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Consensus statement

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Diagnosis of hypochondroplasia: international Delphi consensus recommendations

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Abstract

Hypochondroplasia is a skeletal dysplasia caused by pathogenic variants in *FGFR3* and characterized 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 can be affected by medical complications and psychosocial consequences 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 two-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 health-care 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 standardize timely and accurate diagnosis of hypochondroplasia in clinical practice and research.

Sections

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Introduction

Hypochondroplasia is a rare genetic skeletal dysplasia caused by pathogenic variants in the fibroblast growth factor receptor 3 gene (*FGFR3*)[1]. Although there are multiple characteristic physical and radiographic signs associated with hypochondroplasia, the broad spectrum of phenotypic variability can hinder clinical identification[2–5]. The most prevalent signs associated with hypochondroplasia are disproportionate short stature and relative macrocephaly (a head that is disproportionately large relative to body size)[1,6,7]. Height in hypochondroplasia can lie within the norms for the average-stature population[8,9]. In addition, the majority of individuals with hypochondroplasia 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 might be undiagnosed[10].

Severe hypochondroplasia can phenotypically overlap with the allelic condition achondroplasia, but skeletal features tend to be more subtle in hypochondroplasia[1]. Historically, this similarity between conditions led to rare cases of misdiagnosis in some patients with more severe hypochondroplasia[11], although such misdiagnoses are 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 hypochondroplasia is related to the role of the FGFR3 protein as a physiological negative regulator of skeletal growth[12,13]. In hypochondroplasia, gain-of-function variants in different domains of *FGFR3* lead to functional inhibition of natriuretic peptide receptor-B and reduced activity of C-type natriuretic peptide, a key positive regulator of endochondral bone development[12–14].

Diagnostic criteria for hypochondroplasia 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 hypochondroplasia and the difficulty of applying these features to distinguish hypochondroplasia from idiopathic short stature and from other forms of skeletal dysplasia[2–4,16,17]. Many of the initially proposed criteria were developed before the availability of molecular diagnosis and thus the cohorts probably represented a genetically heterogeneous group of patients. The genetic causes of hypochondroplasia are now reasonably well characterized, with numerous hypochondroplasia-associated variants identified within *FGFR3*[1,17]. The availability of genetic testing has helped to provide molecular confirmation of hypochondroplasia for many patients, and helped to differentiate it from other skeletal dysplasias[5,17,18]. However, in a substantial minority of patients with clinically defined hypochondroplasia (30–40% in some reports), no identifiable *FGFR3* variants have been found[5,17]. This fact could be due to historical limitations of the genetic testing performed in these cohorts, and in some individuals, due to misdiagnosis.

The effect of hypochondroplasia 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, can require surgical intervention), as well as ear, nose and throat, and respiratory complications[1–3,15]. Cases of foramen magnum stenosis have also been reported[1,20]. Neurodevelopmental and neurological complications of hypochondroplasia are also increasingly recognized. These complications can include learning difficulties, attentional disorders, mild intellectual disability, temporal lobe dysgenesis and epilepsy[1,8,20]. Hypochondroplasia is also associated with a substantial psychosocial burden, resulting from functional limitations and limb disproportion[19]. Together, this array of symptoms and effects of hypochondroplasia often requires a coordinated multidisciplinary approach[19].

Early and accurate diagnosis of hypochondroplasia 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 patients with hypochondroplasia[21–23]. If approved for use, these therapies have the potential to improve growth and reduce skeletal complications in individuals with hypochondroplasia[24]. However, hypochondroplasia remains frequently underdiagnosed or misdiagnosed[10,16,23]. 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, 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 hypochondroplasia[10]. Several small cohort studies have been published, but with diverse methodological approaches[2,8,24]. Developments in the recognition and diagnosis of hypochondroplasia over the past 3 years include neonatal imaging criteria, hypochondroplasia-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. Such recommendations are required to improve recognition and facilitate earlier diagnosis in individuals with hypochondroplasia, and to support optimal care, which could 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 hypochondroplasia, 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 hypochondroplasia experts (A.D., M.S.C., S.O.F., J.H.-F. and R.S.) was established to lead the Delphi process.

