**Article:**
Dauber, A., Cheung, M.S., Hoover-Fong, J. et al. (2026) Diagnosis of hypochondroplasia: international Delphi consensus recommendations. Nature Reviews Endocrinology. ISSN: 1759-5029

https://doi.org/10.1038/s41574-026-01296-z

# Diagnosis of hypochondroplasia: International Delphi consensus recommendations

**Authors:** Andrew Dauber,[1,2] Moira S Cheung,[3] Julie Hoover-Fong,[4] Svein Otto Fredwall,[5,6] Moeenaldeen AlSayed,[7,8] Silvio Boero,[9] Alistair D Calder,[10] Valérie Cormier-Daire,[11,12] Virginia Fano,[13] Takuo Kubota,[14] Philip Kunkel,[15] Juan Llerena Junior,[16] Mohamad Maghnie,[17,18] Geert Mortier,[19] Noriyuki Namba,[20] Amaka C Offiah,[21,22] Keita Okada,[23] Sérgio B. Sousa,[24,25] Ravi Savarirayan[26]

**Author affiliations:**

[1]Division of Endocrinology, Children's National Hospital, Washington, DC 20010, USA; [2]Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC 20052, USA; [3]NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London, UK; [4]Department of Genetic Medicine, Greenberg Center for Skeletal Dysplasias, Johns Hopkins School of Medicine, Baltimore, MD, USA; [5]Norwegian Centre for Rare Diseases, unit Sunnaas, Nesodden, Norway; [6]Oslo University Hospital, Oslo, Norway; [7]Department of Medical Genomics, Center for Genomic Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [8]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; [9]Istituto Giannina Gaslini, Genoa, Italy; [10]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [11]Reference Center for Skeletal Dysplasia, Hôpital Necker Enfants Malades AP-HP, Paris, France; [12]Paris Cité University, INSERM UMR 1163, Imagine Institute, Paris, France; [13]Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan, Autonomous City of Buenos Aires, Argentina; [14]Department of Pediatric Nephrology and Metabolism, Osaka Women's and Children's Hospital, Osaka Prefectural Hospital Organization, Izumi, Japan; [15]Department of Neurological Surgery, University Medical Center Hamburg-Eppendorf,

Hamburg, Germany; [16]Centro de Genética Médica, FIOCRUZ, Rio de Janeiro, Brazil; [17]Paediatric Endocrinology Unit, Department of Pediatrics, IRCCS Istituto Giannina Gaslini, 16147 Genoa, Italy; [18]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, 16132 Genoa, Italy; [19]Center for Human Genetics, University Hospital Leuven, Leuven, Belgium; [20]Division of Pediatrics and Perinatology, Faculty of Medicine, Tottori University, Yonago, Tottori, Japan; [21]Division of Clinical Medicine, University of Sheffield, Sheffield, UK; [22]Department of Radiology, Sheffield Children's NHS Foundation Trust, Sheffield, UK; [23]Department of Orthopedic Surgery, The University of Tokyo Hospital, Tokyo, Japan; [24]Medical Genetics Department, Hospital Pediátrico de Coimbra, Unidade Local de Saúde de Coimbra, Coimbra, Portugal; [25]Faculty of Medicine, University of Coimbra, Coimbra, Portugal [26]Murdoch Children's Research Institute, Royal Children's Hospital Melbourne, University of Melbourne, Parkville, Victoria, Australia

**Co-first authors:** Andrew Dauber and Moira Cheung contributed equally to this work.

**Corresponding author:** Ravi Savarirayan MB, BS, MD, Murdoch Children's Research Institute, University of Melbourne, Parkville, Australia 3054

ravi.savarirayan@mcri.edu.au

## Abstract

Hypochondroplasia is a skeletal dysplasia caused by pathogenic variants in *FGFR3* and characterised by disproportionate short stature and relative macrocephaly. Diagnostic uncertainty remains common, particularly in early childhood and in individuals with mild or atypical presentations, leading to delayed diagnosis, inconsistent management, and challenges in counselling and care planning. Individuals may be affected by medical complications and psychosocial impacts, and have unmet needs for multidisciplinary care.

To address these unmet needs, an international, multidisciplinary panel of experts and patient representatives convened to develop consensus-based diagnostic recommendations using a modified 2-stage Delphi approach, with a predefined consensus threshold of 70% of respondents rating statements ≥70 (on a scale of 0 to 100). The panel integrated clinical, anthropometric, radiographic, neuroimaging and genetic criteria to define diagnostic categories that can be applied across diverse healthcare settings globally. Major and minor diagnostic criteria are proposed, alongside guidance on the appropriate use of molecular testing, radiographic evaluation, and brain magnetic resonance imaging.

These recommendations provide a practical framework to help standardise timely and accurate diagnosis of hypochondroplasia in clinical practice and research.



### Keywords

Skeletal dysplasia, short stature, *FGFR3*, macrocephaly

## Introduction

Hypochondroplasia (HCH) is a rare genetic skeletal dysplasia caused by pathogenic variants in *FGFR3*.[1] Although there are multiple characteristic physical and radiographic signs associated with HCH, the broad spectrum of phenotypic variability can hinder clinical identification.[2-5] The most prevalent signs associated with HCH are disproportionate short stature and relative macrocephaly.[1,6,7] Height in HCH can lie within the norms for the average-stature population.[8,9] Additionally, the majority of individuals with HCH have a head circumference within the population norms although it is increased relative to their overall stature.[6,9] Estimates of prevalence range from approximately 1 in 15,000 to 1 in 75,000 live births,[2,10] but the true frequency is probably higher because milder cases may be undiagnosed.[10]

Severe HCH can phenotypically overlap with the allelic condition achondroplasia, but skeletal features tend to be more subtle in HCH.[1] Historically, this led to rare cases of misdiagnosis in some patients with more severe HCH,[11] although this is becoming less common as our understanding of both conditions has improved, and genetic testing techniques have developed and become more widespread.[1]

The pathophysiology of HCH is related to the role of the FGFR3 protein as a physiological negative regulator of skeletal growth.[12,13] In HCH, gain-of-function variants in different domains of *FGFR3* leads to functional inhibition of natriuretic peptide receptor-B and reduced activity of C-type natriuretic protein, a key positive regulator of endochondral bone development.[12-14]

Diagnostic criteria for HCH were initially proposed by Hall and Spranger in 1979, who noted its autosomal dominant inheritance, characteristic but non-unique radiologic pattern, and frequent macrocephaly.[15] Subsequent reports highlighted the high clinical and radiological variability of HCH and the difficulty of applying these features to distinguish HCH from idiopathic short stature and from other forms of skeletal dysplasia.[2-4,16,17] Many of the initially

proposed criteria were developed prior to the availability of molecular diagnosis and thus the cohorts likely represented a genetically heterogeneous group of patients. The genetic causes of HCH are now relatively well characterised, with numerous HCH-associated variants identified within *FGFR3*.[1,17] The availability of genetic testing has helped to provide molecular confirmation of HCH for many patients, and helped to differentiate from other skeletal dyplasias.[5,17,18] However, in a substantial minority of patients with clinically defined HCH (30–40% in some reports), no identifiable *FGFR3* variants have been found.[5,17] This may be due to historical limitations of the genetic testing performed in these cohorts, and in some individuals, due to misdiagnosis.

The impact of HCH on individuals extends beyond reduced stature.[1,16,19] Complications can include orthopaedic issues such as genu varum, lumbar lordosis, spinal deformity and spinal stenosis (which in rare cases may require surgical intervention), as well as ENT and respiratory complications.[1-3,15] Cases of foramen magnum stenosis have also been reported.[1,20] Neurodevelopmental and neurological complications of HCH are also increasingly recognised. These can include learning difficulties, attentional disorders, mild intellectual disability, temporal lobe dysgenesis, and epilepsy.[1,8,20] HCH is also associated with a substantial psychosocial burden, resulting from functional limitations and limb disproportion.[19] Together, this array of symptoms and impacts of HCH often requires a coordinated multidisciplinary approach.[19]

Early and accurate diagnosis of HCH offers opportunities for monitoring and intervention, and for the timely delivery of developmental support and genetic counselling. In addition, several growth-modifying therapies are undergoing clinical evaluation in HCH.[21-23] If approved for use, these have the potential to offer benefits to individuals following diagnosis.[24] However, HCH remains frequently under- or misdiagnosed.[10,16,24] Clinical presentation is variable, radiographic signs are age dependent and often subtle in infancy.[2-4,25] Phenotypic overlap with other causes of short-limbed or disproportionate short stature,

including idiopathic short stature (ISS), achondroplasia, SHOX-related dysplasia and other metabolic or syndromic conditions, further complicates accurate diagnosis.[1,5,17,18]

There is a paucity of large epidemiological studies of individuals with HCH;[10] several small cohort studies have been published, but with diverse methodological approaches.[2,8,24] Recent developments in recognition and diagnosis of HCH include neonatal imaging criteria, HCH-specific growth charts[9] and the Head Circumference Height Index (HCH-I; used to quantify relative macrocephaly).[6] However, these developments have not yet been widely implemented.

There is therefore a need for diagnostic recommendations that integrate clinical, radiographic, and genetic approaches. This is required to improve recognition and facilitate earlier diagnosis in individuals with HCH, and to support optimal care which may in future include precision treatments currently in development.[21,22] To this end, the International Achondroplasia Forum (IAF), an independent network of specialists managing achondroplasia and related conditions, used a modified Delphi process to consolidate their insights and expertise, alongside those of other experts in HCH, into a set of diagnostic recommendations. The outcomes of that Delphi process are reported here.

# Methods

## Overview of Delphi methodology

A core group of five HCH experts (AD, MSC, SOF, JHF, RS) was established to lead the Delphi process.

Experts from the International Achondroplasia Forum steering committee (AD, BF, EG-N, GM, JCL, JH-F, KO, KM, MS, MI, MA, MM, PK, RS, SS, SB, SOF, TB-O, VC-D, VF), additional experts with specific clinical, molecular and/or global expertise in HCH (AC, ACO, DPC, MC, NN, TK) and patient representatives (JA, KR, MS, VK) were approached to be part of the insight gathering group and subsequent Delphi panel.

Expert IAF Steering Committee Members and the additional clinical/molecular experts were invited to participate in the Delphi process; those completing the Delphi process are included as authors. Patient representatives were included in the Delphi discussions to provide perspective but were not included as part of the Delphi voting.

Members of the different groups involved in the process are shown in **Supplementary Table S1**.

## Literature search

An initial literature search on PubMed was conducted using the search term "hypochondroplasia" and limited to English-language publications, published from 2001 onwards. The resulting publications were screened for studies/analyses that included at least ten individuals with HCH. These references, along with any additional key references identified by the core group, were shared with the Delphi panel members prior to voting **(Supplementary Table S2)**.

