González-del Angel et al.

Further delineation of ACH-HCH complex

TITLE PAGE**Title:****FURTHER DELINEATION OF ACHONDROPLASIA-HYPOCHONDROPLASIA
COMPLEX WITH LONG-TERM SURVIVAL****Running title: Further delineation of ACH-HCH complex**Ariadna González-del Angel¹,Rocío Rius²,Miguel A Alcántara-Ortigoza¹,Elaine Spector³,Victoria del Castillo²,Luis Enrique Mata-García⁴.

¹Laboratorio de Biología Molecular, Departamento de Genética Humana, Instituto Nacional de Pediatría, Avenida Insurgentes Sur 3700-C, Insurgentes Cuicuilco, Coyoacán, Ciudad de México, México

²Departamento de Genética Humana, Instituto Nacional de Pediatría, Avenida Insurgentes Sur 3700-C, Insurgentes Cuicuilco, Coyoacán, Ciudad de México, México.

³University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, Colorado, 80045, USA.

⁴Médico Residente de Genética Médica, Departamento de Genética Humana, Instituto Nacional de Pediatría, Ciudad de México, México

Corresponding author:

Ariadna González-del Angel, MD, PhD

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González-del Angel et al.

Further delineation of ACH-HCH complex

Laboratorio de Biología Molecular, Departamento de Genética Humana, Instituto Nacional de Pediatría, Secretaría de Salud. Avenida Insurgentes Sur 3700-C, Insurgentes Cuicuilco, Coyoacán, C.P. 04530, Ciudad de México, México.

E-mail: ariadnagonzalezdelangel@gmail.com

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González-del Angel et al.

Further delineation of ACH-HCH complex

ABSTRACT

Achondroplasia-hypochondroplasia (ACH-HCH) complex is caused by the presence of two different pathogenic variants in each allele of *FGFR3* gene. Only four patients with confirmed molecular diagnoses have been reported to date, and the phenotype has not been fully defined. Here, we describe a Mexican patient with a confirmed molecular diagnosis of ACH-HCH complex. This patient exhibits intellectual disability, has a history of seizures, experienced multiple cardiorespiratory complications during early childhood, and required foramen magnum decompression. However, he now shows a stable health condition with long-term survival (current age, 18 years). This case is particularly relevant to our understanding of ACH-HCH complex and for the genetic counseling of couples who are affected with ACH or HCH.

KEY WORDS

Achondroplasia, bone dysplasia, compound heterozygous genotype, fibroblast growth factor receptor 3, hypochondroplasia

INTRODUCTION

Achondroplasia (ACH, OMIM #100800) and hypochondroplasia (HCH, OMIM #146000) are common skeletal dysplasias that exhibit autosomal dominant inheritance. They are caused by recurrent mutations in the gene encoding fibroblast growth factor receptor 3 (*FGFR3* gene; OMIM *134934), which is located on 4p16.3. The FGFR3 protein contains four domains: an extracellular domain comprising three immunoglobulin-like domains; a transmembrane (TM) domain; and two cytoplasmic tyrosine kinase domains (Heuertz et al. 2006).

Almost all (98%) of ACH cases arise from an arginine-to-glycine substitution at position 380 in the TM domain of FGFR3 [NM_000142.4: c.1138G>A or p.(Gly380Arg); rs28931614] (Bellus et al. 1995; Heuertz et al. 2006). The clinical manifestations are a disproportionately short stature, an enlarged head with frontal bossing and midface hypoplasia, rhizomelic limb shortness, genu varum, exaggerated lumbar lordosis, and short/broad hands with a trident configuration (Bellus et al. 1995). Homozygous ACH patients are more severely affected than heterozygotes, and have a short survival due to respiratory complications arising from upper airway obstruction, a small thoracic cage, and cervicomedullary stenosis (Bellus et al. 1995).

HCH is an allelic disease of ACH that is characterized by a less severe phenotype (Song et al. 2012). Most HCH patients are heterozygous for the gain-of-function pathogenic variant p.(Asn540Lys) [NM_000142.4: c.1620C>A or c.1620C>G; rs28933068], which is located in the proximal tyrosine kinase domain of FGFR3 (Heuertz et al. 2006; Song et al. 2012).

Couples in which one partner has ACH and the other has HCH experience a 25% risk of having a compound heterozygous child in each gestation (Chitayat et al. 1999). The phenotype of patients with the so-called ACH-HCH complex has not been well defined, as

González-del Angel et al.

