CLINICAL STUDY

Hypochondroplasia and acanthosis nigricans: a new syndrome due to the p.Lys650Thr mutation in the fibroblast growth factor receptor 3 gene?

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Abstract

Background: Hypochondroplasia (HCH) is a skeletal dysplasia inherited in an autosomal dominant manner due, in most cases, to mutations in the fibroblast growth factor receptor 3 (FGFR3). Acanthosis nigricans (AN) is a velvety and papillomatous pigmented hyperkeratosis of the skin, which has been recognized in some genetic disorders more severe than HCH involving the FGFR3 gene.

Objective and design: After initial study of the proband, who had been consulted for short stature and who also presented AN, the study was extended to the patient’s mother and to 12 additional family members.

Methods: Clinical, biochemical and radiological studies were performed on the family. In addition, exons 11 and 13 of FGFR3 were analyzed.

Results: The proband and ten relatives presented HCH plus AN and the analysis of FGFR3 showed the p.Lys650Thr mutation. The members with normal phenotypes were non-carriers of the mutation.

Conclusion: This is the first report of a large pedigree with the clinical phenotype of HCH plus AN due to a FGFR3 mutation, p.Lys650Thr. This finding demonstrates the coexistence of both conditions due to the same mutation and it might represent a true complex, which should be further established by searching for AN in mild HCH patients or for HCH in patients with AN.

Introduction

Hypochondroplasia (HCH) (OMIM 146000) is a skeletal dysplasia similar to achondroplasia but less severe and rarely recognized before the age of 2 years. It is characterized by short stature, short limbs and lumbar lordosis, although these features are variable and can be almost normal in mildly affected subjects. The diagnosis of HCH on clinical and radiological grounds is often difficult and some patients may be diagnosed as idiopathic short stature. As with other skeletal dysplasias, HCH is caused by heterozygous mutations in the fibroblast growth factor receptor 3 gene (FGFR3); nevertheless, genetic heterogeneity is suspected because not all patients with presumed HCH have demonstrable mutations in FGFR3 (1). HCH is inherited in an autosomal dominant manner, and in the majority of new cases of HCH, the mutations appear de novo. Other skeletal dysplasias associated with mutations in FGFR3 include achondroplasia, thanatophoric dysplasia types I and II, and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN). FGFR3 mutations have also been described in Muenke and Crouzon syndromes with acanthosis nigricans (AN) (2); camptodactyly, tall stature and hearing loss syndrome (3); lacrimo-auriculo-dento-digital syndrome (4) and, recently, in familial AN (5).

FGFR3 is a member of a family that comprises four related receptors (FGFR1–4). Structurally, they are characterized by an extracellular ligand-binding domain consisting of three immunoglobulin-like subdomains (Ig-like domains I–III), a transmembrane domain and two intracellular tyrosine kinase domains responsible for the catalytic activity (6). Up to now, different mutations in FGFR3 have been identified in HCH patients: two of them, which result in p.Asn540Lys exchange (6–11), account for 72% of cases. There are other mutations that account for fewer than 2% of cases (12–17) and two among them are associated with a slightly milder skeletal phenotype, p.Lys650Asn and p.Lys650Gln (16).
FGFR3 is a negative regulator of bone growth and all mutations characterized to date in skeletal dysplasias and cancer cause constitutive activation of the receptor. These are gain-of-function mutations that activate the negative growth control exerted by the FGFR3 pathway (18, 19). Hence, the different phenotypes related to FGFR3 mutations are due to various degrees of ligand-independent activation of the receptor (2). The Lys650 residue of FGFR3, which is located within a critical region of the tyrosine kinase domain activation loop, has been particularly studied because amino acid substitutions at this site result in the autophosphorylation of tyrosine residues within the intracellular domain. Mutations at this site are responsible for developmental disorders that show different clinical severity. Thus, p.Lys650Glu and p.Lys650Met mutations strongly activate the receptor and are associated with two severe forms of dwarfism: thanatophoric dysplasia type II (20) and SADDAN syndrome (21) respectively. By contrast, p.Lys650Asn and p.Lys650Gln mutations that activate the receptor to a lesser degree are associated with milder forms of dysplasia, such as HCH. The mutation p.Lys650Thr also showed weak activation in vitro (16).

