Achondroplasia and nail-patella syndrome: the compound phenotype

EDITOR—Achondroplasia (MIM 100800) is one of the most common chondrodysplasias with a prevalence rate of around 1 in 26 000 live births. Inheritance is autosomal dominant, but in around 85% the phenotype is the result of a new mutation. Common features include disproportionate short stature with short limbs, particularly rhizomelic shortening, true megalecephaly with hydrocephalus in a minority, midface hypoplasia, a trident hand configuration, and joint hyperextensibility. Motor development delay is common owing in part to generalised mild hypotonia and in part to megalecephaly. Otitis media (OM) is a common complication with around 95% of subjects having an episode of OM at some time and over 80% requiring the insertion of PE tubes on at least one occasion. Neurological compromise can result from either stenosis of the foramen magnum usually presenting in childhood or stenosis of the thoracolumbar spine in adults. Hydrocephalus, thought to result from stenosis of the jugular foramina, requires the insertion of ventriculoperitoneal shunts in around 95% of subjects having an episode of OM at some time and over 80% requiring the insertion of PE tubes on at least one occasion. Neurological compromise can result from either stenosis of the foramen magnum usually presenting in childhood or stenosis of the thoracolumbar spine in adults. Hydrocephalus, thought to result from stenosis of the jugular foramina, requires the insertion of ventriculoperitoneal shunts in approximately 10% of cases; however, benign ventriculomegaly is a common finding. Bowing of the legs with proximal and distal tibial varus is common but is often asymptomatic. Cognitive function is normal. In 1994 specific mutations in the FGFR3 gene were found to cause achondroplasia.

Nail-patella syndrome (MIM 161200) (NPS) is an autosomal dominant disorder characterised by dysplasia of the nails, hypoplastic or absent patellae, and dysplasia of the elbow, with nephropathy in around 30% of cases. Iliac horns are not always observed but are a pathognomonic radiographic sign when present. Cognitive function is again normal. Recently, loss of function mutations in the LMX1B gene were found in patients with nail-patella syndrome. We report the case of a child, born to unaffected parents, with phenotypic features of both achondroplasia and NPS. De novo heterozygous mutations were identified in both the FGFR3 and LMX1B genes, confirming the presence of both conditions in the one person.

The proband was born at 36 weeks’ gestation after an uncomplicated pregnancy. Birth weight was 2580 g and there were no neonatal problems. He was the third child of a non-consanguineous Asian couple. At the time of conception, the father was 33 years of age and the mother 27 years. There was no family history of either achondroplasia or NPS. Examination of the parents and sibs showed no clinical features of NPS.

At birth he was noted to have macrocephaly, frontal bossing, rhizomelic limb shortening, a trident hand configuration, and generalised hypotonia. A clinical diagnosis of achondroplasia was made and this was confirmed radiographically (fig 1). The patient was also noted to have dysplastic nails and hypoplastic patellae with iliac horns (fig 1). The clinical and radiographic diagnosis of NPS was therefore also made.

Developmental progress was normal with only the expected gross motor delay associated with achondroplasia. Cognitive function was normal. General health was good and renal function normal. An MRI scan of the brain showed minimal ventricular dilatation; however, head growth was consistently 1 SD above the mean on growth charts for children with achondroplasia. Height at the age of 6 was also 1 SD above the mean. A polysomnogram performed in response to snoring showed no evidence of obstructive or central sleep apnoea.

Marked genu valgum with lateral instability developed initially unilaterally but subsequently affected both knees. This became sufficiently severe that gait was compromised with a fibular thrust. Bilateral fibular and tibial osteotomies were performed at 7 years with good results. Elbow movements were only mildly affected with mild limitation of extension and supination.

To determine whether the phenotype in the proband was the result of the coincidental occurrence of distinct genetic disorders or a previously undescribed condition, molecular studies were undertaken. DNA was extracted from whole blood samples from the proband and his parents and tested for the common achondroplasia mutation in FGFR3, G380R, using standard techniques. A number of different LMX1B mutations have been reported in NPS patients, so sequencing of the entire LMX1B gene was initiated as previously described. Analysis of the homeodomain identified a single base change resulting in the replacement of an arginine at codon 198 by a stop codon. Restriction enzyme digestion indicated that both mutations had arisen de novo.