## Development of initial statements

An insight-gathering step was conducted in August 2025. Based on the literature search, core themes and areas of interest relating to the diagnosis of HCH were identified and shared with the insight gathering group. This was a non-anonymised step in which experts and patient representatives were asked to provide their perspectives and share their experiences. Based on this feedback, preliminary Delphi statements were developed by the core group at a face-to-face meeting on 19 October 2025.

Additional statements relating to the radiographic criteria for HCH diagnosis were developed with input from two radiologists with a joint >35 years' experience in HCH and other skeletal dysplasia (ACO, AC) at an online meeting on 2 December 2025.

## Delphi voting round 1

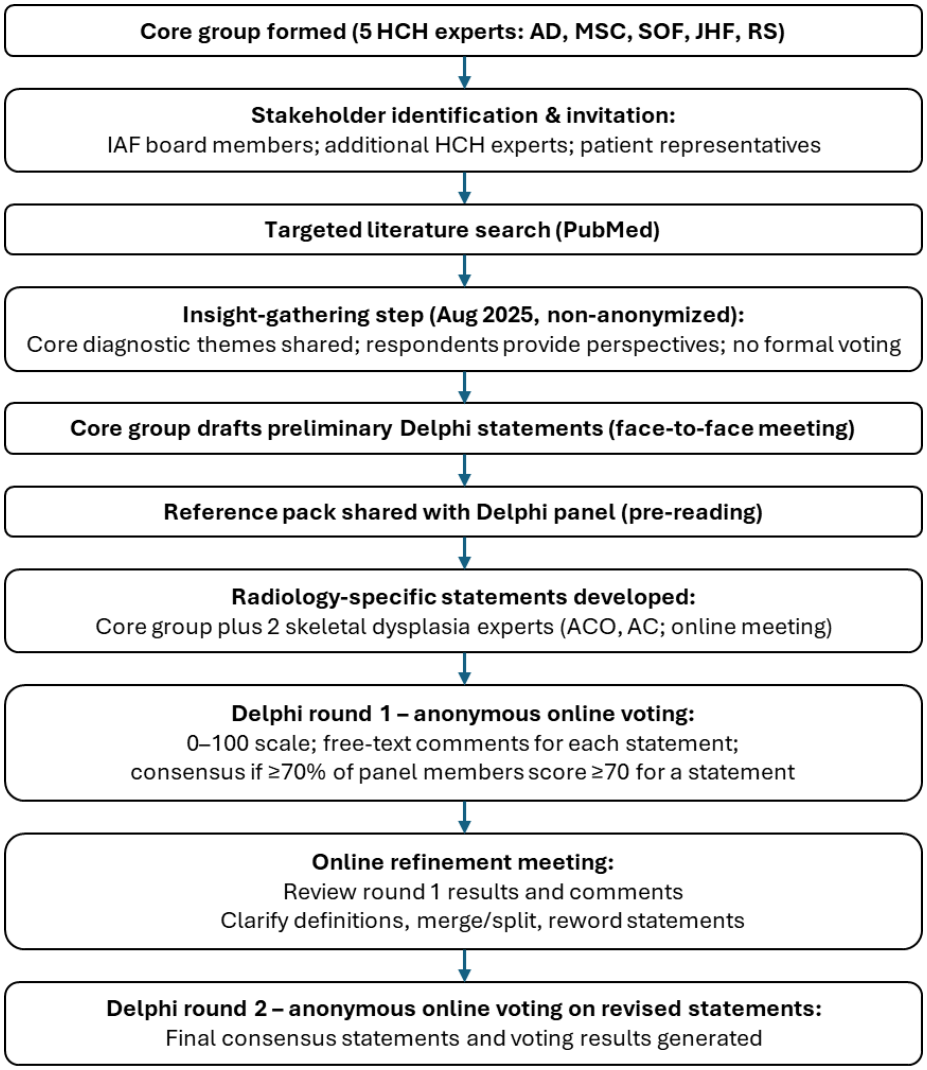
Statements were shared with the Delphi panel for anonymised voting using an online voting system. Panel members were requested to vote using a sliding scale: 0 (completely disagree) to 100 (completely agree). Members were also asked for any additional comments, which could be provided as free text.

Consensus was considered to have been reached if at least 70% of panel members scored a statement with at least 70% agreement; levels of consensus and agreement are shown to help provide context.

## Online meeting and Delphi voting round 2

Following the first round of voting, an online meeting was held on 11 December 2025 to refine criteria and address any concerns and comments from the Delphi panel. This was followed by a second round of anonymised voting to gain input on the updated statements. The modified Delphi process is shown in **Figure 1.**

**Fig. 1|Modified Delphi process**




HCH, hypochondroplasia

# Recommendations and discussion

## Consensus building and Delphi panel results

In the first round of voting, 15 statements were shared with the Delphi panel. In total, 19 responses were received (17 experts, two patient representatives) and all statements gained consensus. The full list of statements, associated diagnostic criteria and voting results from round one of Delphi voting can be seen in **Supplemental Tables S3 and S4**. MC and AD selected areas to focus on based on the free text comments received from the Delphi panel as part of the voting process as well as opening discussion of all statements during the

online meeting. As a result, one statement was removed, one statement was added, and six statements updated. A second round of anonymised voting was then conducted. 20 responses were received (19 experts, one patient representative). The statements and results from this final round of voting are reported here.

These recommendations are intended to support a phenotype-led diagnostic approach, with genetic testing used to confirm and refine diagnosis where available. Initial diagnostic assessments may occur outside specialist centres; these recommendations are intended to support both general and expert clinical settings.

## Diagnosis of HCH

**R1.** Accurate and early diagnosis of HCH is important to facilitate appropriate monitoring, management and potential treatment (mean score: 98; proportion scoring ≥70: 100%)

**R2.** A **definitive diagnosis of HCH** can be made in the presence of a pathogenic or likely pathogenic variant in *FGFR3* plus a combination of phenotypic criteria. As detailed in **Box 1** (mean score: 93; proportion scoring ≥70: 95%)

**Box 1.** Scenarios leading to a definitive diagnosis of hypochondroplasia (HCH)

1. Pathogenic variant in *FGFR3* plus at least 1 major criterion
2. Pathogenic variant in *FGFR3* plus at least 3 minor criteria
3. Likely pathogenic variant in *FGFR3* plus at least 2 major criteria
4. Likely pathogenic variant in *FGFR3* plus 1 major criterion and at least 3 minor criteria

**Box 2.** Major and minor criteria for hypochondroplasia (HCH) diagnosis

**Major criteria for HCH diagnosis**

1. Disproportionate short stature for age and sex, defined as both:
   Height or length below −2 SD* for age and sex
   **AND**
   Evidence of disproportion, defined as one of the following:
   i. Sitting height to standing height ratio >2 SD*
   ii. Upper-to-lower body segment ratio >2 SD*
2. Relative macrocephaly with no alternative cause, defined as a Head Circumference Height Index (HCH-I)** below a score of −2
3. The major radiographic criterion – **Table 1**
4. Characteristic brain MRI finding in the temporal lobes defined as at least one of the following:
   a. Temporal lobe dysgenesis including hippocampal dysgenesis
   b. Sagittal aberrant sulcus and/or deep transverse sulcus within the temporal lobe
   c. Incomplete hippocampal inversion
5. Family history in a first-degree relative who meets the criteria for a definitive diagnosis of HCH

**Minor criteria for HCH diagnosis**

1. Short stature defined as a height or length below −2 SD* for age and sex**
   AND/OR
   Height or length below genetic potential defined as a height or length >2 SD* below mid-parental target height**
2. Evidence of body disproportion, defined as one of the following**:
   a. Sitting height to standing height ratio >2 SD*
   b. Upper-to-lower body segment ratio >2 SD*
3. Absolute macrocephaly defined as a head circumference >2 SD*, with no alternative cause
4. Clinical evidence of changes in the upper limbs consistent with hypochondroplasia (rhizomelia, limited arm extension and/or broad hands)
5. Asymptomatic ventriculomegaly and/or increased extra-axial fluid
6. History of at least one afebrile seizure
7. History of ADHD, diagnosed learning difficulties or executive function abnormalities
8. At least two minor radiographic criteria – **Table 1**

9. Family history: a first-degree relative who meets the suspected HCH diagnostic criteria (see below)

*Standard deviation of appropriate unaffected background population distribution. **HCH-I = height Z-score minus ½ head circumference Z-score.[6] MRI, magnetic resonance imaging

**If the patient meets major criterion 1 (disproportionate short stature), minor criteria 1 and 2 may not be used

**Table 1.** Major and minor radiographic criteria for hypochondroplasia (HCH) diagnosis by age group (neonate/infant and ≥12 months old)

| **Age group** | **Major radiographic criterion for HCH diagnosis** | **Minor radiographic criteria for HCH diagnosis** |
|---|---|---|
| Neonates and infants (<12 months old): | No major criteria | 1. Short sciatic notches<br>2. Short, relatively broad long bones<br>3. Broad femoral necks<br>4. Horizontal acetabular roofs<br>5. Small iliac bones, with reduced diameter in craniocaudal and transverse directions |

| | | |
|---|---|---|
| Individuals ≥12 months old | Radiological signs of progressive lumbar canal stenosis (L1–L4), defined as:<br>• On anteroposterior view of lumbar spine: Lack of normal widening of the L1 to L4 interpedicular distance<br>**AND**<br>• On lateral view of lumbar spine: L1 to L4 progressive lumbar pedicle shortening | 1. Relatively long distal fibulae, defined by position of lower fibular growth plate at or below level of ankle mortice (lower border of lower tibial epiphysis)*<br>2. Small iliac bones, with reduced diameter in craniocaudal and transverse directions<br>3. Short and/or broad femoral necks<br>4. Short, relatively broad long bones; metaphyses may appear flared<br>5. Prominent sites of muscular insertion, e.g., at deltoid insertion in humeral diaphysis<br><br>**In children 3 years and older, to qualify for minor radiographic criteria, criterion #1 must always be met.* |

Clinical features of HCH

The major and minor clinical and radiographic criteria have been developed to reflect data from published cohort studies and the Delphi panel's experience of which signs and symptoms of HCH are most characteristic of and specific to HCH when seen in combination. Unless stated, these criteria can be applied from birth onwards. The most commonly reported phenotypic feature among cohorts of individuals with HCH is disproportionate short stature, but with broad phenotypic variability, including individuals with milder forms where these phenotypic characteristics can overlap with the background population distribution.[5,9,15,26] The ratio of sitting height to standing height (or upper body segment to

lower body segment, in neonates and infants) is markedly different for individuals with HCH compared with the average-stature population, with clear differentiation apparent from birth.[8] This warrants its inclusion both as a component of a major criterion, and as a separate minor criterion.

