CLINICAL REPORT

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Homozygous *N540K* Hypochondroplasia—First Report: Radiological and Clinical Features

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We describe a 16-month-old male with N540K homozygous mutation in the *FGFR3* gene who showed a more severe phenotype than hypochondroplasia (HCH). To our knowledge, a homozygous state for this mutation causing HCH has not been reported before. The clinical and radiological characteristics of our patient represent an intermediate condition between achondroplasia and achondroplasia/hypochondroplasia compound heterozygosity. This case represents a new expression of *FGFR3* spectrum and it is of considerable importance for the genetic counseling in cases where both parents are affected with HCH. © 2014 Wiley Periodicals, Inc.

Key words: hypochondroplasia; achondroplasia; phenotypic overlap; homozygosity

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INTRODUCTION

Hypochondroplasia (HCH, OMIM #146000) is an autosomal dominant skeletal dysplasia. Although usually caused by mutation of the fibroblast growth factor receptor 3 gene (*FGFR3*), located on *4p16.3* [Bellus et al., 1995; Prinos et al., 1995; Bonaventure et al., 1996; Rousseau et al., 1996], there is locus heterogeneity: a minority of individuals with the clinical diagnosis of HCH do not have any detectable change in *FGFR3* [Stoilov et al., 1995; Flynn and Pauli, 2003; Fano et al., 2005; Heuertz et al., 2006; Del Pino et al., 2011; Song et al., 2012]. Even within those with detectable *FGFR3* mutations, the clinical variability of HCH appears to be greater than that seen in individuals with achondroplasia.

We describe the clinical and radiological findings and molecular analysis of a 16-month-old male with a skeletal dysplasia with a severe phenotype, intermediate between achondroplasia and achondroplasia/hypochondroplasia compound heterozygosity. Molecular analysis showed *N540K* homozygous mutation in the *FGFR3* gene.

To our knowledge, a homozygous state for this mutation has not been reported before.

CLINICAL REPORT

The patient is the first child of nonconsanguineous, Argentinian parents. The mother was 29 years old and the father was 31 years old at the time of conception. Both parents are affected with HCH due to *N540K* heterozygous mutation. The mother also has another son from a previous relationship with HCH and *N540K* heterozygous mutation. She received genetic counseling regarding this condition after his first son was born. No other family background is relevant.

Pregnancy was uneventful but femoral shortening was detected by ultrasonographic examination. The patient was delivered by cesarean because of fetal-pelvic disproportion at 38 weeks of gestation. Birth weight was 3,600 g (50th centile); length was 46.1 cm (3rd centile); and OFC 38.2 cm (+2.3 SD). Apgar score was normal. During his first days, cardiac, ophthalmological, and hearing evaluations were normal.

The patient came to our clinic at the age of 16 days, upon examination his appearance was suggestive of ACH, with frontal bossing, midface hypoplasia, small thorax with bell-shaped chest, trident hand configuration with short fingers, and rhizomelic shortness of arms and legs. A skeletal survey showed shortness of the long bones with mild flaring of the metaphyses, short and squared ilia and narrow sacrosciatic notches, the femurs had the characteristic translucency of the proximal ends seen in ACH.

At 16 months of age, he had been hospitalized three times for cyanotic episodes with crying spells and twice for respiratory infections with decreased oxygen saturation. On physical exami-

