Adv Ther (2026) 43:2018–2033
https://doi.org/10.1007/s12325-026-03526-2

ORIGINAL RESEARCH

Pathways to Facilitate Early Recognition and Diagnosis of Hypochondroplasia

Melita Irving · Elena Greco · Alessandra Cocca · Andrew Dauber · Alexander Augusto de Lima Jorge · Svein Fredwall · Amy Patterson · Juan Llerena Jr. · Keiichi Ozono · Rui Santos · Dominique Kelly · Elena Muslimova · Tejaswini Reddi · Renée Shediac · Ravi Savarirayan · V. Reid Sutton · Julie Hoover-Fong · Moira Cheung

Received: December 24, 2025 / Accepted: February 3, 2026 / Published online: February 28, 2026
© The Author(s) 2026, modified publication [2026]

ABSTRACT

Introduction: Hypochondroplasia (HCH) is a disproportionate short-statured skeletal dysplasia condition caused by gain-of-function pathogenic variants in the fibroblast growth receptor 3 gene (*FGFR3*). Although HCH typically becomes clinically apparent after the first year of life, when height discrepancy compared with the general population becomes more pronounced, diagnosis is often delayed by several years. Early recognition of HCH is challenging because of wide phenotypic variability and subtle clinical and radiographic features, leading to delayed or missed diagnosis. Furthermore, wide variant heterogeneity and restrictive testing criteria can contribute to diagnostic delays. Early diagnosis may facilitate timely clinical management and psychosocial support. However, no standardized diagnostic criteria for HCH currently exist, nor are diagnostic pathways well described in the literature.

Prior Presentation: This article is based on work that was previously presented at the Joint Congress of the European Society for Paediatric Endocrinology (ESPE) and the European Society of Endocrinology (ESE), May 10–13, 2025, Copenhagen, Denmark: https://www.endocrine-abstracts.org/ea/0110/ea0110p249.

M. Irving (✉) · A. Cocca · R. Santos
Guy's and St Thomas' NHS Trust, London, UK
e-mail: melitairving@nhs.net

E. Greco
Women's Health Research Unit, Wolfson Institute of Population Health, Queen Mary University London, London, UK

A. Dauber
Children's National Hospital, Washington, DC, USA

A. A. L. Jorge
Genetic Endocrinology Unit (LIM25), Endocrinology Division, Faculdade de Medicina da, Universidade de São Paulo (HC-FMUSP), São Paulo 01246-903, Brazil

S. Fredwall
National Centre for Rare Diseases, Unit Sunnaas & Oslo University Hospital Rikshospitalet, Oslo, Norway

A. Patterson · J. Hoover-Fong
Johns Hopkins University, Baltimore, MD, USA

J. Llerena Jr.
Instituto Nacional Fernandes Figueira, Rio de Janeiro, Brazil

K. Ozono
ISEIKAI International General Hospital, Osaka, Japan

D. Kelly · E. Muslimova · T. Reddi · R. Shediac
BridgeBio Pharma, San Francisco, CA, USA

R. Savarirayan
Murdoch Children's Research Institute, Melbourne, Australia

V. R. Sutton
Baylor College of Medicine & Texas Children's Hospital, Houston, TX, USA

***Methods*:** In October 2024, 14 experts across multiple specialties completed an online survey on current clinical practices for diagnosing HCH. A subset convened in person to discuss strategies to optimize clinical diagnostic pathways, which were subsequently refined by the collective group.
***Results*:** Age-specific diagnostic opportunities were identified. Prenatally, sonographic features of HCH may be detectable from approximately 20 weeks' gestation. Postnatally, features suggestive of HCH include a sustained fall in length/height centiles over the first 2 years of life, relative macrocephaly, neonatal seizures, and specific radiographic and neuroimaging findings. Between ages 2–3 years, a characteristic growth pattern including limb shortening and body disproportion may become evident. Neurocognitive involvement including neurodevelopmental challenges may become apparent. HCH should be considered in the differential diagnosis of idiopathic or isolated short stature. Genetic testing panels that include *FGFR3* and evaluation of short-statured parents can support diagnosis.
***Conclusion*:** Early diagnosis of HCH is achievable when age-specific key clinical and radiologic features are recognized and supported by molecular testing using appropriate diagnostic platforms. This work represents an important first step towards developing consensus-based diagnostic guidelines for HCH.

Keywords: Hypochondroplasia; Skeletal dysplasia; FGFR3; Short stature; Diagnosis

M. Cheung
Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK

Key Summary Points

Why carry out this study?

Hypochondroplasia (HCH) is a disproportionate short-statured skeletal dysplasia condition that can potentially lead to medical complications and psychosocial challenges

Early diagnosis facilitates timely implementation of condition-specific management and access to support networks, but diagnosis of HCH can be challenging and is often delayed

A multidisciplinary expert panel sought to identify early diagnostic opportunities spanning the prenatal and neonatal periods, infancy, and early childhood

What was learned from the study?

Early diagnosis of HCH is achievable through recognition of key clinical and/or radiologic features at age-specific timepoints and supported by molecular testing using appropriate diagnostic platforms

The practical strategies and pathways developed in this work represent a significant step toward the development of consensus-based diagnostic guidelines for HCH

INTRODUCTION

Hypochondroplasia (HCH, OMIM #146,000) is a skeletal dysplasia condition characterized by disproportionate short stature [1]. Gain-of-function variants in the fibroblast growth receptor 3 (*FGFR3)* gene underlie the pathophysiology and cause reduced and disordered endochondral bone growth [1–3]. The most common variants associated with HCH are c.1620C > A and c.1620C > G, both of which result in an asparagine-to-lysine substitution at amino acid position 540 (p.Asn540Lys, or N540K) localized in the tyrosine kinase domain of FGFR3 [1, 3]. HCH is transmitted in an autosomal dominant manner but in most cases the condition occurs de novo [1]. The natural history of HCH is not well characterized. There

is wide phenotypic variability [1], and comorbidities may include otitis media, language and speech developmental delay, seizures, and learning difficulties [1, 4–7]. Height is generally – 3 to – 2 SD below the mean in childhood, and due to cumulative height deficit over time and the absence of a pubertal growth spurt, heights of – 6 to – 3 SD below the mean have been reported for affected adolescents and adults [1, 8, 9].

Prevalence estimates of HCH range from 1 in 15,000 to 1 in 100,000 live births [1, 10], but the true prevalence is likely higher because of underdiagnosis and misdiagnosis [9, 10]. Although a reduction in linear growth relative to unaffected children is usually evident by age 1 year [8, 9], children with HCH are often not diagnosed until early childhood or even in adulthood; contributing factors include limited awareness of the condition, a wide phenotypic spectrum, subtle clinical and radiologic features, and a tendency to attribute growth failure to "idiopathic short stature" without further evaluation. Although there are currently no standardized diagnostic criteria for HCH, specific radiologic and clinical features associated with the condition are being investigated for their potential as diagnostic markers [11–13]. Furthermore, the increasing availability of molecular genetic testing offers the potential for earlier—and even prenatal—diagnosis; however, the allelic heterogeneity of HCH means that variant interpretation can be challenging, often leading to further diagnostic delays.