Further delineation of ACH-HCH complex

only four patients with confirmed molecular diagnoses have been reported in the literature (Bober et al. 2012; Chitayat et al. 1999; Huggins et al. 1999; McKusick et al. 1973; Prinos et al. 1995; Sommer et al. 1987). In the present report, we describe a Mexican patient with ACH-HCH complex and long-term survival. This information contributes to delineating the phenotype of this entity and adds information relevant to the genetic counseling of couples who are affected with ACH or HCH.

CLINICAL REPORT

The index case is an 18-year-old boy who was the first child of two Mexican parents: his mother has ACH and his father HCH. The parents did not receive genetic counseling or molecular testing before the patient's birth. The patient was born at 38 weeks of gestation by Cesarean section, due to cephalopelvic disproportion. His birth weight was 2,450 g; his length at birth and APGAR score are unknown. The child failed to breathe spontaneously and required tactile stimulation. Six days after birth, the patient had a bronchoaspiration. At 7 months of age, he was admitted to the National Institute of Pediatrics in Mexico City with significant respiratory distress due to bronchopneumonia. On physical examination, he had a head circumference of 45 cm (-2 standard deviations [SD] relative to the ACH growth curve; Horton et al. 1978), a weight of 4.4 kg (below the 10th percentile relative to the ACH growth curve; Tofts et al. 2017) and a height of 54 cm (-2 SD relative to the ACH growth curve; Horton et al. 1978). He had an enlarged head with a large anterior fontanel, frontal bossing, midface hypoplasia, a small chest, protuberant abdomen, rhizomelic limb shortness, and short and broad hands with a trident configuration (Fig. 1). X-ray evaluation showed enlarged calvaria, with a small skull base, shortness of the tubular bones, wide

metaphyses, squared ilia with horizontal acetabula and narrowing of the interpedicular distances of the lumbar vertebrae (Fig.1).

The family history and clinical manifestations suggested that the patient might have ACH-HCH complex. PCR amplification and subsequent bi-directional Sanger sequencing of *FGFR3* exons 9 and 12 (reference sequence NM_000142.4) confirmed that the patient inherited the common ACH and HCH mutations from his parents, and was a compound heterozygote c.[1138G>A];[1620C>G] or p.[Gly380Arg];[Asn540Lys] (Fig.1).

The patient required foramen magnum decompression at 7 months. During his 10 first months of life, he had seven episodes of eye deviation, with increased generalized muscle tone, cyanosis and post-somnolence. Electroencephalogram showed diffuse alteration without paroxistic phenomena. The patient was thought to have tonic generalized epilepsy, and pharmacological treatment was begun with valproic acid. He have not present any subsequent seizures; the anti-epileptic medication was suspended at 5 years of age, and there was no seizure relapse thereafter. During early childhood, the patient was hospitalized 11 times for the treatment of bronchopneumonia, and he suffered cardiac arrest on one occasion. His clinical course improved after the age of 5 years, and there was no subsequent acute respiratory illness.

The patient showed psychomotor developmental delay. At 3 years of age, he began to pronounce his first words; at 4 years of age, he was able to sit unsupported; and at 5 years, he was able to walk. Developmental assessment at 9 years revealed age-equivalent scores of 3 years 2 months in motor skills, 3 years 10 months in self-help, 3 years 9 months in sociability, 2 years 10 months in cognition and 2 years 6 months in communication.

At the patient's most recent clinical consult (age 18) (Fig.1), he spoke using three- to four-word sentences with poor articulation and attended special education classes. He did not

complain of dyspnea, fatigue, or inappropriate daytime sleepiness. According to ACH growth charts, his head circumference (54.5 cm) was -2 SD (Horton et al. 1978) and his weight (34 kg) was between the 25th and 50th percentiles, although his body mass index (31.4) was above the 90th percentile (Tofts et al. 2017). His height (104 cm) and lower limb segment length (38 cm) were more than -2 SD, while his upper limb segment length (66 cm) was -2 SD (Horton et al. 1978).

Cerebral computed tomography (CT) showed only moderate ventricular enlargement, and no other brain dysgenesis was found by magnetic resonance imaging. Polysomnography identified a severe obstructive sleep apnea (apnea hypopnea index of 37); echocardiography was normal (systolic pulmonary artery tension 25-30 mmHg), and whereas the somatosensory evoked potentials of his median nerves were normal, those of his tibial nerves showed a decreased amplitude with normal absolute latencies.