There are a number of previous reports of children heterozygous for two dominant chondrodysplasias. In 1987, Sommer et al reported follow up of a patient first described by McKusick et al in 1973 with achondroplasia and hypochondroplasia. This child had unique clinical and radiographic features distinct from both achondroplasia and hypochondroplasia including more marked short stature than seen in achondroplasia with severe shortening of the long bones, both proximal and distal segments being involved, severe foramen magnum and spinal stenosis, flaring of the metaphyses, and large cartilaginous structures in the joints. Recently, two further cases of compound achondroplasia hypochondroplasia were reported. Both of these children had more severe features than would be expected in either achondroplasia or hypochondroplasia alone. One child had seizures on day 2 of life and both had significant respiratory distress. The features of these cases can be explained in the context of what we now know about mutations in FGFR3. Both achondroplasia and hypochondroplasia are caused by mutations in FGFR3 which cause activation of the receptor and inhibit endochondral ossification. Compound heterozygosity for mutations in FGFR3 would therefore be expected to cause additive effects on bone growth. The mental retardation is more difficult to explain although children with the recently described SADDAN (severe achondroplasia, developmental delay, acanthosis nigricans) phenotype also caused by mutations in FGFR3 also have mental retardation and exhibit greater activation of FGFR3. A number of CNS abnormalities, thought to be the result of neuronal migration defects, have been shown in thanatophoric dysplasia (MIM 187600) and in situ hybridisation experiments have shown that FGFR3 is expressed in the developing brain. Other cases have been reported where the two conditions are not allelic. Young et al described the male child of a father with spondyloepiphyseal dysplasia congenita (SEDc) (MIM 183900) and a mother with...
achondroplasia whom they believed on clinical and radiological grounds had inherited both conditions. The child died at 9 days of age from pulmonary hypoplasia and the authors postulated that the effects of the two mutations were additive. Kitoh et al. described a child who inherited pseudoachondroplasia (MIM 177170) from his mother and osteogenesis imperfecta (Sillence type III) (MIM 259420) from his father. The child died of respiratory distress at 15 months of age. Again it is postulated that the effects of the two mutations were additive. Langer et al. reported a child with both pseudoachondroplasia and achondroplasia. She had clinical and radiographic features of both conditions but these did not appear to be additive in nature.

In the case presented here, it does not appear that the mutations have an additive effect. Growth has been that expected of a child with achondroplasia. Motor development was also typical of achondroplasia and cognitive development was normal. It is of note that the knees were more severely affected than would have been expected in either condition and that the pattern of abnormality was not typical of either. Subjects with achondroplasia can develop genu valgum thought to be the result of ligamentous laxity. In NPS this type of deformity is secondary to a

Figure 1  AP radiographs of the lumbar spine, pelvis and bilateral lower extremities, knee, upper extremity, and hand at 3 months of age are shown. (A) The lumbar spine shows failure of progression of interpediculate distance. The iliac wings are small in both vertical and horizontal dimensions with iliac horns present. The long bones are shortened with proximal “fade” of the femurs. (B) The metaphyses are widened and epiphyses are small and poorly separated from the metaphyses. The patella has not yet ossified. (C) The long bones of the upper extremity are shortened with less marked metaphyseal abnormality than in the lower extremity. The radial head is dislocated. (D) There is generalised brachydactyly with a trident hand configuration.

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small, flat distal femoral condyle. In this aspect there may, therefore, have been some additive effect. The elbows show posterior dislocation of the radial head found both in those with achondroplasia and those with NPS. The degree of restriction of movement was less than is often seen in NPS.

The underlying molecular basis of achondroplasia and NPS is now understood. Mutations in FGFR3 disrupt endochondral ossification as described above. In limb development, FGFR3 acts to regulate bone growth negatively, thus limiting extension of the proximodistal axis. Upregulation of this pathway via gain of function mutations results in short limbs. LMX1B plays a role in the definition of the dorsoventral axis of the limb and is required for the development of dorsal structures and repression of ventral structures. NPS results from loss of function mutations in LMX1B. The reduction in dorsalising signal results in the failure of dorsal specific structures such as nails and patellae to develop normally.

The previous reports of children with compound skeletal phenotypes discussed above were the result of inheritance from two affected parents. The mutations in both FGFR3 and LMX1B in this child were de novo point mutations. This is the case in over 80% of those with achondroplasia and in approximately 20–25% of subjects with NPS. Paternal age at the time of conception was 33 years. It is well established that the risk of de novo point mutations increases with paternal age and that in non-familial cases of achondroplasia the mutation always occurs on the paternal allele. These data do not exist for NPS. Given that the particular nucleotide at which the FGFR3 mutation occurred is thought to be the most mutable in the genome, it is perhaps not surprising that this mutation would be seen in tandem with other mutations. It should also be noted that the R198X mutation in LMX1B is a recurrent mutation; the patient described here represents the fourth independent occurrence of the mutation. We have no evidence to suggest at this stage that there is any relationship between the FGFR3 mutation and the LMX1B mutation at a molecular level.

In summary we report a child with de novo mutations in the FGFR3 and the LMX1B genes. As a result the child has phenotypic features of both achondroplasia and nail-patella syndrome. Other than in the knee deformity, there is no evidence of a synergistic effect of these mutations.

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