Early diagnosis of HCH facilitates timely initiation of condition-specific care, such as the use of HCH growth charts [8, 9] and the Head Circumference Height Index [13], and empowers families to connect early with support communities as well as to anticipate potential challenges, including seizures and learning differences. Rapid advances in the development of precision drug therapies for HCH [14–18] further underscore the importance of earlier diagnosis. Drawing on growing evidence and collective clinical experience, our author group has developed practical strategies and pathways that aim to improve recognition of key clinical and radiologic features associated with HCH, thereby supporting earlier—and potentially prenatal—diagnosis of this condition.

METHODS

In October 2024, 14 healthcare professionals from six countries completed an online survey on current clinical practices for diagnosing HCH. These experts were identified and selected based on their extensive (5–20 + years) experience diagnosing and managing children with skeletal dysplasia, including HCH. The medical specialties/subspecialties represented were pediatric endocrinology, medical genetics, maternal fetal medicine, pediatrics, family medicine, radiology, and genetic counseling. Key findings from the survey, which are summarized in Table 1, highlighted the need to identify opportunities for earlier diagnosis of HCH and provided the framework for ensuing discussions and for this article. A subset of the experts (10/14) convened in person to discuss strategies to optimize clinical diagnostic pathways, and insights and recommendations were subsequently refined by the collective author group in the development of this article. The survey was developed by authors R.S., E.M., D.K., and T.R. from BridgeBio Pharma Inc., with input from M.I., and the meeting was organized by BridgeBio. All survey participants are authors of this article. This article is based on previously conducted studies and expert consensus discussions and does not contain any new studies with human participants or animals performed by any of the authors; therefore, formal ethics committee approval was not required. Written consent was obtained to publish the images and clinical information described in illustrative cases.

RESULTS AND DISCUSSION

Clinical Suspicion and Pathways to Earlier Diagnosis

Early opportunities to establish a definitive diagnosis of HCH rely on recognition of age-specific radiologic and clinical features, as summarized in Fig. 1. The key early signs and symptoms that should raise suspicion of HCH are described in this section. Additionally, and importantly, a family history of short stature

Table 1 Clinical experience with HCH diagnosis: summary of key findings from a survey of the expert clinician authors

Survey question	Responses, *n* (%)
Approximately how many patients with HCH have you seen in your practice in the past 5 years?	
1–5	2 (14)
6–10	3 (21)
> 10	9 (64)
When was the diagnosis of HCH established in these patients?	
Prenatal	6 (43)
Infancy (0– ≤ 1 year)	8 (57)
Toddlerhood (1–3 years)	9 (64)
Early childhood (4–8 years)	9 (64)
Late childhood (9–11 years)	3 (21)
Adolescence (12–18 years)	1 (7)
Adulthood	2 (14)
What signs and symptoms should trigger clinical suspicion of HCH? (open-ended question, top 4 answers listed below)	
Short stature/disproportionate short stature	11 (79)
Macrocephaly	6 (43)
Neurocognitive involvement (learning difficulties, attention deficit, seizures, epilepsy)	3 (21)
Lack of spinal interpedicular widening	3 (21)
What conditions should be ruled out in the differential diagnosis of HCH? (open-ended question, top 4 answers listed below)	
Achondroplasia	11 (79)
Other skeletal dysplasia	8 (57)
SHOX gene conditions	5 (36)
Idiopathic short stature	5 (36)
At your institution, how is a diagnosis of HCH typically established?	
Clinical diagnosis only	0
Clinical diagnosis + genetic testing	4 (29)
Clinical diagnosis + radiologic diagnosis	0
Clinical diagnosis + radiologic diagnosis + genetic testing	10 (71)
Other	0
At your institution, is molecular genetic testing used to confirm a diagnosis of HCH?	
Yes	14 (100)
No	0

Table 1 continued

Survey question	Responses, *n* (%)
What modalities are used by you/your institution to screen/detect skeletal dysplasia prenatally?	
Ultrasound	13 (100)
NIPT	8 (62)
Other (fetal MRI, fetal CT)	3 (23)
What features on ultrasound raise suspicion of HCH? (open-ended question, top 3 responses listed below)	
Short limbs	11 (100)
Macrocephaly	6 (55)
Facial features	3 (27)

HCH, hypochondroplasia; *SHOX*, short stature homeobox-containing gene; NIPT, non-invasive prenatal testing; MRI, magnetic resonance imaging; CT, computed tomography

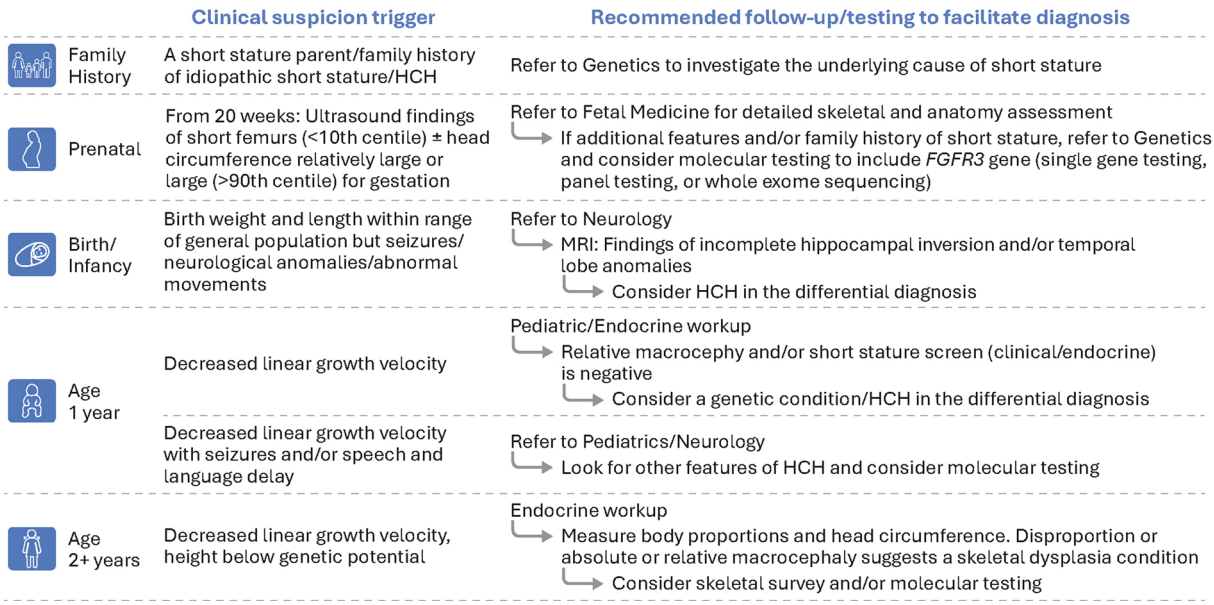


Fig. 1 Pathways to support early suspicion and diagnosis of HCH

can provide an additional clue and may facilitate earlier diagnosis.

Prenatal Period

Ultrasound findings suggestive of HCH include short femurs (< 10th centile for gestation) with either appropriate head circumference for gestational age or a large head circumference (> 90th centile for gestation) and normal bone morphology and mineralization, detectable from approximately 20 weeks gestation [12] (Fig. 2). Additional features may include widening of the femoral diaphysis-metaphysis

angle > 130° [19] and the "collar hoop" sign [20]. These features typically become more pronounced in the third trimester. However, subtle findings in the second trimester, particularly in the context of a family history of short stature, may provide an early opportunity to suspect HCH.