DISCUSSION

To our knowledge, only four other ACH-HCH complex patients have been reported in the medical literature (Table 1) (Bober et al. 2012; Chitayat et al. 1999; Huggins et al. 1999; McKusick et al. 1973; Prinos et al. 1995; Sommer et al. 1987). In accordance with the previously reported cases, our patient's clinical and radiological manifestations suggest that his phenotype is more severe than that seen in heterozygous ACH or HCH patients, but milder than that seen in homozygous ACH individuals (De Rosa et al. 2014; Flynn and Pauli, 2003).

All of the reported patients with ACH-HCH complex had motor developmental delays. In three of these cases, however, the patients were described when they were less than 8 months of age and no additional neurocognitive follow-up has been published (Bober et al. 2012; Chitayat et al. 1999; Huggins et al. 1999). Follow-up information is only available

González-del Angel et al.

Further delineation of ACH-HCH complex

for two ACH-HCH patients: the present case, and one that was first described by McKusick et al. (1973) at age 14 months and later updated by Sommer et al. (1987) at age 14 and by Prinos et al. (1995) at age 24. Both of these patients have evident cognitive disability (Table 1). Mild to moderate intellectual disability (9–20%) has been described in patients heterozygous for the common pathogenic variant of HCH (Linnankivi et al. 2012; Romeo et al. 2014). Thus, the intellectual disability seen in the present case could be considered a primary consequence of the HCH-causing variant. However, we cannot discard the possibility that its severity might be accentuated by the patient's compound heterozygous genotype and/or the cardiorespiratory complications and seizures he experienced during early childhood.

Temporal lobe dysgenesis has been associated with seizures in patients with HCH (Linnankivi et al. 2012; Romeo et al. 2014). The seizures seen in the present case resembled those described in HCH: they started in the first year of life; involved cyanosis, eye deviation and secondary generalization; exhibited a good pharmacological response to valproic acid; and remitted after infancy (Linnankivi et al. 2012; Romeo et al. 2014). However, the cerebral magnetic resonance imaging of our patient did not show any abnormality in the temporal lobe region, so we cannot be sure that the seizures were a clinical manifestation of his *FGFR3* genotype.

Respiratory distress appears to be a constant manifestation in the ACH-HCH complex (Table 1). The apparently narrow chest conformation of these patients might logically cause restrictive lung disease. However, the only reports that offered chest measurements (including the present case) failed to demonstrate an objectively narrow thorax when the chest circumference was plotted (Table 1) (Bober et al. 2012; Chitayat et al. 1999; Hunter et al. 1996). Thus, as argued by Bober et al. (2012), some type of abnormal primary

González-del Angel et al.

Further delineation of ACH-HCH complex

pulmonary anatomy might explain the respiratory distress observed in these individuals. No thoracic CT scan was performed on our patient, so we are currently unable to discard this possibility.

The present case stands as the second longest reported survival of an ACH-HCH complex individual who has remained relatively stable since childhood. It is not possible to define the factors that have allowed our patient to survive longer than some other ACH-HCH complex patients. However, there may have been some contribution from the foramen magnum decompression performed at an early age, as was previously reported in a homozygous ACH patient (Moskowitz et al. 1989).

In the future, additional follow-up studies are needed to further elucidate the survival, neurodevelopment, and pulmonary function of patients with ACH-HCH complex, in order to delineate the natural history of this entity and enable us to provide families with accurate genetic counseling.

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Ethical approval

All procedures performed in studies involving human participants were done in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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González-del Angel et al.

Further delineation of ACH-HCH complex

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González-del Angel et al.