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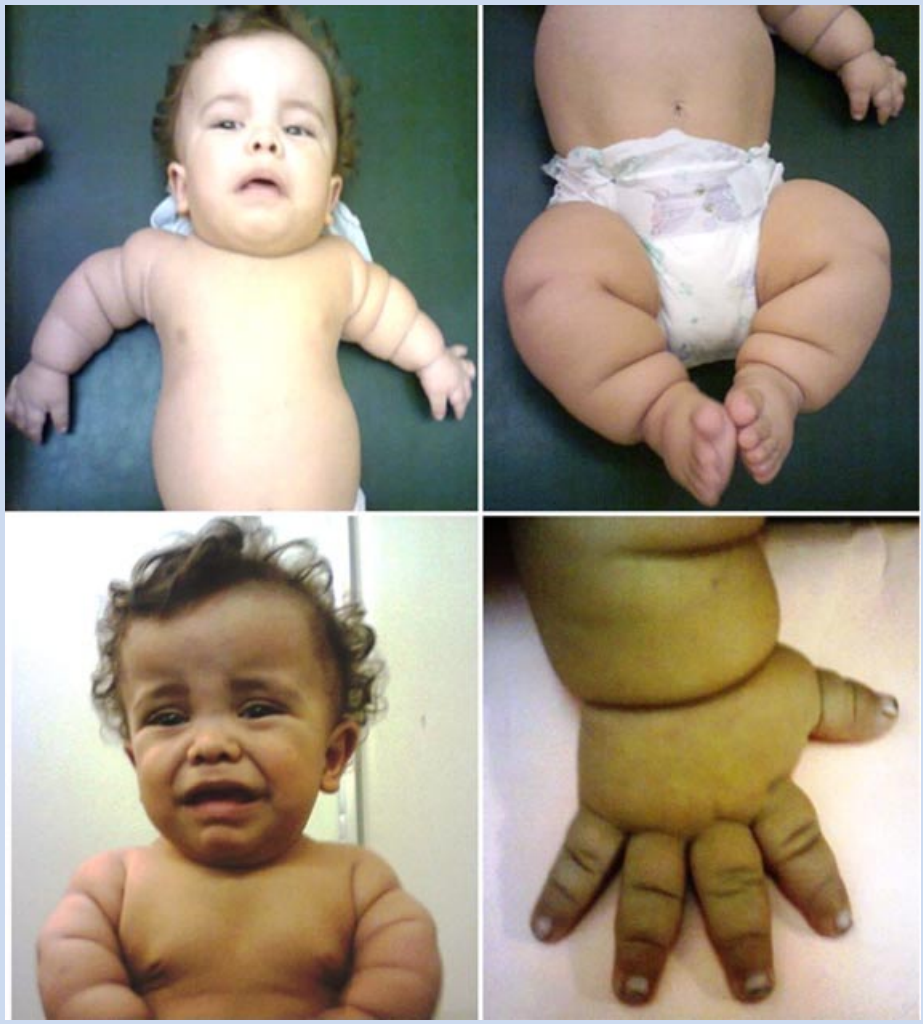

FIG. 1. Patient at 16 months of age. Note frontal bossing with midface hypoplasia and rhizomelic shortness of arms and legs and trident configuration of hand.

nation his length was 68 cm (−4.0 SD) for Argentinian growth standards [Lejarraga et al., 2009] his weight was at 50th centile and OFC at 97th centile, he showed disproportionate short-limb dwarfism with large head, frontal bossing, depressed nasal bridge, narrow thorax, short hands with stubby fingers, trident hand configuration, shortness of arms and legs with bowlegs and excess skin creases (Fig. 1). He showed delay in gross motor skills and language. A skeletal survey revealed marked shortening of the long bones with flaring of the metaphyses, short and squared ilia with marked narrowing of the sacrosciatic notches, oval-shaped lucent appearance of the proximal femora, and mild decreased interpediculate distance in lumbar spine (Fig. 2).

Brain MRI showed nonspecific widening of subarachnoid spaces, bilateral periventricular leukomalacia and temporal lobe dysgenesis with relative enlargement and aberrant sulcation of the inferior surface and deep transverse clefts in the mesial temporal lobe. There was also mild callosal narrowing (Fig. 3).

At the age of 26 months his length was 69.6 cm (−6.2 SD), his weight was 11.5 kg (10th centile), and his OFC was at 97th centile. He had frequent bronchial obstruction intercurrences and episodes of ear infections. Cyanotic episodes did not repeat. Physical examination also showed lumbar lordosis, increased tibial bowing, bilateral limitation of the forearms' supination and dental malocclusion.

Developmental milestones were slowly acquired. There was evidence of psychomotor delay, using screening tests specific for achondroplasia [Todorov et al., 1981]: he was able to roll over, crawl, sit alone, and reverse snow plough, but he didn't stand independently, neither pull up to stand. Communication skills were delayed, he only said "mama," "dada" and used body language like shaking his head.

Molecular studies revealed HCH *N540K* homozygous mutation in the proband by PCR-RFLP from genomic DNA from peripheral blood leukocytes [Bonaventure et al., 1996; Prinster et al., 1998].