Birth/Infancy

At birth, children with HCH often fall within the general population ranges for length and weight. While head circumference may lie within the typical range, relative macrocephaly for length is suggestive of HCH, and this can be screened using the Head Circumference Height Index (HCH-I, defined as *height Z-score – ½head circumference Z-score*), a new diagnostic tool designed to aid identification of HCH in children [13]. An HCH-I below the cutoff of – 2 indicates substantial head-height disproportion and identified 63% of infants with HCH compared to 2.7% of the background population [13]. According to Saito et al., it is possible to detect radiographic features consistent with HCH in the neonatal period [21]. HCH may also clinically manifest as seizures in the neonatal period and in early infancy [6]. The neurologic presentation

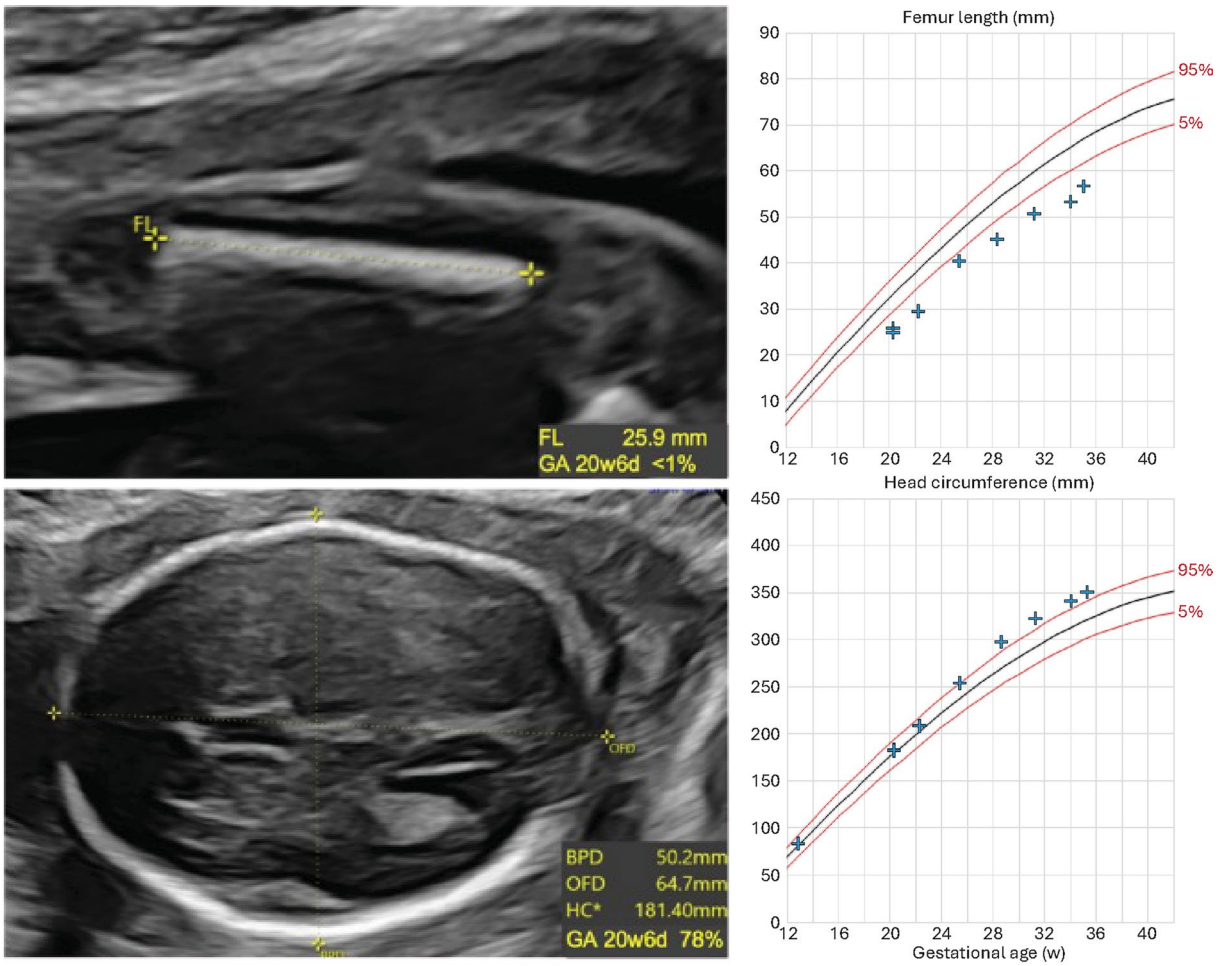


Fig. 2 Prenatal findings suggestive of HCH. Femur length (FL) was short (< 1st centile for gestational age, GA) and head circumference (HC) relatively large (78% for GA) at 20w + 6d of gestation. Growth charts for HC and FL throughout gestation show these features becoming more pronounced as pregnancy progresses. In this case, *FGFR3* on non-invasive prenatal diagnosis at 29 weeks' gestation was negative and HCH diagnosis was made postnatally

is highly variable and may include absence seizures and episodes of cyanosis, apnea, and eye deviation [1]. HCH should be considered in the differential diagnosis if incomplete hippocampal inversion (Fig. 3d and 4a and b) and/or sagittal aberrant sulcus and/or deep transverse sulcus within the temporal lobe (Fig. 4c) are evident on magnetic resonance imaging (MRI), as these findings have been reported to be highly suggestive of HCH [11]. Electroencephalography (EEG) findings may be consistent with temporal lobe epilepsy [6] and therefore should form part of the neurologic assessment; however, in some cases, the EEG findings may be normal, as illustrated by the case presented in Fig. 3.

Age 1 +year

After age 1 year, a deceleration in linear growth relative to the general population may become evident, representing an opportunity to investigate the cause of short stature. HCH should be considered in the differential diagnosis if relative macrocephaly for height (e.g., as measured using the HCH-I, for which 90% of children aged > 1 year with HCH have a score < – 2 compared to 1.9% of the background population [13]) is present and/or if a short stature screen is negative. Suspicion of HCH should be triggered if a child with short stature also presents with a history of seizures and/or other neurocognitive issues such as a speech or language delay.

Age 2 + years

After age 2 years, short stature is evident [8, 9], and body disproportionality may become increasingly apparent [8, 22]. Assessments of head circumference and body proportions (sitting height-to-standing height ratio; upper-to-lower body segment ratio) [13, 23–25] are recommended, as relative macrocephaly and body disproportion are highly suggestive of skeletal dysplasia/HCH. A skeletal survey may also reveal subtle radiologic evidence of skeletal dysplasia (Fig. 3a–c), including lack of widening of the interpedicular distances of the lumbar spine (Fig. 3c) and a relatively long fibula [1, 26], but the absence of radiographic involvement at this stage does not rule out the possibility of HCH. Indeed, because these radiographic features are non-specific, seeking them out may not be necessary as part of a diagnostic workup. Additionally, if a child with disproportionate short stature presents with mild-to-moderate neurocognitive differences or with epilepsy at this age, HCH should be suspected.