Relative macrocephaly is another core feature. Although absolute macrocephaly shows strong predictive value for HCH,[7] justifying its inclusion as a minor criterion, multiple cohorts have shown that head circumference is often normal or only modestly raised in absolute terms but clearly increased when expressed relative to height.[1,2,7,15,16] The recently developed Head Circumference Height Index (HCH-I) formalises head–height disproportion as height Z-score – ½ head circumference Z-score. The HCH-I discriminates HCH from population controls with good sensitivity and specificity in infants and children. Indeed, when applied to a large average-stature cohort of children (n=4620), only 2.4% had an HCH-I score below −2 compared with 78% of children with HCH (n=364). This improved for those >12 months where 1.9% of the average-stature compared with 90% of HCH children had an HCH-I score below −2. [6] These findings support its use as an objective major criterion.

Evaluation of changes in the upper limbs, consistent with hypochondroplasia can include: a reduced arm-span-to-overall-height ratio,[2,5] rhizomelia[2,3] (assessed from skeletal radiography and defined as a radial/humeral length ratio greater than 2 standard deviations above the population norm),[27] assessment of reduced range of movement at the elbows,[1-3] and brachydactyly (broad, short hands).[2,3,17,18]

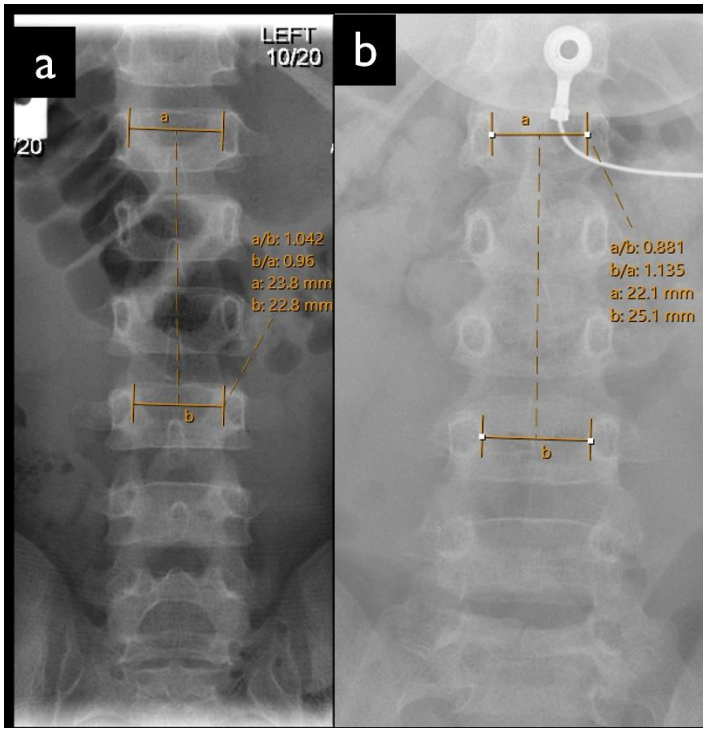
In addition to the signs and symptoms of HCH classified as major and minor criteria, additional phenotypic characteristics are present in some individuals with HCH. These may include: lumbar lordosis,[3,15,26] tibial bowing,[1,9] genu varum,[2,18,24] spinal stenosis,[18] foramen magnum stenosis,[1,20] and hydrocephalus (reported but rare in HCH).[2,20] Symptoms of spinal stenosis may need intervention more commonly in adults with HCH than in children with HCH, in whom it rarely causes problems.[1]

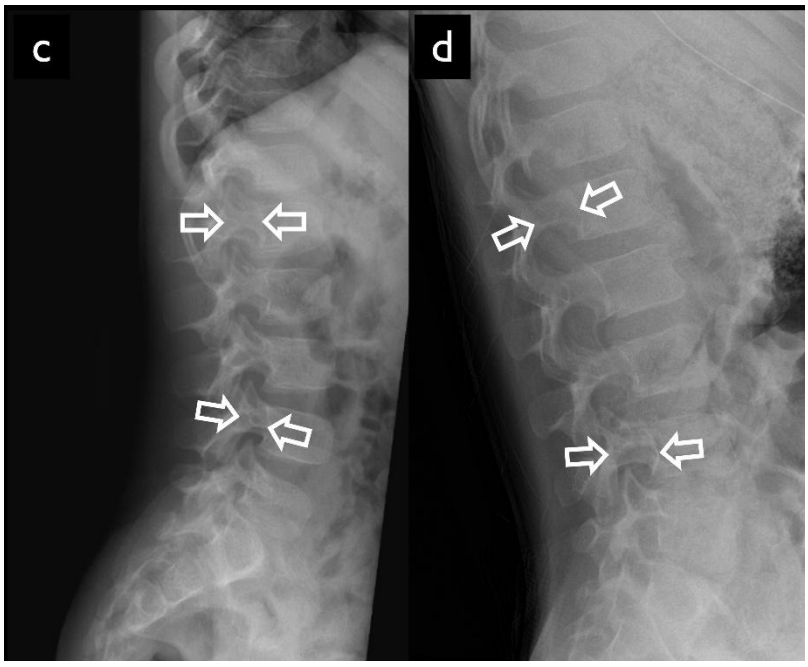
Radiographic features of HCH

Radiographically, failure of the normal cranio-caudal increase in lumbar interpedicular distance, secondary to short lumbar pedicles, is recognised as the most characteristic spinal feature of HCH and underpins the major radiographic criterion in children aged ≥12 months.[2,3,15,26] This is often seen in conjunction with posterior vertebral scalloping,[3,15] but this feature was not considered specific enough to be included as a criterion. Figure 2 shows examples of these radiographic features.

Radiographic and neuroimaging findings should be interpreted in the context of age, clinical presentation, and available expertise. It should be noted when interpreting radiographic assessments of neonates, infants or young children with suspected HCH, that findings meeting the major criterion may develop as the child ages. Because of this, in individuals who fail to meet the major criterion, or where equivocal results are observed, radiographic assessment can be repeated one year later, or after the child's third birthday (whichever is later).

**Fig. 2|Radiographs showing key features of hypochondroplasia (HCH).**
**a,b.** Anteroposterior view of lumbar spine (**a**) in a 5-year-old boy with a c.1620C>A variant in *FGFR3* and corresponding view (**b**) in a healthy 5-year-old boy without HCH. Callipers highlight the lack of normal widening of the L1 to L4 interpedicular distances in HCH, with the interpedicular distance at L1 wider than at L4. **c,d.** Lateral view of lumbar spine (**c**) in a 7-year-old girl with a c.1620C>A variant in *FGFR3* and corresponding view (**d**) in a healthy 7-year-old boy without HCH. Arrows highlight L1 to L4 progressive lumbar pedicle shortening in HCH.




In neonates and infants, lumbar changes are often subtle or absent, hence no radiographic signs were considered to meet the threshold to be included as a major criterion for HCH diagnosis. However, a separate set of radiographic signs has been proposed, all of which showed sufficient discriminatory performance in neonates with HCH-associated pathogenic *FGFR3* variants to form the basis for the neonatal minor radiographic criteria.[25] In older

children and adults, additional radiographic features that are highly characteristic, though individually non-specific comprise the minor radiographic criteria.[1-3,15,26]

Brain MRI and neurocognitive features of HCH

The major criterion related to brain magnetic resonance imaging (MRI) findings reflects accumulating evidence that temporal lobe malformations are common in HCH. In a series of 13 patients with HCH and pathogenic variants within *FGFR3* leading to the p.N540K substitution, temporal lobe dysgenesis with abnormal transverse temporal sulci, hippocampal malrotation or dysplasia, and abnormal configuration of the temporal horns and adjacent white matter were observed in all eight individuals with MRI assessments.[20] Brain MRI is not required for an HCH diagnosis if the patient fulfils the other diagnostic criteria, but should be performed if clinically indicated, such as in a child with seizures, developmental concerns, or increasing head circumference.

Brain MRI findings of asymptomatic ventriculomegaly and/or increased extra-axial fluid have been observed in patients with HCH and are therefore included as a minor criterion.[2,20] Although hydrocephalus has been reported in HCH patients with the p.N540K substitution,[2,20] this is a rare complication.

Across several HCH cohorts, seizures (often focal or temporal lobe in origin), learning disabilities, specific learning disorders, attention difficulties and broader executive function problems have been reported at higher frequency than in the general population.[2,19,20]

Clearly more study is needed, but these observations prompted the inclusion of the minor criteria relating to a history of afebrile seizures and to ADHD, diagnosed learning difficulties or executive dysfunction.

**R3.** If a patient does not meet the criteria for a diagnosis of definitive HCH, consider performing additional evaluations that will increase the chances of reaching a specific diagnosis (mean score: 97; proportion scoring ≥70: 100%)

The goal of performing additional evaluations should be to help guide a diagnosis, so that appropriate management and care can be provided. Based on clinical judgement, and guided by results from previous assessments, these evaluations may be clinical, radiographic or genetic. In the case of clinical and radiographic assessments, it should be noted that some signs of HCH may become more apparent as children age (see R7 and associated discussion). In individuals where certain assessments have not previously been performed, additional assessments may help to confirm a diagnosis, either of HCH or of another skeletal dysplasia. This may occur where initial diagnostic assessments are performed outside specialist centres.

If there is a strong clinical suspicion of HCH, but previous genetic assessments have not identified an HCH-associated variant within *FGFR3* (**Table 2**), a clinician may consider the possibilities of technical/lab error affecting the initial genetic findings or incomplete genetic testing. Relevant *FGFR3* variants may have been missed in different scenarios: genetic analysis only focused on specific pathogenic variants or specific exons; exons or regions of the gene included in the test but not well covered; rare deep intronic variants not assessed in routine testing.[28] Case-by-case discussion with a reference skeletal dysplasia genetics laboratory is important. Repeating genetic testing and/or undertaking more comprehensive genetic analysis may be considered. This should also include the confirmation that genetic testing for HCH differential diagnoses has been performed. This may include *SHOX*-deletions testing, or skeletal dysplasia multigene next-generation sequencing panel and/or whole-exome/genome sequencing to confirm whether variants are present in non-*FGFR3* genes that may have overlapping phenotypes with HCH (e.g., *SHOX, ACAN, GNAS, NPR2, COL2A1, IHH*).[1,29-31]