Further delineation of ACH-HCH complex

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FIGURE LEGEND

Fig. 1. Clinical photographs of index case at the ages of 1 year (A) and 17 years (B), showing an enlarged head, frontal bossing, midface hypoplasia, short limbs, an apparently small chest, a protuberant abdomen, and small hands. At 17 years of age, a prominent thoraco-lumbar kyphosis is evident. (C) Partial electropherograms (forward strands) of exon 9 reveal the heterozygous c.1138G>A or p.(Gly380Arg) [rs28931614] pathogenic variant conditioning the ACH phenotype (arrow) in both the proband and his mother. In exon 12, the heterozygous c.1620C>G or p.(Asn540Lys) [rs28933068] pathogenic variant, which conditions the HCH phenotype (arrow), is observed in both the proband and his father. These results confirm the diagnosis of ACH-HCH complex in the proband, due to a compound heterozygous *FGFR3* genotype c.[1138G>A];[1620C>G] or p.[Gly380Arg];[Asn540Lys]. (D) Skeletal radiographs at age 1 year showing enlarged calvaria, short bones of the hands with a trident position of the fingers, shortening of the long bones with wide metaphyses, narrowing of lumbar interpedicular distance, and thoraco-lumbar kyphosis.

Fig. 1

292x391mm (96 x 96 DPI)

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Table 1. Phenotypes and Genotypes of Reported Achondroplasia-Hypochondroplasia Complex Patients

	Present case	Bober et al. 2012	Huggins et al. 1999	Chitayat et al. 1999	McKusick et al. 1973; Sommer et al. 1987; Prinos et al. 1995
Genotype (NM_000142.4)	c.[1138G>A]; [1620C>G] or p.[Gly380Arg]; [Asn540Lys]	p.[Gly380Arg]; [Asn540Lys]	c.[1138G>A]; [1620C>G] or p.[Gly380Arg]; [Asn540Lys]	c.[1138G>A]; [1620C>A] or p.[Gly380Arg]; [Asn540Lys]	c.[1138G>A]; [1620C>A] or p.[Gly380Arg]; [Asn540Lys]
Sex	Male	Male	Female	Male	Female
Age of diagnosis	1yr	Prenatal	Neonatal	Prenatal	14m
Last published follow up	18yr	7mo	8mo	2wk	24yr
Birth weight (g)	2450	1800	2588	3335	3362
Birth length (cm)	NA	38	NA	42	NA
Birth head circumference	NA	34	35.5	39	40
Disproportionate short-limb stature	+	+	+	+	+
Gross motor developmental delay	+	+	+	NA	+
Cognitive developmental delay	+	-	-	NA	+
Seizures	+	-	-	+ 2d	+ 4m
Hypotonia	+	+	+	+	+
Hydrocephalus	+	-	-	-	+
FM stenosis/spinal stenosis	+	+	NA	NA	+
Frontal bossing	+	+	+	+	+
Midface hypoplasia	+	+	+	+	+
Depressed nasal bridge	+	+	+	+	+
Narrow chest*	- (Chest circumference 80 cm, +2 SD, chest circumference for length)	- (Chest circumference 33 cm, -1 SD, chest circumference for length)	+	- (Chest circumference 30.5 cm, -1 SD, chest circumference for age)	+

Brachydactyly/trident	+	+	+	+	+
Shortness of long bones	+	+	+	+	+
Metaphyseal flare	+	+	+	+	+
Narrowing of lumbar interpedicular distances	+	+	+	+	+
Squared ilia	+	+	+	+	+
Gastroenterology	Gastro esophageal reflux and aspiration	Poor feeding, reflux and aspiration, required Nissen fundoplication and G-tube placement. Hypoglycemia	Gastroesophageal reflux	NA	-
Cardio-Pulmonary	Mild respiratory distress at birth, bronchoaspiration episode at neonatal period, significant respiratory distress by 5 mo. Recurrent pneumonia. Cardiac arrest on one occasion	Chronic respiratory insufficiency requiring tracheostomy and mechanical ventilation at 6 mo. Abnormal pulmonary anatomy (right lung had two lobes, left lung had three lobes)	Pulmonary hypoplasia. Mechanical ventilation assistance as a neonate and oxygen in times of distress	Mild respiratory distress at birth requiring supplemental oxygen and intermittent nasal continuous positive airway pressure	Recurrent pneumonia, respiratory arrest, chronic respiratory insufficiency requiring tracheostomy at 14 yr
Other		Left inguinal hernia		Partial agenesis of the corpus callosum and grey matter heterotopia	Bilateral inguinal hernia

Abbreviations: FM, foramen magnum; mo, months; NA, not available; SD, standard deviation; wk, weeks, yr, years.

* According to Standard Curves of Chest Circumference in Achondroplasia, Hunter et al. 1996.

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Author/s:

Gonzalez-del Angel, A;Rius, R;Alcantara-Ortigoza, MA;Spector, E;del Castillo, V;Enrique Mata-Garcia, L

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