Key Differential Diagnosis

Achondroplasia (ACH): ACH is allelic to HCH with ~ 98% of cases due to *FGFR3* variants c.1138G > A and c.1138G > C (p.Gly380Arg) (G380R) [27–29]. ACH is also characterized by disproportionate short stature and macrocephaly with frontal bossing but is associated with more multisystem involvement and less phenotypic variability [29] compared to HCH. There can be substantial clinical overlap between ACH and the more severe phenotypes of HCH. The two conditions may also share similar radiologic features, but in HCH, these tend to be less pronounced; for example, narrowing of the interpedicular distance in the lumbar spine, pronounced radiolucency at the femur head ("ice cream scoop" sign), trident pelvis, and posterior scalloping of the spine are radiologic features typically seen in ACH but are generally subtle or absent in HCH [1]. Although MRI findings of incomplete hippocampal inversion and deep transverse temporal sulcus are associated with both conditions [11, 30], seizures and neurocognitive involvement are considered more common in HCH. Based on limited evidence, characteristic prenatal ultrasound findings of short femurs and macrocephaly may be detectable earlier in HCH (by 20 weeks gestation) [12] compared to ACH, in which these features are almost invariably observed after ~ 24 weeks gestation [31]. Definitive differentiation between the two conditions requires *FGFR3* genetic testing.

SHOX anomalies: Anomalies of the short stature homeobox-containing gene (*SHOX*) include point mutations, large deletions (including of the entire gene), or changes in its enhancer in the pseudoautosomal region of the X and Y chromosomes [32]. The phenotypic spectrum of *SHOX* anomalies is broad and may manifest

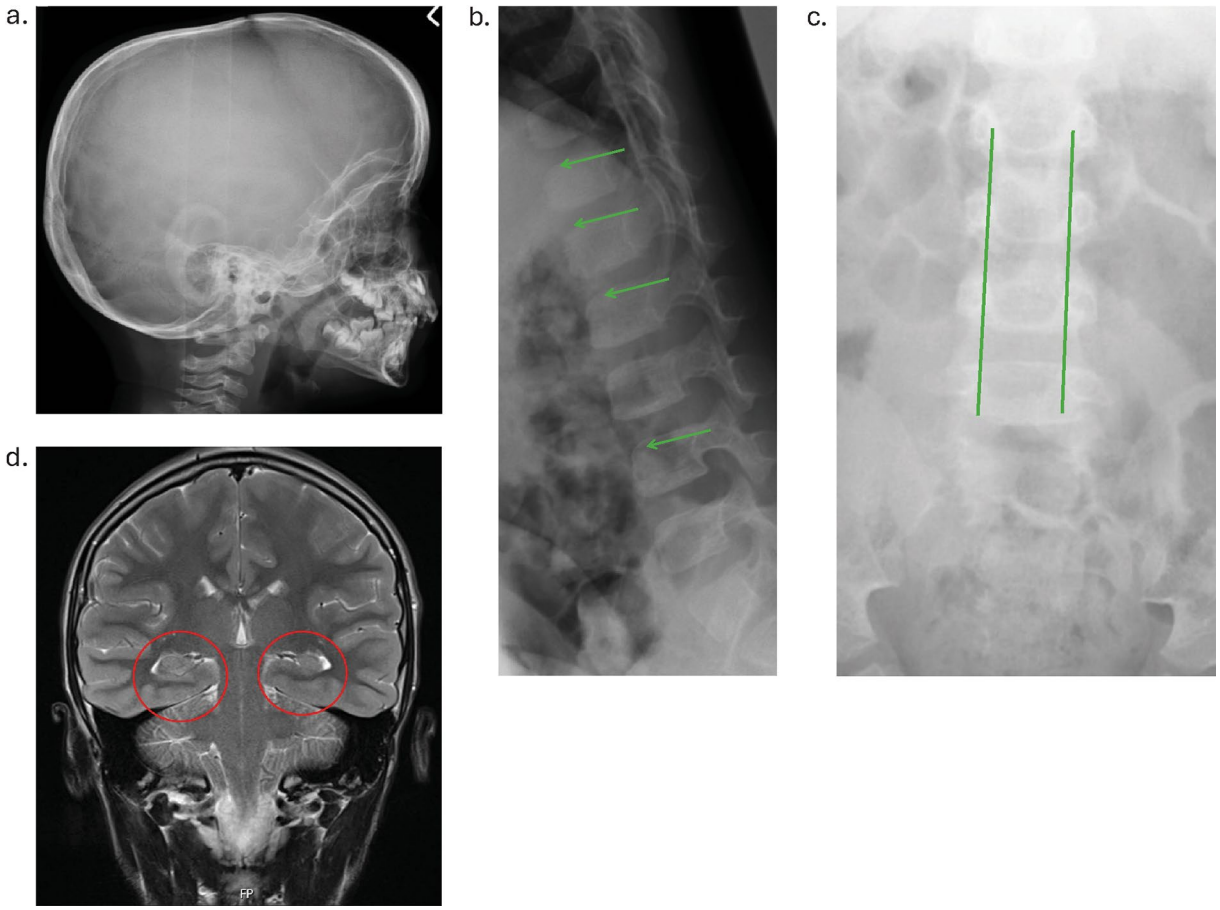


Fig. 3 Illustrative case of a delayed HCH diagnosis that underscores the importance of ongoing growth monitoring and consideration of all clinical information obtained at key diagnostic opportunity time points (from the prenatal and neonatal periods and through infancy and early childhood). A boy aged 2 years 8 months, the first child of unrelated parents, presented to pediatric endocrinology with "growth failure." His height was 82.6 (− 3.0 SD) cm, weight was 11.9 kg (2nd–9th centile), head circumference was 25–50th centile, sitting height was − 0.5 SDS, and subischial leg length was − 4.5 SDS. The mid-parental height was 25–50th centile. Body disproportion with mainly proximal limb shortening was apparent, as was joint hypermobility associated with frequent falls. In the prenatal history, unexplained short fetal long bones were detected in the third trimester. He had neonatal seizures for which he was treated with sodium valproate; a breakthrough seizure consistent with temporal lobe epilepsy seizure occurred at 11 months, although the EEG was normal. He was weaned from treatment by age 2.5 years and remained seizure-free. Issues with growth, in the face of age-appropriate development, observed prior to discharge from neurology follow-up prompted onward assessment. Skeletal survey imaging demonstrated (**a**) relative macrocephaly with prominent frontal bones; (**b**) mild posterior scalloping of the vertebral bodies; (**c**) lack of widening of the interpedicular distances in the lumbar spine. Review of the historical MR brain images (**d**) identified incomplete hippocampal inversion. *FGRF3* testing confirmed the clinical diagnosis of HCH (c.1620C > A; p.Asn540Lys; de novo). **a** Lateral skull X-ray at age 2 years 8 months show prominent frontal bones. **b** Lateral lumbar spine X-ray at age 2 years 8 months shows mild posterior scalloping of the vertebral bodies (arrows). **c** Lumbar spine X-ray at age 2 years 8 months shows that the interpedicular distances do not widen (as indicated by the parallel lines). **d** Brain MRI at age 11 months revealed incomplete hippocampal inversion. SDS, standard deviation score