**Table 2.** Selected Pathogenic (P) and Likely Pathogenic (LP) *FGFR3* variants related to hypochondroplasia (HCH).

| **Nucleotide Change [exon number] (NM_000142.5)** | **Protein Change [Protein domain] (NP_000133.1)** | **ACMG class-ification** | **Key Citations** | **Comments (genotype-phenotype, #ClinVar ID, variant frequency)** |
|---|---|---|---|---|
| **c.251C>T** [exon 3] | **p.Ser84Leu** [IgI] | **P** | Heuertz et al. (2006)[32] Hasegawa et al. (2014)[5] Andrade et al. (2022)[33] Plachy et al. (2023)[34] MacCarrick et al. (2024)[35] | #16358 Moderate phenotype[32] |
| **c.598C>T** [exon 5] | **p.Arg200Cys** [IgII] | **LP** | Heuertz et al. (2006)[32] Almeida et al. (2009)[18] Hasegawa et al. (2014)[5] | #287276 |
| **c.667C>T** [exon 6] | **p.Arg223Cys** [IgII] | **LP** | Mejia et al. (2020)[36] Andrade et al. (2022)[33] MacCarrick et al. (2024)[35] | #838879 |
| **c.791C>T** [exon 7] | **p.Thr264Met** [IgII-IgIII linker] | **LP** | Song et al. (2012)[3] MacCarrick et al. (2024)[35] | #1680030 |
| **c.802G>T** [exon 7] | **p.Gly268Cys** [IgII-IgIII linker] | **LP** | Heuertz et al. (2006)[32] | #1680033 |
| **c.833A>G** [exon 7**]** | **p.Tyr278Cys** [IgIII] | **P** | Heuertz et al. (2006)[32] Song et al. (2012)[3] Chen et al. (2013)[37] Xue et al. (2014)[17] Li et al. (2013)[38] Zhao et al. (2015)[39] Chandler et al. (2018)[40] Cheung et al. (2024)[9] | #16357 Severe phenotype, overlapping with ACH in some cases[37,38] |
| **c.835A>T** [exon 7] | **p.Ser279Cys** [IgIII] | **LP** | Heuertz et al. (2006)[32] Friez et al. (2008)[41] | #16356 |

| | | | | |
|---|---|---|---|---|
| | | | | Severe skeletal phenotype overlapping with ACH at birth, then evolving to mild-moderate HCH[41] |
| **c.970C>G** [exon 7] | **p.Leu324Val** [IgIII] | **LP** | Saito et al. (2012)[42]<br>Ishii et al. (2022)[43]<br>MacCarrick et al. (2024)[35] | #1680048 |
| **c.971T>A** [exon 7] | **p.Leu324His** [IgIII] | **LP** | Nagahara et al. (2016)[44]<br>Ishii et al. (2022)[43] | #noclinvarID |
| **c.983A>T** [exon 7] | **p.Asn328Ile** [IgIII] | **LP** | Winterpacht et al. (2000)[45]<br>Heuertz et al. (2006)[32] | #65916 |
| **c.1043C>G** [exon 7] | **p.Ser348Cys** [IgIII] | **LP** | Couser et al. (2017)[46]<br>Bengur et al. (2020)[47]<br>Hasegawa et al. (2016)[48]<br>Chaudhry et al. (2021)[49] | #1526266<br>Severe HCH phenotype, overlapping with mild ACH, acanthosis nigricans |
| **c.1052C>T** [exon 7] | **p.Ser351Phe** [IgIII] | **LP** | Yao et al. (2019)[50]<br>MacCarrick et al. (2024)[35] | #649812 |
| **c.1052C>G** [exon 7] | **p.Ser351Cys** [IgIII] | **LP** | Ishii et al. (2022)[43]<br>MacCarrick et al. (2024)[35] | #372751 |
| **c.1075+95C>G** [intron 8] | p.A359delinsG TGFCCCCCSAL SGGRWLGTR QSCQDGRESS [TM] | **LP** | Xu et al. (2021)[28]<br>Ouedraogo et al. (2021)[51] | #2664079 |

| | | | | |
|---|---|---|---|---|
| **c.1138_1139GG>AA** [exon 10] | **p.Gly380Lys** [TM] | **LP** | Almeida et al. (2009)[18] Santos et al. (2007)[52] | #noclinvarID |
| **c.1612A>G** [exon 13] | **p.Ile538Val** [TK1] | **P** | Grigelioniene et al. (1998)[53] Plachy et al. (2023)[34] MacCarrick et al. (2024)[35] | #16345 |
| **c.1618A>G** [exon 13] | **p.Asn540Asp** [TK1] | **LP** | - | #374828 |
| **c.1619A>C** [exon 13] | **p.Asn540Thr** [TK1] | **P** | Deutz-Terlouw et al. (1998)[54] Barbour et al. (1987)[55] MacCarrick et al. (2024)[35] | #16344 |
| **c.1619A>G** [exon 13] | **p.Asn540Ser** [TK1] | **P** | Mortier et al. (2000)[56] Thauvin-Robinet et al. (2003)[57] MacCarrick et al. (2024)[35] | #16349 |
| **c.1620C>A** [exon 13] | **p.Asn540Lys** [TK1] | **P** | Bellus et al. (1995)[58] Prinos et al. (1995)[59] Xue et al. (2014)[17] MacCarrick et al. (2024)[35] | #16337 Most common HCH causative variant. Variable phenotypes, but often severe and can overlap with ACH[17] |
| **c.1620C>G** [exon 13] | **p.Asn540Lys** [TK1] | **P** | Bellus et al. (1995)[58] Prinos et al. (1995)[59] Xue et al. (2014)[17] MacCarrick et al. (2024)[35] | #16338 Most common HCH causative variant. Variable phenotypes, but often severe and |

| | | | | |
|---|---|---|---|---|
| | | | | can overlap with ACH[17] |
| **c.1948A>C** [exon 15] | **p.Lys650Gln** [TK2] | **P** | Bellus et al. (2000)[60] Blomberg et al. (2010)[61] Ishii et al. (2022)[43] Xue et al. (2014)[17] | #16348 Acanthosis nigricans Mild-moderate skeletal phenotype |
| **c.1949A>C** [exon 15] | **p.Lys650Thr** [TK2] | **P** | Berk et al. (2010)[62] Castro-Feijoo et al. (2008)[63] Muguet Guenot et al. (2019)[64] Xue et al. (2014)[17] MacCarrick et al. (2024)[35] | #65855 Acanthosis nigricans Mild-moderate skeletal phenotype |
| **c.1950G>T** [exon 15] | **p.Lys650Asn** [TK2] | **P** | Bellus et al. (2000)[60] | #16346 Mild-moderate skeletal phenotype |
| **c.1950G>C** [exon 15] | **p.Lys650Asn** [TK2] | **P** | Bellus et al. (2000)[60] | #16347 Mild-moderate skeletal phenotype |
| **c.2005C>G** [exon 16] | **p.Arg669Gly** [TK2] | **LP** | Spurna et al. (2024)[65] Patani et al. (2016)[66] | #579912 |

The information in this table was based on literature review and the authors' experience. Certain variants reported in the literature to be related to HCH were not included in this table when evidence thus far was insufficient to declare it as P/LP, or phenotypic data were not available. Examples of this include: p.Asn262His[32]; p.Ser269Cys[67]; p.Leu326Trp[68]; p.Gly342Cys[69]; p.Glu360Lys[18]; p.Val381Glu[32]; p.Gly382Asp[70]. Variants considered causative for HCH and their degree of pathogenicity will change over time. Clinical descriptions with familial segregation analysis, functional studies and deep mutational screening are relevant for this reclassification process. A maintained list of variants linked to HCH can be found on the IAF website at: achondroplasiaforum.com/resources. If ambiguity persists,

multidisciplinary expert opinion, including clinicians and molecular genetics with experience in skeletal dysplasia genetic studies, is encouraged.

ACH, achondroplasia; ACMG, American College of Medical Genetics

**R4.** A diagnosis of **suspected HCH** can be made based on a combination of genetic and phenotypic criteria. As detailed in **Box 3**. (Mean score: 96; proportion scoring ≥70: 100%)

The terminology for this situation was discussed and after various suggestions, the term "suspected HCH" was selected by most Delphi panel members (63%).

**Box 3.** Scenarios in which a diagnosis of suspected hypochondroplasia can be made

The absence of a definitive diagnosis of an alternate skeletal dysplasia, but with one of the following:

1. Likely pathogenic variant in *FGFR3* with no major criteria but at least 6 minor criteria
2. Variant of uncertain significance (VUS) in *FGFR3* plus at least 2 major criteria
3. VUS in *FGFR3* plus 1 major criterion and at least 3 minor criteria
4. No variant detected in *FGFR3* and at least 4 major criteria

**R5.** In individuals with at least 4 major criteria for HCH diagnosis (**Box 2**), in whom genetic testing has not been performed (or is not available), a diagnosis of **HCH, genetically unconfirmed** can be made (mean score: 92; proportion scoring ≥70: 100%).

The diagnostic category "HCH, genetically unconfirmed" should be used to differentiate from cases where genetic testing for HCH-associated *FGFR3* variants was performed but none was detected.

**R6.** Individuals with a suspected HCH diagnosis require further clinical and/or genetic evaluation and periodic re-evaluation of variant interpretation (mean score: 97; proportion scoring ≥70: 100%).

**R7.** Physical features of HCH typically become more pronounced as the child ages; in some less severe cases, first presentation may be in late childhood or adulthood (mean score: 94; proportion scoring ≥70: 95%).

Clinical features of HCH are often subtle in early life. Many affected infants have normal or only mildly reduced birth length, with relative macrocephaly and minimal limb–trunk disproportion.[16,26] In many cases, short stature is frequently not recognized until late infancy or early school age when slowing of growth and clearer disproportion become apparent.[1,24] As growth proceeds, heights in children with HCH tend to diverge progressively from average-stature populations. An often blunted or absent pubertal growth spurt can lead to height deficit and body disproportion becoming more obvious over time.[9,26] This is reflected in observational cohorts documenting individuals first diagnosed in late childhood or adulthood, often during evaluation of short stature, back or limb symptoms, or when a relative is diagnosed.[1,15,19,24]

Although many features of HCH become more pronounced as the child ages, seizures are more common in infants with HCH than in children and adults with HCH.[1,19,20]

## Prenatal diagnosis of HCH

**R8.** Features of HCH may be detectable prenatally by ultrasound, and as early as 20 weeks of gestation (mean score: 85; proportion scoring ≥70: 89%).

Features of HCH most commonly identifiable prenatally by ultrasound are shortening of the long bones and relative macrocephaly.[24] Detection as early as 20 weeks has been documented.[24] Although many countries do not schedule routine ultrasound assessments

after 20 week, signs of HCH become more pronounced in assessments performed at 24–28 weeks.[71]

While prenatal detection is possible, there are many cases where HCH is not detected antenatally.[10] This may be due to the variable presentation of HCH – prenatally identifiable features can be within the normal range of the general population. However, it is also the panel's view that greater awareness of the prenatal signs of HCH could lead to earlier diagnosis in individuals with HCH. Indeed, when retrospectively examining ultrasonography images in individuals diagnosed antenatally, it is not unusual to see prenatal signs of HCH that were not identified as being indicative of skeletal dysplasia at the time.[24]

**R9.** Non-invasive prenatal screening (NIPS) is available in some countries to screen for variants in *FGFR3* associated with HCH (mean score: 93; proportion scoring ≥70: 94%).

**R10.** If a pathogenic or likely pathogenic variant in *FGFR3* associated with HCH is identified via NIPS, definitive testing should be offered, which may include amniocentesis or postnatal genetic testing (mean score: 97; proportion scoring ≥70: 100%).