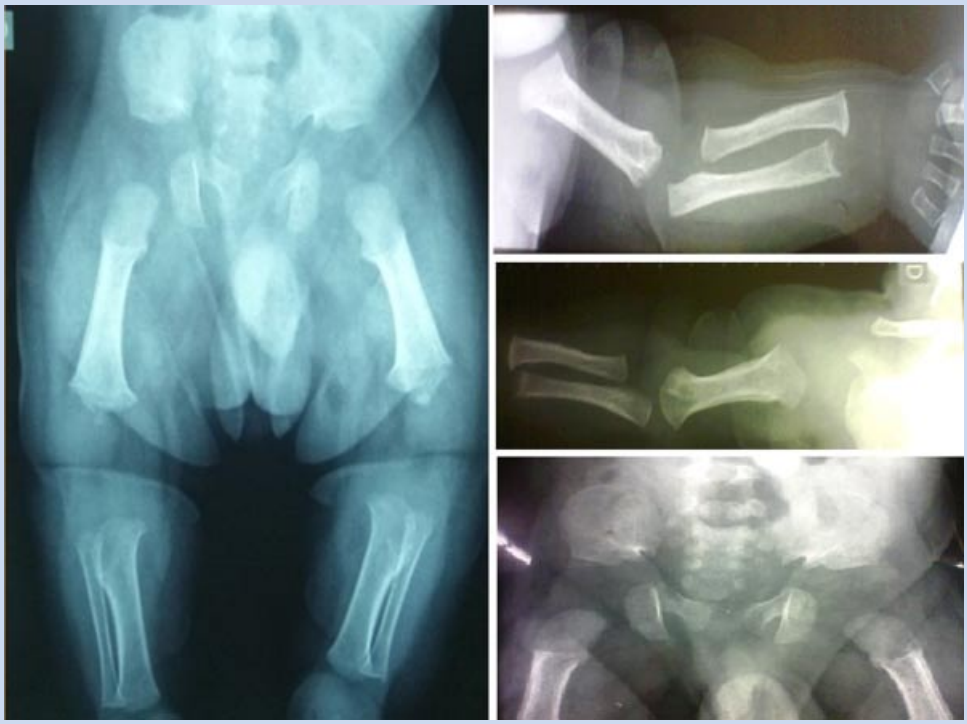

FIG. 2. Patient's X-rays at 16 months of age. Note shortness of the long bones, short and squared ilia and sacrosciatic notches.

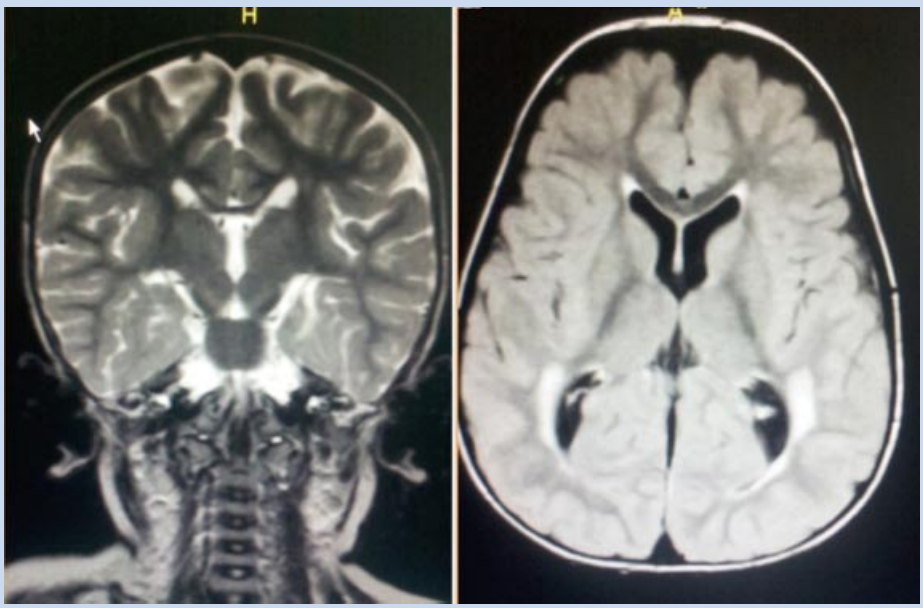

FIG. 3. Patient's brain MRI. Note aberrant sulcation of the inferior surface and deep transverse clefts in the mesial temporal lobe.

TABLE I. Comparison of Homozygous and Heterozygous ACH, Heterozygous HCH, Compound ACH/HCH Heterozygous Patients and Our Case

	Homozygous ACH	Compound ACH/HCH heterozygous	Heterozygous ACH	Heterozygous HCH	Our patient
Clinical features					
Frontal bossing/depressed nasal bridge/ midface hypoplasia	Severe	Moderate/severe	Moderate/severe	−/mild	Moderate/ severe
Disproportionate short-limb stature	Severe	+	+	+ (mild)	+
Brachydactyly and trident hand	Severe	+	+	−	+
Bowlegs	Severe	+	+	+	+
Developmental delay	Severe	Gross motor moderate/severe Cognitive mild to severe	Early gross motor, improves with age No cognitive delay	Gross motor-cognitive variable (10% mental retardation)	Gross motor moderate cognitive severe
Hypotonia	Severe	Moderate/severe	+	−	Moderate
Radiological findings					
Shortening of long bones with metaphyseal flare	Similar to thanatophoric dysplasia	Moderate/severe	Moderate/severe	Mild	Moderate to severe
Narrowing of the inferior lumbar interpedicular distances	Severe	Moderate/severe	Moderate	Mild	Mild
Squared shortened ilia/narrowed sacrociatic notches	Similar to thanatophoric dysplasia	Moderate/severe	Moderate	Mild	Moderate/ severe

References: +, present; −, not present.