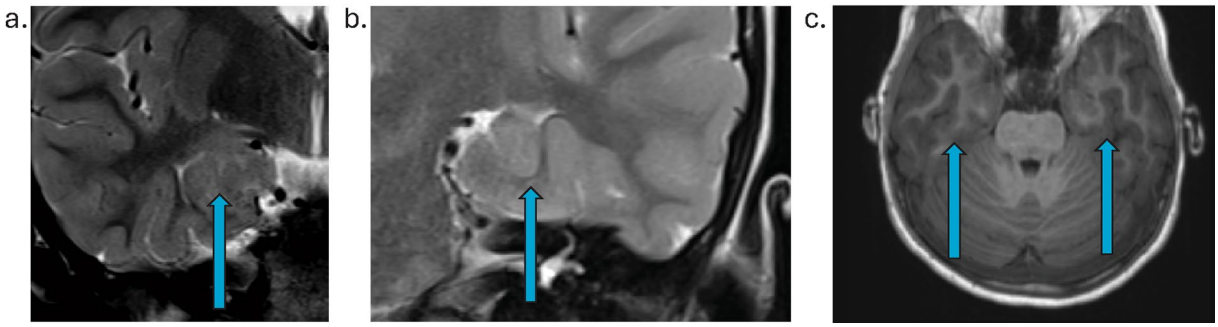


Fig. 4 Incomplete hippocampal inversion and transverse sulcus abnormalities in a child with HCH. **a** T2 coronal image temporal lobe dysgenesis including hippocampal dysgenesis. **b** T2 coronal image showing incomplete hippocampal inversion. **c** T2 axial image showing transverse sulcus abnormality

as disproportionate short stature, but mesomelic limb shortening is characteristic of *SHOX* gene conditions in contrast to the rhizomelic shortening characteristic of HCH. *SHOX* anomalies can lead to a Madelung deformity, which is not a finding in HCH. Short fourth metacarpals, cubitus valgus, and a high palate are other features of *SHOX* anomalies that are not associated with HCH. Additionally, relative macrocephaly is a common feature in children with HCH but is not a prominent finding in children with *SHOX* anomalies.

Idiopathic/isolated short stature (ISS): Children with milder phenotypes of HCH may be described as having ISS if no other cause of short stature is identified after clinical evaluation. In these cases, the correct diagnosis may be significantly delayed, as illustrated by the case in Fig. 5. A relatively large head circumference for age, an increased sitting-to-standing height ratio for age, radiologic features consistent with a distinctive skeletal dysplasia condition, and a family history of short stature (if present) may provide important diagnostic clues, as underscored by the illustrative case study. Brain MRI findings as previously described in this article and/or a history of seizures, neurodiversity, and/or neurocognitive delay in a child with disproportionate short stature should also increase suspicion of HCH.

Molecular Genetic Testing

Once clinical suspicion of HCH has been established, molecular genetic testing can be used to reach a definitive diagnosis. Approximately 70–80% of affected individuals are estimated to have the p.Asn540Lys variant [1, 33], but other *FGFR3* variants associated with HCH have been described (Table 2 and Fig. 6) [1, 3, 34–39]. The allelic heterogeneity of HCH can cause the interpretation of genetic tests to be unclear, particularly when new variants or only variants of unknown significance are identified. The increasing use of molecular genetic testing for confirmatory diagnosis underscores the importance of reporting gene variants with their assessed pathogenicity [40] and updating publicly available reference genetic databases to include all known variants.

The most appropriate genetic test will be based on several considerations including the level of clinical suspicion, availability/access, cost, and parent preferences. Close consultation with geneticists/skeletal dysplasia specialists and genetic counselors is advised in the selection and interpretation of genetic investigations and in the communication of the test results to families.

Postnatal Testing

When the suspicion of HCH is high, targeted *FGFR3* testing is recommended.

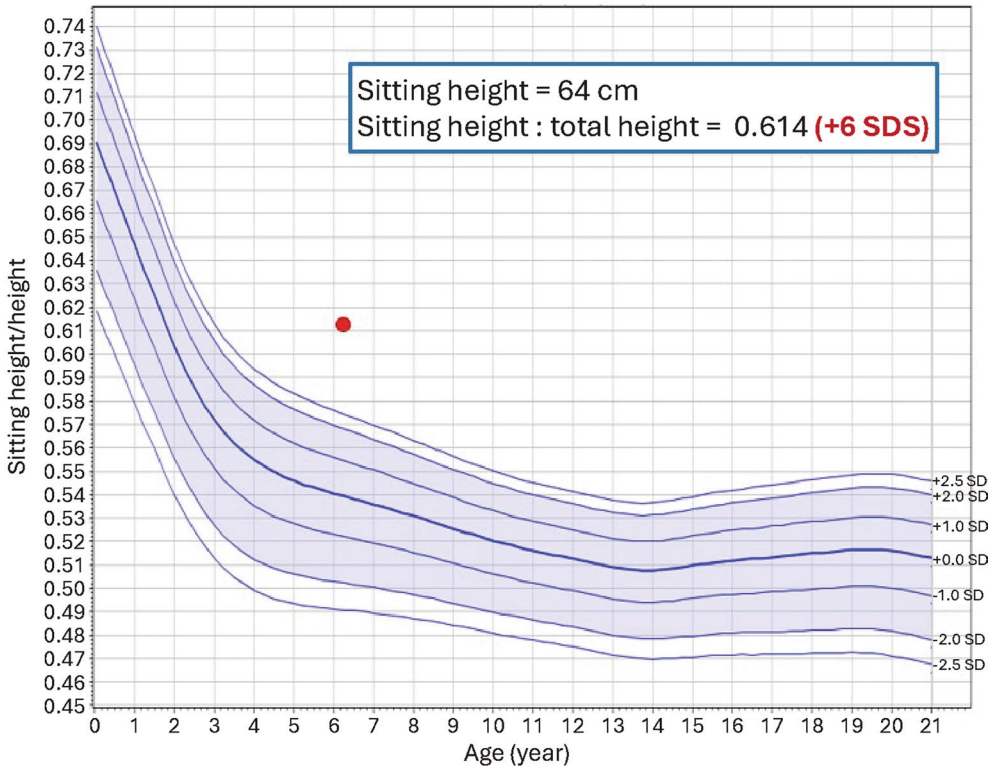


Fig. 5 Illustrative case of a delayed HCH diagnosis that underscores the importance of a full anthropometric evaluation. A 6-year-old boy presented to the clinic with short stature. His height was 104.2 (−2.3 SDS) cm, and his weight was 20 kg (BMI SDS + 1.6). The height of the father was 162 (−1.9 SDS) cm. No other remarkable clinical features were identified upon initial pediatric evaluation, and the child was referred to pediatric endocrinology with suspected idiopathic short stature (ISS). The boy underwent growth hormone simulation tests, which ruled out ISS. A comprehensive anthropometric evaluation was performed and the head circumference (95th percentile, + 1.7 SDS) and sitting height-to-total height ratio (0.614, + 6 SDS, as shown above) prompted suspicion of HCH. A subsequent skeletal survey was initially reported as normal, but the pediatric endocrinologist noted subtle narrowing of the interpedicular distance of the lumbar spine, a feature suggestive of HCH. The boy was diagnosed with HCH at age 7.4 years using a short stature gene panel. SD, standard deviation

Skeletal dysplasia or short stature gene panels that include *FGFR3* or whole exome sequencing (WES) or whole genome sequencing (WGS) may increase the efficiency of the diagnostic process when HCH is not specifically suspected. WES/WGS may be considered when more comprehensive differential diagnosis testing is required but is associated with more data complexity and analysis requirements and may not be readily available as the cost is typically higher and turnaround time is longer than for a gene panel.