NIPS of cell-free foetal DNA (i.e., of placental trophoblast origin) is being used increasingly in routine prenatal care,[72,73] starting from around 10 weeks' gestation. In some settings, this includes single-gene screening for variants in *FGFR3*, including those associated with HCH. However, at present, NIPS is still not available to many people, and it remains a screening tool rather than a diagnostic test. Where a pathogenic or likely pathogenic *FGFR3* variant associated with HCH is identified, confirmatory invasive prenatal testing (typically amniocentesis) should be offered, or genetic testing can be deferred until after birth. If there is a known family history of HCH, chorionic villus sampling may be considered or non-invasive testing (if the father is the affected parent).

A variety of genetic testing approaches are available, including skeletal dysplasia panel analysis, whole genome sequencing, whole exome sequencing, and targeted sequencing of specific variants or genes.[1,74] How these are used in the diagnostic process will be guided by the clinical situation and established processes within individual healthcare systems with appropriate pre-test genetic counselling.

**R11**. Infants with a clinical suspicion of HCH but negative NIPS (or in the absence of prenatal genetic testing) should undergo postnatal assessment (mean score: 98; proportion scoring ≥70: 100%).

## Family history

**R12.** In individuals with suspected HCH and/or skeletal dysplasia, family history should be considered to identify potential cases of autosomal dominant inheritance (mean score: 99; proportion scoring ≥70: 100%).

Consideration of family history should initially focus on whether first-degree relatives have clinical signs of HCH or other skeletal dysplasia. This can help to inform the diagnostic process, based on current understanding of relevant autosomal dominant inherited conditions.

**R13.** HCH is most frequently caused by a *de novo* heterozygous pathogenic variant in *FGFR3* (mean score: 96; proportion scoring ≥70: 100%).

There are diverse published findings regarding the proportion of patients with HCH but lacking a variant within *FGFR3*.[4,5,18] It had previously been reported that this figure was approximately 30% of HCH cases.[17] However, a more recent study of 29 HCH patients found that only two lacked an HCH-associated variant within *FGFR3*; the authors suggested that incomplete genetic screening of *FGFR3* in previous studies may account for this apparent disparity.[17]

Based on available published literature, the proportion of HCH caused by *de novo* variants is thought to be less than in achondroplasia.[10] However, it is hard to estimate the true proportion of HCH caused by *de novo* vs inherited variants due to the paucity of large epidemiological studies, and because cohort studies to date have been limited in size and scope.[17,18]

**R14.** Although the most common HCH-causing variants are those leading to the p.N540K (p.Asn540Lys) substitution, several other variants causing HCH have been identified within *FGFR3* (mean score: 99; proportion scoring ≥70: 100%).

Genetic testing and clinical interpretation of *FGFR3* variants are often complex. Different germline variants in this gene are known to cause a variety of distinct phenotypes,[75] primarily driven by missense variants. While some genotype-phenotype correlations are well established, others remain challenging to define. A striking feature of *FGFR3* is that different substitutions at the same amino acid residue can result in vastly different clinical outcomes. The most notable example involves the lysine residue at position 650: p.Lys650Glu causes thanatophoric dysplasia type II (MIM#187601), p.Lys650Met causes severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) syndrome (OMIM#616482) while p.Lys650Asn, p.Lys650Gln and p.Lys650Thr cause milder phenotypes fitting HCH.[60] The diagnostic criteria refer to heterozygous pathogenic or likely pathogenic variants (per ACMG/AMP guidelines)[76] specifically linked to HCH, for which **Table 2** provides a selection. Variants should be annotated using the “standard” MANE transcript (NM_000142) to avoid misinterpretation.

HCH is typically caused by *FGFR3* gain-of-function heterozygous missense variants,[1] although one deep intronic variant affecting splicing and leading to an in-frame insertion has been described.[28,51] No deletions or duplications involving *FGFR3* have been reported to cause HCH.[1] At the time of writing, there is not yet a comprehensive database focused on *FGFR3* variant classification nor specific ClinGen recommendations. There are still a

significant number of variants that should be classified as of unknown significance (VUS), not only the ones affecting amino acid residues previously unreported. Difficulties in interpretation derive from lack of detailed phenotypic descriptions or functional studies in the literature, making it difficult to apply ACMG criteria confidently even when one identifies some of the previously reported variants (see **Table 2** footnote). When a VUS is identified, it is important to reassess the possibilities of reclassification, focusing on the location of affected amino acid residue, the *in silico* deleteriousness prediction, the regional missense constraint, the parents' phenotype and segregation studies (*de novo* vs inherited).We anticipate additional HCH-associated variants will continue to be identified, and because of this, genetic analysis of *FGFR3* in individuals with suspected HCH should refer to online resources (e.g., ClinVar, LOVD)[77,78] for the latest data, and expert consultation may be required.

**R15.** In cases where an individual is diagnosed with HCH due to a pathogenic or likely pathogenic variant, first-degree relatives should be assessed for potential signs of HCH and referred for genetic counselling as appropriate (mean score: 96; proportion scoring ≥70: 100%).

Depending on the care pathways within the healthcare system, this assessment and (if appropriate) the subsequent genetic counselling may be undertaken by a variety of specialists. Where possible, these specialists should have previous experience with HCH and skeletal dysplasia. As previously mentioned, it is not uncommon for a diagnosis of HCH to lead to further diagnoses within a family. Multiple family members carrying the same variant may have differing severities of clinical phenotype due to variable penetrance.

## Areas of future research

The recommendations within this consensus statement have been developed based on the available published literature and the expert opinions of the Delphi panel. Following their publication, there is a need for real-world testing and validation of these recommendations.

This will provide data to further strengthen and develop our understanding of the diagnostic process for HCH, and to inform future recommendations. There is also a need for testing, implementation and validation of the various grading/classification systems that have been developed to assess different aspects of HCH.[3,6,9,25] This will help to further refine how and when these systems should be used, and how they fit within the overall diagnostic process.

While acknowledging the work over recent years to improve our understanding of the impact of the various identified variants within *FGFR3*, further work is needed to help characterise the potential impact of variants of uncertain significance. It is also expected that, with rigorous genetic analysis more widely available, additional variants within *FGFR3* will be identified. Research is needed into the ways these variants affect individuals with HCH and genotype-phenotype correlations. With the increasingly availability of massively parallel sequencing (MPS) customisable gene panels, and the sharing of resulting data, it is also important to characterise the proportion of individuals with suspected HCH, or HCH "genetically unconfirmed" who subsequently receive an alternative diagnosis driven by non-*FGFR3* genes.

Finally, there is a need for research to help increase our understanding of the role of neuroimaging in HCH; for example, how neuroimaging findings are associated with neurological clinical findings and what these can tell us about the true prevalence of neurological complications in HCH.

## Strengths and limitations

The main strengths of this consensus statement are that it builds on the findings of multiple studies in HCH and combines these with the experience from a broad international panel of HCH experts from a variety of relevant fields (endocrinology, genetics, radiology). The use of the widely accepted Delphi methodology further strengthens the validity of these recommendations.

A major limitation of this consensus statement is that there are few large epidemiological studies published. Because of this, statements are often based on findings from small cohort studies. Also, older studies often lacked comprehensive genetic assessment of *FGFR3*. It is also limited by selection bias of the participating experts and the definition of “consensus” (set here at 70%) that is inherent to all such Delphi processes.

The panel recognises that access to molecular diagnostics varies globally. These recommendations are intended to be flexible and applicable across diverse healthcare settings, with clinical and radiographic criteria remaining central to diagnosis when genetic testing is unavailable.

## Conclusions

These expert guidelines provide a practical framework to help guide the diagnosis of HCH in both general and expert clinical settings. They include guidance on which assessments (clinical, radiographic and genetic) should be performed as part of the diagnostic process and how results should be interpreted to reach an overall diagnosis.

## Acknowledgements

Editorial support was provided by CESAS Medical. The authors thank the patient representatives: Marco Sessa, Jessica Aboo, Katie Rose and Vidya Kanthi for their input. The following experts contributed to the initial insights gathering phase but did not take part in the Delphi process: Tawfeg Ben-Omran, Brigitte Fauroux, Encarna Guillen-Navarro, Melita Irving, Klaus Mohnike, and Denise Pontes Cavalcanti.

## Author contributions

All authors contributed to all aspects of the article.

## Competing interests

This work was supported by an unrestricted educational grant from BioMarin. AD has served as a consultant for BioMarin, Ascendis, QED Pharmaceutical, Novo Nordisk, Pfizer, Sandoz, and Eton Pharmaceuticals and received grant funding from BioMarin and Pfizer. MSC is an investigator for BioMarin trials in achondroplasia and hypochondroplasia, has received consulting fees and payments for honoraria for lectures, presentations, and manuscript writing from BridgeBio Pharma and BioMarin, and has received consulting fees from Tyra BioScientifica. MSC is also an unpaid member of the Drug Medical Committee for a trial in achondroplasia for Ascendis, and holds unpaid leadership or fiduciary roles in the Skeletal Dysplasia Group, Skeletal Dysplasia Management Consortium, and the Achondroplasia Network Meeting. JHF has received grants and contracts for clinical trials from BioMarin, BridgeBio Pharma and Pfizer, has received consulting fees from BioMarin, BridgeBio Pharma, Ascendis, Tyra and Novo Nordisk, has received honoraria for Medscape and BioMarin, and has participated on advisory boards with MCDS-Therapy Clinical Trial (unpaid), BioMarin, and BridgeBio Pharma. SOF has participated in advisory boards and given presentations for BioMarin, Sanofi, Ascendis Pharma, BridgeBio Pharma and Novo Nordisk, and honoraria have been paid to his institution and he is principal investigator in

ongoing clinical trials for BridgeBio Pharma and Ascendis Pharma. MA has received honoraria for lectures and educational events from BioMarin, Sanofi and AstraZeneca, has received travel support for educational events and conferences from BioMarin, Sanofi and AstraZeneca. SB, AC, VC-D and PK report no competing interests. VF has participated in HCH and achondroplasia clinical research at the Garrahan Hospital in BMD and QED. TK has received lecture fees and Kyowa Kirin and Novo Nordisk, consulting fees from BioMarin and Kyowa Kirin and grants from BioMarin and Kyowa Kirin. JLJ has participated in advisory boards for BioMarin, has received grants and fees for research, and participated in scientific and advisory board meetings for BioMarin and Ascendis, and is a medical consultant for the Brazilian Achondroplasia Patient Organization (ANNABRA). MM has received grant support from Pfizer, Novo Nordisk, Merck Serono, and Rhythm Pharmaceuticals; consulting fees and honoraria for lectures, presentations, speaker bureau activities, manuscript writing, or educational events from Pfizer, Novo Nordisk, Sandoz, Merck Serono, Rhythm Pharmaceuticals, Ascendis, and BioMarin; and has participated on a data safety monitoring board/advisory board for Pfizer. GM has received consulting fees and payment for lectures or presentations and financial support for attending meetings from BioMarin, Pfizer and Sanofi. NN has received consultancy/advisory board honoraria from BioMarin, Kyowa Kirin, Ascendis and Teijin, speaking fees from BioMarin, Kyowa Kirin, Teijin and Novo Nordisk, and is a current or prior investigator on trials for BioMarin, Kyowa Kirin, Ascendis, and Teijin. ACO has received grant funding from Alexion, and honoraria from Alexion and BioMarin. KO has received fees for lectures and brochure production from BioMarin, and lecture fees from Alexion and Sanofi Japan. SS has received honoraria for lectures, advisory board participation, and/or travel support from BioMarin, Ascendis Pharma, and Kyowa Kirin, and has served as an investigator in observational studies and/or clinical trials for Pfizer, Ascendis Pharma, BioMarin, and QED/BridgeBio Pharma. RS has received honoraria from BioMarin, QED and Ascendis pharma.