AN is a velvety and papillomatous pigmented hyperkeratosis of the skin, which appears mainly on the flexures and neck. It is recognized in some genetic disorders involving FGFR3 (22) like Crouzon syndrome (23), SADDAN syndrome (21), long-term survivors of thanatophoric dysplasia (24), one single case of achondroplasia (25) and one single case of osteochondrodysplasia (26).

In this report, we present an extended family with a phenotype of mild HCH plus AN associated with the p.Lys650Thr mutation in FGFR3.

**Patient and family**

The proband was a boy from northwestern Spain, who was referred to the paediatric endocrinologist at 12.5 years of age because of short stature. He was born at term from non-consanguineous parents. Pregnancy was uncomplicated and the delivery was by cesarean section. Birth weight was 3515 g (SDS +0.06), birth length 51 cm (SDS +0.32) and head circumference (HC) 35 cm (SDS +0.12). The patient presented poor growth and clinical features of HCH including relative macrocephaly, high arched palate and slightly abnormal body proportions with short upper arms and thighs (Fig. 1). He also presented mild limitation in elbow extension and small and broad hands. He complained of mild knee and ankle pain while doing exercise.

**Figure 1** Overall appearance of patients. (a–e) Hypochondroplasia characterized by relatively short extremities. Arrows, specific acanthosis nigricans areas in patients (more severe in women). (f and g) Pattern of acanthosis nigricans in the back (observe the hyperchromic spot in (g)). (h) Skin detail of acanthosis nigricans characterized by thick, velvety and hyperpigmented plaque. (a) II.5, (b) III.3, (c) III.4, (d) III.5, (e) III.7, (f) II.5, (g) III.4 and (h) II.9.
His hearing and vision were normal, and his school progress was satisfactory. His growth was uneventful until 6 years of age, when it slowed substantially (Fig. 2). The onset of puberty was at 12.8 years with bone age (BA) of 11 years and his pubertal growth spurt was poor. At 16 years (BA 16 years), his pubertal stage was P5G5 with testis of 20 ml. His anthropometric measurements were as follows: height, 150.3 cm (SDS - 3.4); sitting height %, 55.8 (SDS +4.21); arm span, 147.5 cm (SDS - 3.94); body mass index 24.2 and HC, 56.8 cm (SDS +1.23) (Table 1). In addition, he presented pigmented nevi and AN in the trunk and neck (Fig. 1). The radiological study of the skeleton was concordant with the diagnosis of HCH (27). It showed moderate narrowing of interpedicular distances, anteroposterior shortening of the pedicles and increased dorsal concavity of the vertebral bodies in the lumbar spine, short and broad femoral neck, shortening and relative squaring of the tubular bones, as well as elongated distal end of the fibula with respect to the tibia (Table 1; Fig. 3). All the biochemical studies were within normal limits. Androgen levels, thyroid function tests, liver function test, cholesterol and triglycerides were normal (data not shown). The fasting insulin, fasting glucose, glycosylated haemoglobin, oral glucose tolerance test, homeostasis model assessment (HOMA) index, insulin-like growth factor-I (IGF-I) and IGBP-binding protein-3 (IGFBP-3) were also normal (Table 1). The growth hormone (GH) stimulatory tests showed a GH peak of 17 µg/l.