Prenatal Testing

Prenatal diagnosis of HCH provides important potential benefits by enabling families and clinicians to anticipate neonatal risks, plan perinatal care, and reduce the uncertainty and anxiety associated with a prolonged diagnostic journey. Prenatal diagnosis can be achieved through both invasive (e.g., amniocentesis or chorionic villus sampling) and non-invasive sampling procedures.

Molecular testing of fetal DNA, most commonly sequencing of the *FGFR3* gene, remains critical, especially given the allelic heterogeneity

Table 2 *FGFR3* pathogenic variants associated with HCH. As new variants continue to be discovered and classified, this list may not be exhaustive. There are no clear genotype-phenotype correlations in HCH, but some associations have been reported; for example, the variant causing p.Ser348Cys is associated with a mild ACH/severe HCH phenotype, and the variant causing p.Lys650Thr is associated with the co-occurrence of acanthosis nigricans [1]

Variation	Protein change	References
c.251C > T (p.Ser84Leu)	S84L	Heuertz (2006)
c.598C > T (p.Arg200Cys)	R200C	Heuertz (2006)
c.802G > T (p.Gly268Cys)	G268C	Heuertz (2006)
c.833A > G (p.Tyr278Cys)	Y278C	Bober (2025), Heuertz (2006)
c.1024G > T (p.Gly342Cys)	G342C	Wang (2013)
c.1043C > G (p.Ser348Cys)	S348C	Bober (2025)
c.1052C > T (p.Ser351Phe)	S351F	Yao (2019)
c.1612A > G (p.Ile538Val)	I538V	Grigelioniene (1998)
c.1620C > G; c.1620C > A (p.Asn540Lys)	N540K	Bober (2025); Heuertz (2006)
c.1619A > G (p.Asn540Ser)	N540S	Mortier (2000), Thauvin-Robinet (2003)
c.1619A > C (p.Asn540Thr)	N540T	Deutz-Turlouw (1998)
c.1950G > C; c.1950G > T (p.Lys650Asn)	K650N	Bober (2025)
c.1948A > C (p.Lys650Gln)	K650Q	Bober (2025)
c.1949A > C (p.Lys650Thr)	K650T	Bober (2025)

FGFR3, fibroblast growth factor receptor 3 gene; nucleotide bases A, adenine; C, cytosine; G, guanine; T, thymine. Amino acids Arg (R), arginine; Asn (N), asparagine; Cys (C), cysteine; Gln (Q), glutamine; Gly (G), glycine; Ile (I), isoleucine; Leu (L), leucine; Lys (K), lysine; Phe (F), phenylalanine; Ser (S), serine; Thr (T), threonine; Tyr (Y), tyrosine; Val (V), valine

of HCH. A recent case report described a fetus with suspected skeletal dysplasia whose prenatal hotspot testing was negative, with definitive diagnosis only achieved postnatally through full gene sequencing [41]. However, many pregnancies in which prenatal skeletal features are subtle or borderline may not meet local criteria for invasive testing or prompt referral, leading to missed diagnostic opportunities. By the third trimester, when skeletal features may become more apparent, invasive testing is generally avoided because of the increased risk of precipitating preterm birth. Under current practice, the anticipated benefit of a prenatal diagnosis is often considered insufficient to justify that risk, so testing is usually deferred until after delivery. This balance may shift if future perinatal interventions demonstrate efficacy in improving outcomes in HCH.

Non-invasive molecular prenatal diagnosis (NIPD) analyzing cell-free fetal DNA isolated from a maternal blood sample offers a low-risk alternative [42]. However, many centers do not yet offer clinically validated NIPD for skeletal dysplasia; hence, access may be restricted or absent. Even where available, strict eligibility criteria, such as gestational age and ultrasound findings, often preclude use in cases with subtle early features. Finally, even when NIPD identifies a likely pathogenic variant, re-testing after birth should be considered if further diagnostic evaluation is clinically warranted.

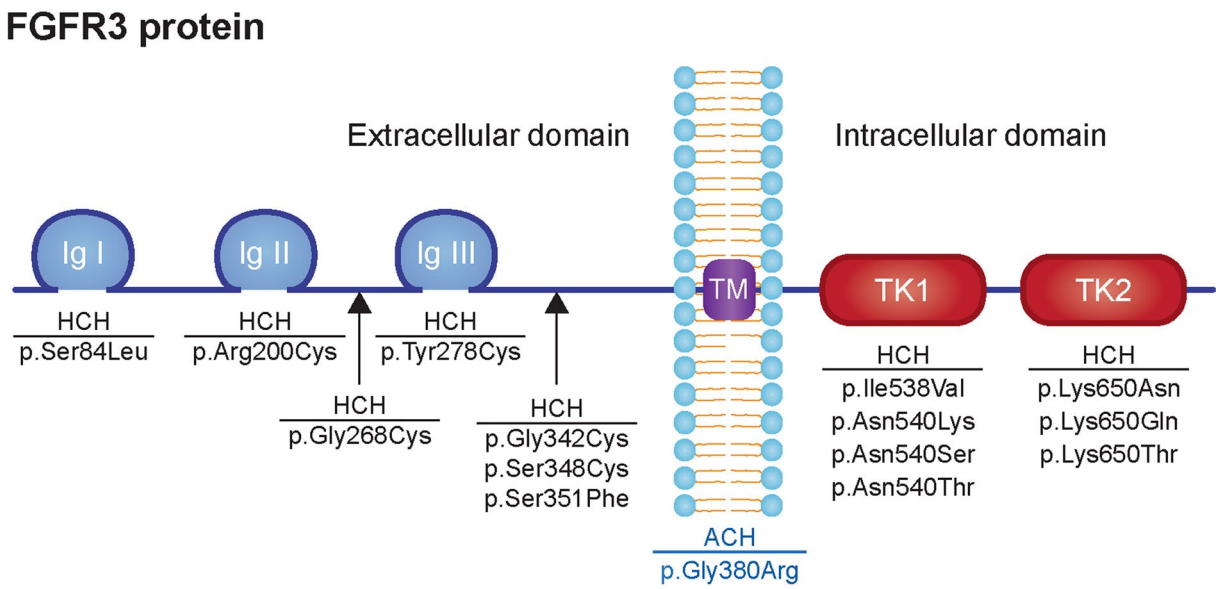


Fig. 6 Topology of FGFR3 showing variants associated with HCH. The amino acid substitutions resulting from recognized pathogenic variants in *FGFR3* are depicted. The common variant associated with achondroplasia (ACH) is also included. FGFR3: fibroblast growth factor receptor 3. Ig, immunoglobulin domain; TM, transmembrane; TK, tyrosine kinase domain; Amino acids Arg (R), arginine; Asn (N), asparagine; Cys (C), cysteine; Gln (Q), glutamine; Gly (G), glycine; Ile (I), isoleucine; Leu (L), leucine; Lys (K), lysine; Phe (F), phenylalanine; Ser (S), serine; Thr (T), threonine; Tyr (Y), tyrosine; Val (V), valine

CONCLUSIONS

HCH may be challenging to diagnose early but is feasible, including prenatally, with the recognition of key clinical and radiologic features supported by genetic testing. More natural history data and more education would better prepare clinicians to diagnose HCH earlier. Early diagnosis enables implementation of condition-specific management, facilitates access to psychosocial and educational support as needed, and empowers families to make informed decisions regarding their child's health. This work adds to the currently limited literature on HCH diagnosis and may serve as a foundation for future efforts to establish standardized HCH diagnostic guidelines.