# References


1 Bober, M. B. *et al.* in *GeneReviews((R))* (eds M. P. Adam *et al.*) (1993).

2 Kim, H. Y., Lee, Y. A., Shin, C. H., Cho, T. J. & Ko, J. M. Clinical Manifestations and Outcomes of 20 Korean Hypochondroplasia Patients with the FGFR3 N540K variant. *Exp Clin Endocrinol Diabetes* **131**, 123-131, doi:10.1055/a-1988-9734 (2023).

3 Song, S. H. *et al.* New proposed clinico-radiologic and molecular criteria in hypochondroplasia: FGFR 3 gene mutations are not the only cause of hypochondroplasia. *Am J Med Genet A* **158A**, 2456-2462, doi:10.1002/ajmg.a.35564 (2012).

4 Prinster, C. *et al.* Diagnosis of hypochondroplasia: the role of radiological interpretation. Italian Study Group for Hypochondroplasia. *Pediatr Radiol* **31**, 203-208, doi:10.1007/s002470000398 (2001).

5 Hasegawa, K. & Tanaka, H. Children with short-limbed short stature in pediatric endocrinological services in Japan. *Pediatr Int* **56**, 809-812, doi:10.1111/ped.12511 (2014).

6 Cheung, M. S., Lanzafame, R., Low, K. J. & Cole, T. J. The Head Circumference Height Index (HCH-I) to Quantify Relative Macrocephaly and Aid Identification of Hypochondroplasia in Children. *Am J Med Genet A* **200**, 353-359, doi:10.1002/ajmg.a.64266 (2026).

7 Fano, V. *et al.* High specificity of head circumference to recognize N540K mutation in hypochondroplasia. *Ann Hum Biol* **32**, 782-788, doi:10.1080/03014460500268481 (2005).

8 Arenas, M. A., Del Pino, M. & Fano, V. FGFR3-related hypochondroplasia: longitudinal growth in 57 children with the p.Asn540Lys mutation. *J Pediatr Endocrinol Metab* **31**, 1279-1284, doi:10.1515/jpem-2018-0046 (2018).

9 Cheung, M. S. *et al.* Growth reference charts for children with hypochondroplasia. *Am J Med Genet A* **194**, 243-252, doi:10.1002/ajmg.a.63431 (2024).

10 Baujat, G., Hamandjian, M. A., Jannot, A. S., Karam, P. & Cormier-Daire, V. Achondroplasia and hypochondroplasia in France: a nationwide epidemiological analysis. *Orphanet J Rare Dis* **20**, 555, doi:10.1186/s13023-025-04069-5 (2025).

11 Wynne-Davies, R., Walsh, W. K. & Gormley, J. Achondroplasia and hypochondroplasia. Clinical variation and spinal stenosis. *J Bone Joint Surg Br* **63B**, 508-515, doi:10.1302/0301-620X.63B4.7298674 (1981).

12 Guasto, A. & Cormier-Daire, V. Signaling Pathways in Bone Development and Their Related Skeletal Dysplasia. *Int J Mol Sci* **22**, doi:10.3390/ijms22094321 (2021).

13 Foldynova-Trantirkova, S., Wilcox, W. R. & Krejci, P. Sixteen years and counting: the current understanding of fibroblast growth factor receptor 3 (FGFR3) signaling in skeletal dysplasias. *Hum Mutat* **33**, 29-41, doi:10.1002/humu.21636 (2012).

14 Olney, R. C. *et al.* C-type natriuretic peptide plasma levels are elevated in subjects with achondroplasia, hypochondroplasia, and thanatophoric dysplasia. *J Clin Endocrinol Metab* **100**, E355-359, doi:10.1210/jc.2014-2814 (2015).

15 Hall, B. D. & Spranger, J. Hypochondroplasia: clinical and radiological aspects in 39 cases. *Radiology* **133**, 95-100, doi:10.1148/133.1.95 (1979).

16 Chiaramonte, S. S., Del Pino, M. & Fano, V. Prevalence of low birth weight, short length, and body disproportion at birth in patients with skeletal dysplasias: A retrospective study. *Arch Argent Pediatr*, e202510663, doi:10.5546/aap.2025-10663.eng (2025).

17 Xue, Y. *et al.* FGFR3 mutation frequency in 324 cases from the International Skeletal Dysplasia Registry. *Mol Genet Genomic Med* **2**, 497-503, doi:10.1002/mgg3.96 (2014).

18 Almeida, M. R. *et al.* Clinical and molecular diagnosis of the skeletal dysplasias associated with mutations in the gene encoding Fibroblast Growth Factor Receptor 3

(FGFR3) in Portugal. *Clin Genet* **75**, 150-156, doi:10.1111/j.1399-0004.2008.01123.x (2009).
19 Oehrlein, E. M. *et al.* Living With Hypochondroplasia: A Qualitative Exploration of Children's and Caregivers' Experiences, Challenges, and Unmet Needs. *Mol Genet Genomic Med* **13**, e70151, doi:10.1002/mgg3.70151 (2025).
20 Linnankivi, T., Makitie, O., Valanne, L. & Toiviainen-Salo, S. Neuroimaging and neurological findings in patients with hypochondroplasia and FGFR3 N540K mutation. *Am J Med Genet A* **158A**, 3119-3125, doi:10.1002/ajmg.a.35642 (2012).
21 Dauber, A. *et al.* Vosoritide treatment for children with hypochondroplasia: a phase 2 trial. *EClinicalMedicine* **71**, 102591, doi:10.1016/j.eclinm.2024.102591 (2024).
22 Demuynck, B. *et al.* Infigratinib low dose therapy is an effective strategy to treat hypochondroplasia. *J Bone Miner Res* **40**, 1255-1264, doi:10.1093/jbmr/zjaf088 (2025).
23 Galetaki, D. *et al.* Phase 2 Trial of Vosoritide Use in Patients with Hypochondroplasia: A Pharmacokinetic/Pharmacodynamic Analysis. *Horm Res Paediatr*, 1-7, doi:10.1159/000542102 (2024).
24 Sabir, A. H. *et al.* Earlier detection of hypochondroplasia: A large single-center UK case series and systematic review. *Am J Med Genet A* **185**, 73-82, doi:10.1002/ajmg.a.61912 (2021).
25 Saito, T. *et al.* Criteria for radiologic diagnosis of hypochondroplasia in neonates. *Pediatr Radiol* **46**, 513-518, doi:10.1007/s00247-015-3518-2 (2016).
26 Ramaswami, U., Rumsby, G., Hindmarsh, P. C. & Brook, C. G. Genotype and phenotype in hypochondroplasia. *J Pediatr* **133**, 99-102, doi:10.1016/s0022-3476(98)70186-6 (1998).
27 Shelmerdine, S. C., Brittain, H., Arthurs, O. J. & Calder, A. D. Achondroplasia: Really rhizomelic? *Am J Med Genet A* **170**, 2039-2043, doi:10.1002/ajmg.a.37776 (2016).
28 Xu, T. *et al.* An intronic variant disrupts mRNA splicing and causes FGFR3-related skeletal dysplasia. *J Pediatr Endocrinol Metab* **34**, 1323-1328, doi:10.1515/jpem-2020-0679 (2021).
29 Wei, S. *et al.* Identification of NPR2 gene mutations affecting chondrocyte differentiation in short stature through JAK2-STAT5. *Orphanet J Rare Dis* **20**, 392, doi:10.1186/s13023-025-03936-5 (2025).
30 Zhan, S. *et al.* Clinical Features of Seven COL2A1 Variations in Chinese Children With Type II Collagen Disorders. *Acta Paediatr* **114**, 1720-1730, doi:10.1111/apa.70029 (2025).
31 Nicolae, R., Navardauskaite, R. & Jee, Y. H. Genetics of short stature. *Curr Opin Pediatr* **37**, 380-385, doi:10.1097/MOP.0000000000001481 (2025).
32 Heuertz, S. *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* **14**, 1240-1247, doi:10.1038/sj.ejhg.5201700 (2006).
33 Andrade, N. L. M. *et al.* Diagnostic yield of a multigene sequencing approach in children classified as idiopathic short stature. *Endocr Connect* **11**, doi:10.1530/EC-22-0214 (2022).
34 Plachy, L. *et al.* Isolated growth hormone deficiency in children with vertically transmitted short stature: What do the genes tell us? *Front Endocrinol (Lausanne)* **13**, 1102968, doi:10.3389/fendo.2022.1102968 (2022).
35 MacCarrick, G. *et al.* Clinical utility of comprehensive gene panel testing for common and rare causes of skeletal dysplasia and other skeletal disorders: Results from the largest cohort to date. *Am J Med Genet A* **194**, e63646, doi:10.1002/ajmg.a.63646 (2024).
36 Ramos Mejia, R. *et al.* Clinical and Radiologic Evaluation of an Individual with Hypochondroplasia and a Novel FGFR3 Mutation. *J Pediatr Genet* **9**, 48-52, doi:10.1055/s-0039-1695056 (2020).

37 Chen, C. P. *et al.* Detection of a de novo Y278C mutation in FGFR3 in a pregnancy with severe fetal hypochondroplasia: prenatal diagnosis and literature review. *Taiwan J Obstet Gynecol* **52**, 580-585, doi:10.1016/j.tjog.2013.10.023 (2013).

38 Li, F. *et al.* [Clinical analysis and genetic diagnosis of short-limb inherited short stature diseases in children]. *Zhongguo Dang Dai Er Ke Za Zhi* **15**, 932-936 (2013).

39 Zhao, R., Ruan, Y. & Wang, X. Whole-exome sequencing and whole genome re-sequencing for prenatal diagnosis of achondroplasia. *Int J Clin Exp Med* **8**, 19241-19249 (2015).

40 Chandler, N. *et al.* Rapid prenatal diagnosis using targeted exome sequencing: a cohort study to assess feasibility and potential impact on prenatal counseling and pregnancy management. *Genet Med* **20**, 1430-1437, doi:10.1038/gim.2018.30 (2018).

41 Friez, M. J. & Wilson, J. A. Novel FGFR3 mutations in exon 7 and implications for expanded screening of achondroplasia and hypochondroplasia: a response to Heuertz et al. *Eur J Hum Genet* **16**, 277-278, doi:10.1038/sj.ejhg.5201931 (2008).