The homozygous mutation c.1620C>A detected was confirmed by direct sequencing of the PCR products on an ABI PRISM 3100 Genetic Analyzer. Both parents and the patient's half brother were studied in our laboratory and had the same mutation in heterozygous state.

DISCUSSION

HCH due to *N540K* heterozygous mutation is currently a well-described and documented skeletal disorder. HCH as well as ACH are autosomal dominant conditions of the *FGFR3* dysplasia family [Spranger et al., 2012]. Compound heterozygosity for HCH/ACH [McKusick et al., 1973; Sommer et al., 1987; Chitayat et al., 1999; Huggins et al., 1999] as well as double heterozygosity have been reported previously [Flynn and Pauli, 2003]. Compound heterozygotes possess two *FGFR3* mutations responsible for the phenotype, whereas double heterozygosity for ACH/HCH is defined as possessing only one *FGFR3* mutation (resulting in ACH) with a mutation in a different gene responsible for HCH [Flynn and Pauli, 2003]. All patients with the mentioned conditions had more severe clinical and radiological features than either condition in the heterozygous state, but less severe than those in homozygous ACH. Homozygous ACH, caused by the presence of two mutant alleles at nucleotide 1,138 of *FGFR3*, is a severe disorder with radiological changes qualitatively different from those of heterozygous ACH. Several bone changes are similar to those in thanatophoric dysplasia. Early death results from respiratory insufficiency because of the small thoracic cage and neurological deficit from cervicomedullary stenosis [Hall, 1988]. The phenotype of heterozygous HCH is qualitatively similar to ACH but quantitatively much milder.

Here we report a patient with two *N540K* mutations and more severe clinical and radiological features than those described for heterozygous HCH, as expected. Concerning the child's growth, the follow-up showed that he was between (−4 SD) and (−6 SD) in height, if we use Argentinian growth charts, but if we use growth references for height, in Argentine children with ACH, he was in 3rd centile. Therefore we can presume that stature in patients with homozygous HCH could be in the lower centiles of the heterozygous ACH charts, or even lower.

Our patient shares with heterozygous HCH the brain MRI characteristics described by Kannu and Aftimos [2007] and Philpott et al. [2013] and cognitive delay, suggesting the importance of *FGFR3* in development and neuronal organization of the temporo-occipital cortex in humans.

In Table I, we compare the present case with ACH/HCH complex patients, heterozygous and homozygous ACH and heterozygous HCH.

Our patient's facial appearance, his hypotonia and the narrowing of the inferior lumbar interpedicular distances are less severe than those of ACH/HCH complex patients. In contrast, clinical features seems to be more pronounced than those of the usual heterozygous ACH, especially in regard to cognitive development. Intellectual disability of unknown cause has been noted in about 9–10% of patients with HCH [Kannu and Aftimos, 2007]. Some studies [Linnankivi et al., 2012] suggest that individuals with the *FGFR3 N540K* mutation may have an increased incidence of mild-to-

moderate intellectual disability or learning disabilities. Our patient showed gross motor and cognitive severe delay and also have temporal lobe abnormalities, this neurological severity could be attributed to having *N540K* mutation in double dose. This is consistent with what Allison and Blumberg [1958] previously suggested, that all so-called dominant disorders of man in fact appear to result in much more severe phenotypic expression when present in double dose.

In 1983, Pauli suggested that compound heterozygosity for ACH/HCH with *FGFR3* mutations appears to have additive effects on the phenotype and may cause additional abnormalities, and this condition is closely analogous to ACH homozygosity, which virtually uniformly seems to result in a very severe phenotype [Pauli et al., 1983]. Flynn and Pauli postulated a gradient of severity for these conditions as follows: homozygous ACH > ACH/HCH compound heterozygosity > ACH/HCH double heterozygosity > heterozygous ACH > heterozygous HCH.

Taking into account this proposed gradient, our patient has clinical and radiological features intermediate between heterozygous achondroplasia and achondroplasia/hypochondroplasia compound heterozygosity.

This patient is the first instance of homozygous hypochondroplasia mutation to be reported, so he represents a new entity, along the continuum of severity for *FGFR3* disorders. Genotype-phenotype correlations in these disorders, long-term follow-up and additional cases are needed to further delineate the natural history and clinical severity of homozygous *N540K* patients.

Information regarding the homozygous state is of considerable importance for genetic counseling in cases where both parents are affected with HCH.

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