ACKNOWLEDGEMENTS

We thank Dr. Felice D'Arco at Great Ormond Street Hospital for Children, London, UK, and Dr. Megan Baxter at Guy's and St Thomas' NHS Trust, London, UK, for providing brain MRI images.

Author Contribution. Melita Irving, Renée Shediac, Dominique Kelly, Elena Muslimova, and Tejaswini Reddi contributed to the conceptualization of this work, the design of the survey, analysis and interpretation of the survey data, and the development of the strategies and pathways described in this article. Elena Greco, Alessandra Cocca, Andrew Dauber, Alexander Augusto de Lima Jorge, Svein Fredwall, Amy Patterson, Juan Llerena Jr, Keiichi Ozono, Rui Santos, Ravi Savirirayan, V. Reid Sutton, Julie Hoover-Fong and Moira Cheung contributed to interpretation of the survey data and development of the strategies and pathways described in this article. All authors contributed to the development of manuscript drafts, provided critical revisions, and approved the final version.

Funding. The survey, study, and the journal's Rapid Service and Open Access Fees were funded by BridgeBio Pharma.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Melita Irving has received honoraria and travel-associated expenses from BridgeBio Pharma Inc., BioMarin Pharmaceutical Inc., Ascendis Pharma, and Tyra. Elena Greco and Alessandra Cocca have participated in an advisory board with BridgeBio. Andrew Dauber has served as a consultant for BioMarin, BridgeBio, Novo Nordisk, Ascendis and Pfizer, and has grant funding from Pfizer and BioMarin. Alexander Augusto de Lima Jorge has received honorarium from BridgeBio, consulting fees from Novo Nordisk, and an independent research grant from BioMarin. Svein Fredwall has participated in advisory boards and given presentations for BioMarin, Sanofi, Ascendis Pharma, BridgeBio and Novo Nordic, honoraria have been paid to his institution, and he is a principal investigator in ongoing clinical trials for Bridgebio and Ascendis Pharma. Amy Patterson has participated in advisory boards with BridgeBio. Keiichi Ozono has received speaker fees from Alexion and Kyowa Kirin. Dominique Kelly, Elena Muslimova, Tejaswini Reddi, and Renée Shediac are employees and shareholders of BridgeBio. Ravi Savarirayan has received consulting fees and grants from BioMarin, has participated on advisory boards with Ascendis and BioMarin, and has received consulting fees from BridgeBio. V. Reid Sutton is a paid consultant to BridgeBio and receives salary support from Baylor Genetics diagnostic laboratory. Julie Hoover-Fong has received grants or contracts from clinical trials from BioMarin, BridgeBio Pharma and Pfizer, has received consulting fees from BioMarin, BridgeBio, Ascendis, Tyra, and Novo Nordisk, has received honoraria from Medscape and BioMarin, and has participated on advisory boards with MCDS-Therapy Clinical Trial (unpaid), BioMarin and BridgeBio. Moira Cheung is an investigator for clinical trials for BioMarin in hypochondroplasia and achondroplasia; has received consulting fees and payment or honoraria for lectures, presentations, and manuscript writing from Bridge Bio, Tyra Scientifica and BioMarin, travel support for attending the Achon Network Meeting, participated on a Drug Medical Committee for Ascendis (unpaid), and holds a leadership or fiduciary role in the Skeletal Dysplasia Group, Skeletal Dysplasia Management Consortium and the Achondroplasia Network Meeting (all unpaid). Juan Llerena Jr and Rui Santos declare no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and expert consensus discussions and does not contain any new studies with human participants or animals performed by any of the authors, therefore formal ethics committee approval was not required. Written consent was obtained to publish the images and clinical information described in illustrative cases.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Bober MB, Bellus GA, Cheung MS, et al. Hypochondroplasia. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors., et al., GeneReviews(®) [Internet]. Seattle: University of Washington; 1999.

2. Bellus GA, McIntosh I, Smith EA, et al. A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet. 1995;10(3):357–9. https://doi.org/10.1038/ng0795-357.

3. Heuertz S, Le Merrer M, Zabel B, et al. Novel FGFR3 mutations creating cysteine residues in the extracellular domain of the receptor cause achondroplasia or severe forms of hypochondroplasia. Eur J Hum Genet. 2006;14(12):1240–7. https://doi.org/10.1038/sj.ejhg.5201700.

4. Linnankivi T, Mäkitie O, Valanne L, et al. Neuroimaging and neurological findings in patients with hypochondroplasia and FGFR3 N540K mutation. Am J Med Genet A. 2012;158a(12):3119–25. https://doi.org/10.1002/ajmg.a.35642.

5. Kim HY, Lee YA, Shin CH, et al. Clinical manifestations and outcomes of 20 Korean hypochondroplasia patients with the FGFR3 N540K variant. Exp Clin Endocrinol Diabetes. 2023;131(3):123–31. https://doi.org/10.1055/a-1988-9734.

6. Okazaki T, Saito Y, Ueda R, et al. Epileptic phenotype of FGFR3-related bilateral medial temporal lobe dysgenesis. Brain Dev. 2017;39(1):67–71. https://doi.org/10.1016/j.braindev.2016.07.004.

7. Ahmadi M, Herting A, Mueffelmann B, et al. Hypochondroplasia and temporal lobe epilepsy - a series of 4 cases. Epilepsy Behav. 2022;126:108479. https://doi.org/10.1016/j.yebeh.2021.108479.

8. Arenas MA, Del Pino M, Fano V. FGFR3-related hypochondroplasia: longitudinal growth in 57 children with the p.Asn540Lys mutation. J Pediatr Endocrinol Metab. 2018;31(11):1279–84. https://doi.org/10.1515/jpem-2018-0046.

9. Cheung MS, Cole TJ, Arundel P, et al. Growth reference charts for children with hypochondroplasia. Am J Med Genet A. 2024;194(2):243–52. https://doi.org/10.1002/ajmg.a.63431.

10. Baujat G, Hamandjian MA, Jannot AS, et al. Achondroplasia and hypochondroplasia in France: a nationwide epidemiological analysis. Orphanet J Rare Dis. 2025;20(1):555. https://doi.org/10.1186/s13023-025-04069-5.

11. Lanzafame R, D'Arco F, Cocca A, et al. Hippocampal malrotation and transverse temporal sulcus abnoramlities: sensitive and specific neuroradiological markers of hypochondroplasia. Endocr Abs. 2025;110:6.

12. Sabir AH, Sheikh J, Singh A, et al. Earlier detection of hypochondroplasia: a large single-center UK case series and systematic review. Am J Med Genet A. 2021;185(1):73–82. https://doi.org/10.1002/ajmg.a.61912.