42 Saito, T. *et al.* Radiological clues to the early diagnosis of hypochondroplasia in the neonatal period: report of two patients. *Am J Med Genet A* **158A**, 630-634, doi:10.1002/ajmg.a.34424 (2012).

43 Ishii, T. *et al.* Molecular Basis for Hypochondroplasia in Japan. *Endocrines* **3**, 428-432, doi:10.3390/endocrines3030034 (2022).

44 Nagahara, K. *et al.* A Japanese familial case of hypochondroplasia with a novel mutation in FGFR3. *Clin Pediatr Endocrinol* **25**, 103-106, doi:10.1297/cpe.25.103 (2016).

45 Winterpacht, A. *et al.* A novel mutation in FGFR-3 disrupts a putative N-glycosylation site and results in hypochondroplasia. *Physiol Genomics* **2**, 9-12, doi:10.1152/physiolgenomics.2000.2.1.9 (2000).

46 Couser, N. L. *et al.* Mild achondroplasia/hypochondroplasia with acanthosis nigricans, normal development, and a p.Ser348Cys FGFR3 mutation. *Am J Med Genet A* **173**, 1097-1101, doi:10.1002/ajmg.a.38141 (2017).

47 Bengur, F. B., Ekmekci, C. G., Karaarslan, E., Gunoz, H. & Alanay, Y. p.Ser348Cys mutation in FGFR3 gene leads to "Mild ACH /Severe HCH" phenotype. *Eur J Med Genet* **63**, 103659, doi:10.1016/j.ejmg.2019.04.016 (2020).

48 Hasegawa, K. *et al.* A novel mutation p.Ser348Cys in FGFR3 causes achondroplasia. *Am J Med Genet A* **170A**, 1370-1372, doi:10.1002/ajmg.a.37557 (2016).

49 Chaudhry, C. *et al.* Achondroplasia-First Report from India of a Rare FGFR3 Gene Variant. *Lab Med* **52**, 499-502, doi:10.1093/labmed/lmaa116 (2021).

50 Yao, G., Wang, G., Wang, D. & Su, G. 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)* **98**, e14157, doi:10.1097/MD.0000000000014157 (2019).

51 Ouedraogo, Z. G. *et al.* Relevance of Extending FGFR3 Gene Analysis in Osteochondrodysplasia to Non-Coding Sequences: A Case Report. *Genes (Basel)* **15**, doi:10.3390/genes15020225 (2024).

52 Santos, H. G., Almeida, M., Fernandes, H. & Wilkie, A. O. Clinical hypochondroplasia in a family caused by a heterozygous double mutation in FGFR3 encoding GLY380LYS. *Am J Med Genet A* **143**, 355-359, doi:10.1002/ajmg.a.31556 (2007).

53 Grigelioniene, G. *et al.* A novel missense mutation Ile538Val in the fibroblast growth factor receptor 3 in hypochondroplasia. Mutations in brief no. 122. Online. *Hum Mutat* **11**, 333, doi:10.1002/(SICI)1098-1004(1998)11:4<333::AID-HUMU18>3.0.CO;2-G (1998).

54 Deutz-Terlouw, P. P., Losekoot, M., Aalfs, C. M., Hennekam, R. C. & Bakker, E. Asn540Thr substitution in the fibroblast growth factor receptor 3 tyrosine kinase domain causing hypochondroplasia. *Hum Mutat* **Suppl 1**, S62-65, doi:10.1002/humu.1380110122 (1998).

55 Barbour, S. D. Acquired immunodeficiency syndrome of childhood. *Pediatr Clin North Am* **34**, 247-268, doi:10.1016/s0031-3955(16)36192-2 (1987).

56 Mortier, G. *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* **37**, 220-224, doi:10.1136/jmg.37.3.220 (2000).

57 Thauvin-Robinet, C. *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* **119A**, 81-84, doi:10.1002/ajmg.a.10238 (2003).

58 Bellus, G. A. *et al.* A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. *Nat Genet* **10**, 357-359, doi:10.1038/ng0795-357 (1995).

59 Prinos, P., Costa, T., Sommer, A., Kilpatrick, M. W. & Tsipouras, P. A common FGFR3 gene mutation in hypochondroplasia. *Hum Mol Genet* **4**, 2097-2101, doi:10.1093/hmg/4.11.2097 (1995).

60 Bellus, G. A. *et al.* Distinct missense mutations of the FGFR3 lys650 codon modulate receptor kinase activation and the severity of the skeletal dysplasia phenotype. *Am J Hum Genet* **67**, 1411-1421, doi:10.1086/316892 (2000).

61 Blomberg, M., Jeppesen, E. M., Skovby, F. & Benfeldt, E. FGFR3 mutations and the skin: report of a patient with a FGFR3 gene mutation, acanthosis nigricans, hypochondroplasia and hyperinsulinemia and review of the literature. *Dermatology* **220**, 297-305, doi:10.1159/000297575 (2010).

62 Berk, D. R. *et al.* Acanthosis nigricans and hypochondroplasia in a child with a K650Q mutation in FGFR3. *Pediatr Dermatol* **27**, 664-666, doi:10.1111/j.1525-1470.2010.01331.x (2010).

63 Castro-Feijoo, L. *et al.* Hypochondroplasia and Acanthosis nigricans: a new syndrome due to the p.Lys650Thr mutation in the fibroblast growth factor receptor 3 gene? *Eur J Endocrinol* **159**, 243-249, doi:10.1530/EJE-08-0393 (2008).

64 Muguet Guenot, L. *et al.* Acanthosis nigricans, hypochondroplasia, and FGFR3 mutations: Findings with five new patients, and a review of the literature. *Pediatr Dermatol* **36**, 242-246, doi:10.1111/pde.13748 (2019).

65 Spurna, Z. *et al.* Clinical-genetic analysis of selected genes involved in the development of the human skeleton in 128 Czech patients with suspected congenital skeletal abnormalities. *Gene* **892**, 147881, doi:10.1016/j.gene.2023.147881 (2024).

66 Patani, H. *et al.* Landscape of activating cancer mutations in FGFR kinases and their differential responses to inhibitors in clinical use. *Oncotarget* **7**, 24252-24268, doi:10.18632/oncotarget.8132 (2016).

67 Takahashi, I. *et al.* A novel S269C mutation in fibroblast growth factor receptor 3 in a Japanese child with hypochondroplasia. *Hum Genome Var* **5**, 1, doi:10.1038/s41439-018-0001-2 (2018).

68 Jacob, P. *et al.* Genetic and allelic heterogeneity in 248 Indians with skeletal dysplasia. *Eur J Hum Genet* **33**, 607-613, doi:10.1038/s41431-024-01776-8 (2025).

69 Wang, H. *et al.* A novel missense mutation of FGFR3 in a Chinese female and her fetus with Hypochondroplasia by next-generation sequencing. *Clin Chim Acta* **423**, 62-65, doi:10.1016/j.cca.2013.04.015 (2013).

70 Chen, J. *et al.* Identification of a novel mutation in the FGFR3 gene in a Chinese family with Hypochondroplasia. *Gene* **641**, 355-360, doi:10.1016/j.gene.2017.10.062 (2018).

71 Jelin, A. C. *et al.* Molecular testing strategies in the evaluation of fetal skeletal dysplasia. *J Matern Fetal Neonatal Med* **35**, 2788-2794, doi:10.1080/14767058.2020.1802715 (2022).

72 Nishimura, G. *et al.* Prenatal diagnosis of bone dysplasias. *Br J Radiol* **96**, 20221025, doi:10.1259/bjr.20221025 (2023).

73 Wang, L. *et al.* Genetic analysis of fetal skeletal dysplasia via whole exome sequencing and non-invasive prenatal diagnosis. *Ann Med* **58**, 2606517, doi:10.1080/07853890.2025.2606517 (2026).

74 Kalimi, E. *et al.* The role of genetic testing in small for gestational age infants. *J Perinatol* **45**, 1183-1190, doi:10.1038/s41372-025-02343-9 (2025).
75 OMIM. *FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3*, <https://omim.org/entry/134934> (2023).
76 Richards, 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* **17**, 405-424, doi:10.1038/gim.2015.30 (2015).
77 ClinVar Miner. *Variants in FGFR3*, <https://clinvarminer.genetics.utah.edu/variants-by-gene/FGFR3> (2025).
78 *Leiden open variation database*, <https://www.lovd.nl/> (2026).

# Supplementary Content

**Supplementary Table S1. Participants in the insight gathering and Delphi process.** Core group members are shown in bold.

| Participant | IAF Steering Committee | Specific clinical, molecular &/or global expertise | Patient representative | Delphi process |
|---|---|---|---|---|
| Alistair Calder | | ✓ | | ✓ |
| Amaka Offiah | | ✓ | | ✓ |
| **Andrew Dauber** | ✓ | | | ✓ |
| Brigitte Fauroux | ✓ | | | |
| Denise Pontes Cavalcanti | | ✓ | | |
| Encarna Guillen-Navarro | ✓ | | | |
| Geert Mortier | ✓ | | | ✓ |
| Jessica Aboo | | | ✓ | ✓* |
| Juan Clinton Llerena Jr | ✓ | | | ✓ |
| **Julie Hoover-Fong** | ✓ | | | ✓ |
| Katie Rose | | | ✓ | |
| Keita Okada | ✓ | | | ✓ |
| Klaus Mohnike | ✓ | | | |
| Marco Sessa | ✓ | | ✓ | ✓* |
| Melita Irving | ✓ | | | |
| Moeenaldeen AlSayed | ✓ | | | ✓ |
| Mohamad Maghnie | ✓ | | | ✓ |
| **Moira Cheung** | | ✓ | | ✓ |
| Noriyuki Namba | | ✓ | | ✓ |
| Philip Kunkel | ✓ | | | ✓ |
| **Ravi Savarirayan** | ✓ | | | ✓ |
| Sérgio B. Sousa | ✓ | | | ✓ |
| Silvio Boero | ✓ | | | ✓ |
| **Svein Otto Fredwall** | ✓ | | | ✓ |
| Takuo Kubota | | ✓ | | ✓ |
| Tawfeg Ben-Omran | ✓ | | | |
| Valérie Cormier-Daire | ✓ | | | ✓ |
| Vidya Kanthi | | | ✓ | |
| Virginia Fano | ✓ | | | ✓ |

Participants not listed as part of the Delphi process participated in insight gathering.
*Patient representatives provided input but were not counted in the Delphi voting