The mother of the patient reported the presence of hyperpigmented areas in her skin as well as in other members of the family. Physical examination revealed an important AN (Fig. 1) in the neck, abdomen (flanks) and back, multiple pigmented nevi over trunk and epidermal nevi in the neck. She also showed an HCH phenotype (Fig. 1), which was confirmed by the radiographic skeletal survey (Table 1; Fig. 3). Therefore, a familial condition was suspected and all the family members were investigated. The study showed that all the members with HCH phenotype also presented AN, while others were normal for both conditions (Table 1; Fig. 4). All affected adults presented short stature with body disproportion and referred to delayed puberty onset (menarche in all females occurred at 14 or 15 years) and failure of the pubertal growth spurt. This growth pattern was revealed by the growth charts of the proband (III.3) and one cousin (III.4) (Fig. 2). Their heights were within normal range during childhood and at the same time they progressively deviate from the
Table 1  Genotype and phenotype of patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>HCH</th>
<th>AN</th>
<th>Age</th>
<th>AH (SDS)</th>
<th>% SH</th>
<th>AS (SDS)</th>
<th>HC (SDS)</th>
<th>BMI</th>
<th>RSS</th>
<th>IGF-I</th>
<th>Gl</th>
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<td>No</td>
<td>48</td>
<td>160 (-2.21)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>54.6 (-0.27)</td>
<td>18.9</td>
<td>NA</td>
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<td>93</td>
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<td>Yes</td>
<td>51</td>
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<td>143 (-4.81)</td>
<td>57 (1.37)</td>
<td>26.4</td>
<td>+</td>
<td>172</td>
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<td>NA</td>
<td>54.6 (-0.27)</td>
<td>18.9</td>
<td>NA</td>
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<td>86</td>
<td>5.2</td>
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<td>55.2</td>
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<td>92</td>
<td>6.1</td>
<td>NA</td>
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HCH, hypochondroplasia; AN, acanthosis nigricans; AH, adult height (cm); SH, sitting height (%); AS, adult arm span in adults (cm); HC, head circumference (cm); BMI, body mass index; RSS, radiographic skeletal survey; IGF-I (ng/ml; normal range: 6–8 years, 52–345; 9–11 years, 74–551; 12–16 years, 143–996; 17–20 years, 127–731; 21–40 years, 109–358; 41–60 years, 81–267); Gl, fasting glucose (mg/dl, normal range: 74–105); Ins, fasting insulin (UI/ml, normal range: 1.5–18.5); OGTT, oral glucose tolerance test; HOMA, homeostasis model assessment index; HbA1c, glycosylated haemoglobin (%); + radiology compatible with HCH: moderate narrowing of interpedicular distances, anteroposterior shortening of the pedicles and increased dorsal concavity of the vertebral bodies in the lumbar spine, short and broad femoral neck, shortening and relative squaring of the tubular bones and elongated distal end of the fibula with respect to the tibia; NA, not available.

<sup>a</sup>Estimated height in paraplegic patient.

<sup>b</sup>Adult onset diabetes mellitus.
analysis for alkaline phosphatase, calcium, phosphorus, androgen levels, thyroid function test, liver function test, cholesterol and triglycerides were within normal limits (data not shown).

Serum hormone assays

GH, IGF-I, IGFBP-3 and insulin were determined by an automated chemoimmunoluminescence assay (Immulus 2000; Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Testosterone and thyroid hormones were determined by chemoimmunoluminescence (ADVIA Centaur; Siemens Medical Solutions Diagnostics). For the OGTT, 1.75 g glucose/kg ideal body weight, not to exceed 75 g, were administered and blood samples were obtained from an antecubital vein immediately before and 120 min after glucose administration for the measurement of plasma glucose and insulin. The HOMA index was calculated as the product of the fasting plasma insulin (µUI/ml) and glucose levels (mmol/l) divided by 22.5.

Genetic analysis

Blood samples were collected after obtaining informed consent from the proband and his relatives. DNA was extracted from leukocytes by standard procedures. Two pairs of primers were used to PCR amplify exons 11 and 13 of FGFR3: 11S, 5'-AGCCTGTCACCCTAGGCTGTA-3'; 11A, 5'-TTGCAGGTCTGAAAAGTAG-3'; 13S, 5'-AGAGGCTTCAGCCCTGCCT-3' and 13A, 5'-CAGGCTCTACTGCTGACGTA-3'. PCR products were purified and directly sequenced using the BigDye terminator kit and run in the 3730xl DNA analyzer (Applied Biosystems, Foster City, CA, USA).

Results

The proband (III.3) was a heterozygous carrier of the c.1988 A>C mutation (GenBank accession number NM_000142), which leads to the p.Lys650Thr mutation at the protein level (Fig. 6). The genetic analysis in the proband’s relatives with the HCH plus AN phenotype (II.1, II.2, II.5, II.7, II.9, III.4, III.5, III.6 and III.7) showed that they were heterozygous carriers of the same mutation (patient I.1 was not available for

Figure 5 Skin biopsy. Acanthosis and papillomatosis with mild hyperkeratosis compatible with acanthosis nigricans (haematoxylin and eosin, 100×).

Figure 6 Electropherogram showing the base change from adenine to cytosine in the FGFR3 gene, which leads to the substitution of lysine 650 by threonine in the FGFR3 protein.
genetic analysis). Whereas the genetic study in the relatives with normal phenotype (II.6, III.1 and III.2) showed that they were not mutation carriers (Fig. 4).