13. Cheung MS, Lanzafame R, Low KJ, et al. The head circumference height index (HCH-I) to quantify relative macrocephaly and aid identification of hypochondroplasia in children. Am J Med Genet A. 2025;200(2):353–9. https://doi.org/10.1002/ajmg.a.64266.

14. Dauber A, Zhang A, Kanakatti Shankar R, et al. Vosoritide treatment for children with hypochondroplasia: a phase 2 trial. EClinicalMedicine. 2024;71:102591. https://doi.org/10.1016/j.eclinm.2024.102591.

15. BioMarin Pharmaceutical. Interventional study of vosoritide for the treatment of children with hypochondroplasia (CANOPY-HCH-3). ClinicalTrials.gov identifier: NCT06873035. Accessed December 11, 2025. https://clinicaltrials.gov/study/NCT06455059.

16. BioMarin Pharmaceutical. Long-term extension study of vosoritide to treat children with hypochondroplasia (CANOPY-HCH-EXT). ClinicalTrials.gov identifier: NCT07073014 Accessed December 11, 2025. https://www.clinicaltrials.gov/study/NCT07073014.

17. BioMarin Pharmaceutical. A study of vosoritide versus placebo in children with hypochondroplasia aged 0 to <36 months. ClinicalTrials.gov identifier: NCT07126262. Accessed December 11, 2025. https://clinicaltrials.gov/study/NCT07126262.

18. QED Therapeutics. An interventional study of infigratinib in children with hypochondroplasia (HCH). ClinicalTrials.gov identifier: NCT06873035. Accessed December 11, 2025. https://clinicaltrials.gov/study/NCT06873035.

19. Khalil A, Morales-Roselló J, Morlando M, et al. Widening of the femoral proximal diaphysis--metaphysis angle in fetuses with achondroplasia. Ultrasound Obstet Gynecol. 2014;44(1):69–75. https://doi.org/10.1002/uog.13339.

20. Boulet S, Althuser M, Nugues F, et al. Prenatal diagnosis of achondroplasia: new specific signs. Prenat Diagn. 2009;29(7):697–702. https://doi.org/10.1002/pd.2280.

21. Saito T, Nagasaki K, Nishimura G, et al. Criteria for radiologic diagnosis of hypochondroplasia in neonates. Pediatr Radiol. 2016;46(4):513–8. https://doi.org/10.1007/s00247-015-3518-2.

22. Grigelioniené G, Eklöf O, Laurencikas E, et al. Asn540Lys mutation in fibroblast growth factor receptor 3 and phenotype in hypochondroplasia. Acta Paediatr. 2000;89(9):1072–6. https://doi.org/10.1080/713794579.

23. Fredriks AM, van Buuren S, van Heel WJ, et al. Nationwide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders. Arch Dis Child. 2005;90(8):807–12. https://doi.org/10.1136/adc.2004.050799.

24. Hawkes CP, Mostoufi-Moab S, McCormack SE, et al. Sitting height to standing height ratio reference charts for children in the United States. J Pediatr. 2020;226:221-227.e215. https://doi.org/10.1016/j.jpeds.2020.06.051.

25. Hoover-Fong J, Semler O, Barron B, et al. Considerations for anthropometry specific to people with disproportionate short stature. Adv Ther. 2025;42(3):1291–311. https://doi.org/10.1007/s12325-024-03061-y.

26. Prinster C, Del Maschio M, Beluffi G, et al. Diagnosis of hypochondroplasia: the role of radiological interpretation. Italian Study Group for Hypochondroplasia. Pediatr Radiol. 2001;31(3):203–8. https://doi.org/10.1007/s002470000398.

27. Bellus GA, Hefferon TW, de Ortiz Luna RI, et al. Achondroplasia is defined by recurrent G380R mutations of FGFR3. Am J Hum Genet. 1995;56(2):368–73.

28. Rousseau F, Bonaventure J, Legeai-Mallet L, et al. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature. 1994;371(6494):252–4. https://doi.org/10.1038/371252a0.

29. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007;370(9582):162–72. https://doi.org/10.1016/s0140-6736(07)61090-3.

30. Manikkam SA, Chetcuti K, Howell KB, et al. Temporal lobe malformations in achondroplasia: expanding the brain imaging phenotype associated with *FGFR3*- Related skeletal dysplasias. AJNR Am J Neuroradiol. 2018;39(2):380–4. https://doi.org/10.3174/ajnr.A5468.

31. Vallin AL, Grévent D, Bessières B, et al. Foetal achondroplasia: prenatal diagnosis, outcome and perspectives. J Gynecol Obst Human Reprod. 2025;54(2):102891. https://doi.org/10.1016/j.jogoh.2024.102891.

32. Binder G, Rappold GA. SHOX deficiency disorders. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle: University of Washington; 2005.

33. Xue Y, Sun A, Mekikian PB, et al. *FGFR3* mutation frequency in 324 cases from the International Skeletal Dysplasia Registry. Mol Genet Genomic Med. 2014;2(6):497–503. https://doi.org/10.1002/mgg3.96.

34. Mortier G, Nuytinck L, Craen M, et al. Clinical and radiographic features of a family with hypochondroplasia owing to a novel Asn540Ser mutation in the fibroblast growth factor receptor 3 gene. J Med Genet. 2000;37(3):220–4. https://doi.org/10.1136/jmg.37.3.220.

35. Thauvin-Robinet C, Faivre L, Lewin P, et al. Hypochondroplasia and stature within normal limits: another family with an Asn540Ser mutation in the fibroblast growth factor receptor 3 gene. Am J Med Genet A. 2003;119a(1):81–4. https://doi.org/10.1002/ajmg.a.10238.

36. Yao G, Wang G, Wang D, et al. Identification of a novel mutation of FGFR3 gene in a large Chinese pedigree with hypochondroplasia by next-generation sequencing: A case report and brief literature review. Medicine Baltimore. 2019;98(4):e14157. https://doi.org/10.1097/md.0000000000014157.

37. Wang H, Sun Y, Wu W, et al. A novel missense mutation of FGFR3 in a Chinese female and her fetus with Hypochondroplasia by next-generation sequencing. Clin Chim Acta. 2013;423:62–5. https://doi.org/10.1016/j.cca.2013.04.015.

38. Deutz-Terlouw PP, Losekoot M, Aalfs CM, et al. Asn540Thr substitution in the fibroblast growth factor receptor 3 tyrosine kinase domain causing hypochondroplasia. *Hum Mutat*. 1998;Suppl 1: S62–65. https://doi.org/10.1002/humu.1380110122

39. Grigelioniené G, Hagenäs L, Eklöf O, et al. A novel missense mutation Ile538Val in the fibroblast growth factor receptor 3 in hypochondroplasia. Mutations in brief no. 122. Online. Hum Mutat. 1998;11(4):333.

40. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24. https://doi.org/10.1038/gim.2015.30.

41. Xie H, Chen Y, Xiong F, et al. Failure to diagnose hypochondroplasia by prenatal diagnosis: a case report. BMC Pediatr. 2023;23(1):100. https://doi.org/10.1186/s12887-023-03917-2.

42. Vivanti AJ, Costa JM, Rosefort A, et al. Optimal non-invasive diagnosis of fetal achondroplasia combining ultrasonography with circulating cell-free fetal DNA analysis. Ultrasound Obstet Gynecol. 2019;53(1):87–94. https://doi.org/10.1002/uog.19018.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.