**Supplementary Table S2. Key references shared with Delphi panel**

| Publication | Population | Study focus |
|---|---|---|
| Chiaramonte, S.S., M. Del Pino, and V. Fano. Arch Argent Pediatr. 2025;e202510663. | 453 patients with skeletal dysplasia; 54 with HCH | Prevalence of low birth weight, short body length, and body disproportion at birth |
| Cheung, M.S., et al., Am J Med Genet A. 2025;e64266. | 72 children with HCH | Disproportion between head circumference and height |
| Kim, H.Y., et al., Exp Clin Endocrinol Diabetes. 2023;131:123-31. | 20 patients with N540K-related HCH | Clinical manifestations |
| Sabir, A.H., et al., Am J Med Genet A. 2021;185:73–82. | 31 HCH patients | Antenatal detection |
| Saito, T., et al., Pediatr Radiol. 2016;46:513–8. | 7 HCH patients, 30 controls | Criteria for radiological diagnosis |
| Xue, Y., et al., Mol Genet Genomic Med. 2014;2:497–503. | 324 patients with skeletal dysplasia | *FGFR3* variant frequency |
| Hasegawa, K. and H. Tanaka. Pediatr Int. 2014;56:809–812. | 193 short stature patients; 47 with HCH | Clinical manifestations and genetic analysis |
| Song, S.H., et al. Am J Med Genet A. 2012;158:2456–62. | 160 short stature patients; 58 diagnosed with HCH | Clinico-radiologic and molecular diagnostic criteria in HCH |
| Almeida, M.R., et al. Clin Genet, 2009;75:150–6. | 125 patients with skeletal dysplasia | Genetic analysis of *FGFR3* and other genes |
| Fano, V., et al. Ann Hum Biol, 2005;32:782–8. | 26 HCH patients | Head circumference |
| Prinster, C., et al. Pediatr Radiol. 2001;31:203–8. | 21 patients with suspected HCH | Radiographic analysis |
| Muguet Guenot, L., et al. Pediatr Dermatol. 2019;36:242–6 | 5 patients with HCH | Acanthosis nigricans |
| Arenas, M.A., M. del Pino and V. Fano. J Pediatr Endocrinol Metab. 2018;31:1279–84 | 57 children with N540K-related HCH | Longitudinal growth |
| Prinster, C., et al. Am J Med Genet A. 1998;75:109–12 | 18 patients with suspected HCH | Clinical-radiological and molecular findings |

| | | |
|---|---|---|
| Cheung, M.S., et al. Am J Med Genet A. 2024;194:243–52 | 188 children with a diagnosis of HCH | HCH-specific growth reference charts |
| Linnankivi, T., et al. Am J Med Genet A. 2012:158:3119–25 | 13 patients with N540K-related HCH | Neuroimaging and neurological findings |
| Hall, B.D. & Spranger, J. Radiology 1979;133:95-100 | 39 patients with HCH | Clinical and radiological features |
| Bober, M.B. *et al.* in GeneReviews (eds M.P. Adam *et al.*) 1993 (Updated 2025) | N/A (review article) | Presentation, testing, diagnosis and management |
| Ramaswami, U., et al. J Pediatr. 1998;133: 99–102 | 65 children with a diagnosis of HCH | Genetic and phenotypic findings |

811

**Supplementary Table S3. Initial Delphi statements and voting result from round one.**

| Statement | Proportion with ≥70% agreement | Outcome |
|---|---|---|
| Accurate and early diagnosis of HCH is important to facilitate appropriate monitoring, management and potential treatment | 100% | No updates made |
| A definitive diagnosis of HCH can be made in the presence of a pathogenic or likely pathogenic variant in *FGFR3* plus a combination of phenotypic criteria. As detailed in **Supplementary Table S4**. | 83% | Comments received resulting in amends to major and minor criteria |
| If a patient does not meet the criteria for a diagnosis of HCH, ensure any additional evaluations are completed that will allow a positive diagnosis to be reached | 89% | Statement updated to reflect comments and discussion |
| A diagnosis of likely/suspected/probable/ genetically unconfirmed HCH can be made based on a combination of genetic and phenotypic criteria, as detailed in **Supplementary Table S4**. | 76% | "Suspected HCH" confirmed as preferred wording. Additional statement (R5) developed |
| Individuals with a likely/suspected/ probable/genetically unconfirmed HCH diagnosis require further clinical and/or genetic evaluation and periodic re-evaluation of variant interpretation | 94% | Statement updated to reflect comments and discussion |
| Clinical features of HCH may become more pronounced/noticeable as the child develops; in some less severe cases first presentation may be in late childhood or adulthood | 94% | Statement updated to reflect comments and discussion |
| Clinical features of HCH may be detectable by prenatal US starting in the 2nd trimester | 82% | Statement updated to reflect comments and discussion |
| NIPS is available in some countries to screen for variants in *FGFR3* associated with HCH | 93% | No updates made |

| | | |
|---|---|---|
| If a pathogenic or likely pathogenic variant in *FGFR3* associated with HCH is identified via NIPS, definitive testing should be offered | 76% | Statement updated to reflect comments and discussion |
| Definitive prenatal genetic testing requires amniocentesis; alternatively, postnatal testing can be pursued | 82% | Statement updated and combined with previous statement |
| Infants with a clinical suspicion of HCH but negative NIPS (or in the absence of prenatal genetic testing) should undergo postnatal assessment | 89% | Statement updated to reflect comments and discussion |
| In individuals with suspected HCH and/or skeletal dysplasia, family history should be considered to identify potential cases of autosomal dominant inheritance | 100% | No updates made |
| HCH is most frequently caused by a de novo autosomal dominant mutation in *FGFR3* | 88% | Statement updated to reflect comments and discussion |
| Although the most common HCH-causing variants are those leading to an N540K substitution, several other variants causing HCH have been identified within *FGFR3* | 100% | Statement updated to reflect comments and discussion |
| In cases where an individual is diagnosed with HCH due to a pathogenic or likely pathogenic variant, first-degree relatives should be assessed for potential signs of HCH and referred for genetic counselling as appropriate | 89% | No updates made |

814

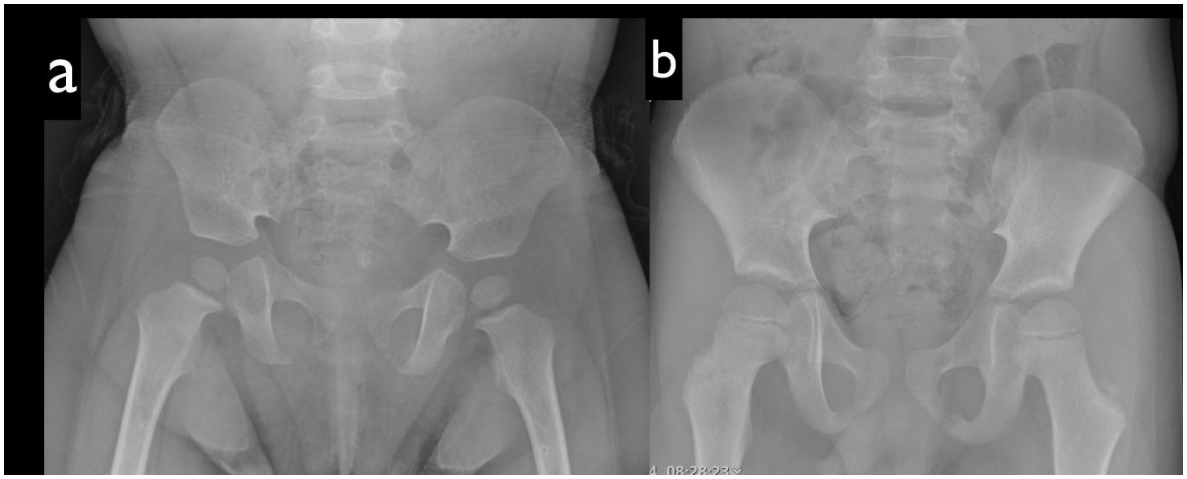
815

**Supplementary Table S4. Initial major and minor criteria proposed as part of round one of Delphi voting.**

| Major criteria for HCH diagnosis | Minor criteria for HCH diagnosis |
|---|---|
| 1. Disproportionate short stature for age and sex, defined as both:<br>a. Height below −2 SD* for age and sex<br>b. Evidence of disproportion, defined as one of the following:<br>iii. Sitting height to standing height ratio >2 SD*<br>iv. Upper-to-lower segment ratio >2 SD*<br>2. Relative macrocephaly with no alternative cause, defined as a Head Circumference Height Index (HCH-I) below a score of −2<br>3. At least one major radiographic criterion – see below<br>4. Characteristic brain MRI finding in the temporal lobes defined as at least one of the following:<br>a. Abnormal transverse sulcus<br>b. Hippocampal malrotation or dysplasia<br>c. Temporal lobe dysgenesis<br>5. Family history in a first-degree relative who meets the criteria for a definitive diagnosis of HCH | 1. Short stature defined as a height below −2 SD* for age and sex<br>2. Height below genetic potential defined as a height >2 SD* below mid-parental target height<br>3. Truncal body disproportion defined as one of the following:<br>a. Ratio of sitting height to standing height >2 SD*<br>b. Ratio of upper to lower segment >2 SD*<br>4. Absolute macrocephaly defined as a head circumference >2 SD*<br>5. Limited elbow extension<br>6. Asymptomatic ventriculomegaly and/or increased extra-axial fluid<br>7. Foramen magnum stenosis<br>8. History of at least one seizure<br>9. History of ADHD, diagnosed learning difficulties or executive function abnormalities<br>10. At least one minor radiographic criterion (see below)<br>11. Family history: a first-degree relative who meets the “likely”/“suspected”/“probable”/ “genetically unconfirmed” HCH diagnostic criteria (see below) |
| Major radiographic criteria<br>*In neonates and infants (<12 months old)*<br>• No major criteria<br>*In individuals ≥12 months old*<br>1. Radiological signs of lumbar spinal stenosis, defined as:<br>o Lack of widening of L1-L5 distances (AP spine) and/or short pedicles (lateral spine)<br>With or without posterior scalloping<br>2. Long distal fibular<br>o Relative to tibia; growth plate extends below ankle joint | Minor radiographic criteria (at least two required)<br>*In neonates and infants (<12 months old)*<br>1. Short sciatic notch<br>2. Short long bones<br>3. Broad proximal femur<br>4. Horizontal acetabular<br>5. Short ilia<br>*In individuals ≥12 months old*<br>1. Short/wide ilia<br>2. Short and broad femoral necks<br>3. Short, broad tubular (long) bones<br>4. Prominent sites of muscular insertion |

*standard deviation of population distribution

**Supplementary Fig. 1|Examples of radiographic minor criteria. a.** Anteroposterior pelvic radiograph in 5-year-old boy with c.1620C>A *FGFR3* variant-related hypochondroplasia, compared with **b.** radiograph of pelvis in skeletally normal 5-year-old, illustrating narrow sacrosciatic notches and small iliac bones in **a**.




**c.** Anteroposterior radiographs of left tibia and fibula in 5-year-old boy with c.1620C>A *FGFR3* variant-related hypochondroplasia, compared with **d.** radiograph of tibia and fibula in skeletally normal 5-year-old. The fibula in **c** is relatively long distally, indicated by the level of the lower fibular physis (dotted line) lying below the level of the ankle mortice. Note also the relative metaphyseal widening in **c**.