Discussion

Here, an extended family with a phenotype that comprises mild HCH plus AN due to the p.Lys650Thr mutation in the FGFR3 gene is presented. All the family members who harbour the mutation have an HCH plus AN phenotype, whereas none of the family members without the mutation present HCH or AN. Other possible causes underlying AN, such as hyperinsulinemia or malignancy were excluded; moreover, the AN appeared in the trunk in addition to the flexures, which is typical of AN in syndromes due to FGFR3 mutations (22).

A partial study of this family has been presented at the 46th European Society for Paediatric Endocrinology Meeting (28) and, recently, the same mutation has also been described in an African-American family with AN (5), where the authors reported no associated anomalies other than slight short stature.

The p.Lys650, which is located in the tyrosine kinase domain of the receptor, is an important residue for the biological function of FGFR3. In fact, different amino acid substitutions at this site have been described in skeletal dysplasias of diverse severity, but also in bladder cancer (29). Bellus and colleagues (16) had investigated, in vitro, the constitutive activation of the receptor by all the possible amino acid substitutions resulting from single-nucleotide changes in the 650 codon of FGFR3. They showed that the p.Lys650Thr mutation leads to a constitutive activation of the FGFR3 tyrosine kinase equivalent to the activation produced by p.Lys650Asn and p.Lys650Gln, which are both associated with mild HCH. At the same time, it leads to a considerably lower activation than that produced by p.Lys650Glu and p.Lys650Met mutations that are associated with more severe phenotypes. Thus, the severity in the skeletal dysplasia was in concordance with the degree of ligand-independent kinase activity of the receptor. Because the growth inhibitory action of FGF signalling is specific to chondrocytes, whereas mitogenic for other cell types such as cells in the bladder epithelium or keratinocytes, this was also in agreement with the fact that only severe forms of skeletal dysplasias had been associated with AN.

Here, we report a family case of HCH associated with AN in the context of the p.Lys650Thr germline mutation. Very recently, this substitution has been described to cause familial AN with no obvious skeletal abnormalities except slight short stature (5). Another report has linked AN to a mild form of osteochondrodysplasia (26). Taken together, these three reports argue against a simple model in which kinase activity of the FGFR3 mutant form explains the severity of the manifestations, being skeletal defects or skin lesions. Complexity of intracellular signalling downstream of the activation of the receptor is likely to explain this phenomenon, uncoupling bone and skin phenotypes in FGFR3 germline mutations. Together with the previous mutation reports, our observation suggests an important role for residue Lys650 in the fine-tuning of FGFR3 function. This is supported by the reports of various clinical phenotypes ensuing from different amino acid substitutions at this same site, in skeletal disorders (Lys650Glu/Asn/Gln/Met), multiple myeloma (Lys650Glu/Met) or bladder cancer (Lys650Glu/Met/Thr). It is also in agreement with the high degree of conservation observed for this residue in other tyrosine kinase receptors. It has been described that FGFR3 signals through the activation of STAT1 and MEK/MAPK pathways, both of which seem to be relevant to the phenotypic consequences of achondroplasia (30). We speculate that Lys650 is a critical residue involved in the activation of one of these downstream pathways, with different consequences depending on the particular influence of the affected pathway on the specific cell type. Thus, it is possible that while sustained activation of MAPK pathway could have mild consequences in chondrocyte differentiation (since STAT1 may be unaffected), it may cause a stronger impact on keratinocyte proliferation.

Alternatively, different mutations in the Lys650 residue could affect different intracellular localizations, which is now believed to have a role in chondrocyte defects observed in skeletal dysplasias (31). It should be noted that FGFR3 can be expressed as different isoforms, and while chondrocytes express the isoform IIIc, epithelial cells present the isoform IIIb. Despite this, there is no apparent link of any isoform with specific responses; we cannot rule out the possibility that the effect of mutations within the tyrosine kinase domain could be modulated for isoform-specific differences. Further investigations are needed to address these issues.

The finding of this family with the clinical phenotype of HCH plus AN associated with the p.Lys650Thr in FGFR3 demonstrates the coexistence of both conditions due to the same mutation, and it might represent a true complex, which should be further established by searching for AN in mild HCH patients or for HCH in patients with AN.

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