosomal dominant mode of inheritance and has a frequency of approximatly 1 in 26,000 to 1 in 40,000 births. Achondroplasia is characterized by short-limbed marked short stature (rhizomelic short stature), a relatively macrocephaly with prominent forehead, midface hypoplasia, lumbar lordosis, a trident configuration of hands and hydrocephalus during growth development caused by narrowing of the foramen magnum. Other symptoms caused by narrowing include apnea (cessation of breathing) and cervical myelopathy. In addition to prepubertal growth failure, achondroplasia patients show decreased pubertal growth spurt.

About 80% of affected individuals result from sporadic mutations without positive family histories. Based on genetic information, molecular genetic testing can provide an exact diagnosis comparing to radiological and prenatal ultrasound evaluations.

Molecular Genetics
Achondroplasia is inherited as an autosomal dominant trait, although most of the cases are sporadic, a result of a de novo mutation. This disorder comes from the genetic point mutations in the fibroblastic growth factor receptor 3 gene (FGFR3), which enables abnormal cartilage growth-plate differentiation and insufficient bony development. 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. Among different populations, the most common genetic mutations in this receptor are G-A at position 1138 (G1138A), which results in the substitution of glycine to arginine at codon 380. This is most uncommon in other autosomal dominant genetic diseases.

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). 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.

Kozma (2006) described some of the earliest biologic evidence of dwarfism from ancient Egypt, dating as far back as 4500 BCE. Due to the hot, dry climate and natural and artificial mummification, Egypt is a major source of archeological information on achondroplasia.

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

Lebanon
Bittar (1998) reported a prospective study of 3,865 consecutive newborns delivered between 1991 and 1993. Major congenital anomalies (MCA) were found in 64 newborns at incidence of 16.5/1000 births. Many of the cases had achondroplasia. Among the malformed infants, the rate of low birth weight and the rate of parental first cousin consanguinity were significantly higher than corresponding rates among normal infants in a control group.

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 G375C mutation (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 these 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) reexamined the two patients in whom the mutation causing the disease was not found showed them to be somewhat atypical of classical achondroplasia. The Arab-Christian patient is a girl, and she was the third child of healthy unrelated parents, a 39-year-old father and a 33-year-old mother. Her two brothers were healthy. The family history was unremarkable and the patient had been delivered normally at term. The clinical and radiological manifestations in this patient were consistent with achondroplasia, but to a milder degree, particularly the normal facial structure and milder metaphyseal modification.

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

United Arab Emirates
Al Talabani et al. (1998) studied the pattern of major congenital malformations in 24,233 consecutive live and stillbirth in Corniche hospital, which is the only maternity hospital in Abu Dhabi, between January 1992 and January 1995. A total of 401 babies (16.6/1,000), including 289 Arabs, were seen with major malformation. Single gene disorders accounted for 24% of the cases, 21% were due to autosomal dominant disorders. In their study, Al Talabani et al. (1998) observed four cases of achondroplasia in families from the United Arab Emirates. Recurrence was not reported in other members of the families. Al Talabani et al. (1998) concluded that their study was very close to representing the true incidence of congenital abnormalities in the United Arab Emirates, as they investigated over 98% of deliveries in Abu Dhabi, the capital of United Arab Emirates.

Eapen et al. (1998) carried out a screening program among school-going children in Al-Ain, United Arab Emirates, to identify children with learning disorders. During the course of one academic year, 34 such children were identified. The cause was judged to be prenatal in 18 cases (53%). Eight cases exhibited dysmorphic features including a case with achondroplasia.

Hosani and Czeizel (2000) evaluated the pilot dataset [March-May 1998] of the UAE National Congenital Abnormality Registry (NCAR). A total of 4,861 births were recorded in this study period, with a birth prevalence of total congenital anomalies being 30.3 per 1,000 births. Achondroplasia was identified in one neonate, resulting in an incidence rate of 0.21 per 1,000 births.

In a 5-year prospective study for newborns at Al Ain Medical District, Al-Gazali et al. (2003) defined the pattern and birth prevalence of the different types of osteochondrodysplasias in the United Arab Emirates. Among the 38,048 births during the study period, 36 (9.46/10,000 births) had some type of skeletal dysplasia of which four had achondroplasia (1.05/10,000 births); however, one case was inherited from the affected father, therefore the birth prevalence rate of non-inherited achondroplasia was 0.78/10,000 births. In three cases, including the inherited form, the parents were consanguineous. The mean paternal and maternal age for thanatophoric dysplasia were 36.6 and 28 years, respectively. Al-Gazali et al. (2003) calculated the mutation rate of this type of osteochondrodysplasia in the United Arab Emirates to be 0.39/10,000. They also noted that all sporadic cases of achondroplasia occurred in one year (January-March 1999). Al-Gazali et al. (2003) also noted that the birth prevalence of sporadic ahondroplasia is higher in the UAE population than those reported for other populations (0.13-0.64/10,000).

Yemen

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

References

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Related CTGA Records

Fibroblast Growth Factor Receptor 3
Hypochondroplasia
Thanatophoric Dysplasia

External Links

http://www.achondroplasia.co.uk/
http://www.emedicine.com/ped/topic12.htm
http://www.genetests.org/profiles/achondroplasia
http://www.hopkinsmedicine.org/greenbergcenter/achon.htm
http://www.marchofdimes.com/professionals/681_1204.asp
http://www.medicinenet.com/achondroplasia/article.htm
http://www.orpha.net/static/GB/achondroplasia.html

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