Experts from the International Achondroplasia Forum steering committee (A.D., B.F., E.G.-N., G.M., J.C.L., J.H.-F., K.O., K.M., M.S.C., M.I., M.A., M.M., P.K., R.S., S.S., S.B., S.O.F., T.B.-O., V.C.-D. and V.F.), additional experts with specific clinical, molecular and/or global expertise in hypochondroplasia (A.C., A.C.O., D.P.C., M.S.C., N.N. and T.K.) and patient representatives (J.A., K.R., M.S. and V.K.) were approached to be part of the insight-gathering group and subsequent Delphi panel.

Expert IAF Steering Committee Members and the additional clinical and 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 presented in Supplementary Table 1.

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 and/or analyses that included at least ten individuals with hypochondroplasia. These references, along with any additional key references identified by the core group, were shared with the Delphi panel members before voting (Supplementary Table 2).

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 hypochondroplasia were identified and shared with the insight-gathering group. This was a non-anonymized 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 hypochondroplasia diagnosis were developed with input from two radiologists with a combined experience of over 35 years in hypochondroplasia and other skeletal dysplasia (A.C.O. and A.C.) at an online meeting on 2 December 2025.

Delphi voting round 1

Statements were shared with the Delphi panel for anonymized 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 after each statement 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 meeting was followed by a second round of anonymized voting to gain input on the updated statements. The modified Delphi process is shown in Fig. 1.

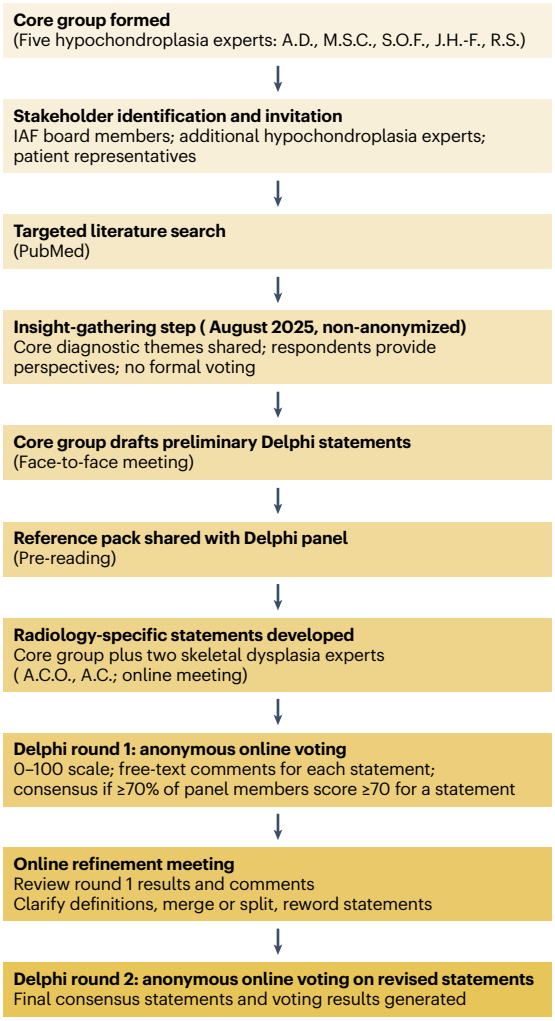

Fig. 1 | Modified Delphi process. A modified Delphi process was used to develop consensus statements for the diagnosis of hypochondroplasia. Two rounds of anonymous online voting were undertaken, with statements refined between rounds; consensus was defined as ≥70% of panel members assigning a score of ≥70 on a 0 to 100 scale. IAF, International Achondroplasia Forum.

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 3 and 4. M.C. and A.D. 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 were updated. A second round of anonymized voting was then conducted and 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 can occur outside specialist centres; these recommendations are intended to support both general and expert clinical settings.

Diagnosis of hypochondroplasia

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

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

Clinical features of hypochondroplasia. 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 hypochondroplasia are most characteristic of and specific to hypochondroplasia 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

hypochondroplasia is disproportionate short stature, with considerable variability in the degree of short stature, including individuals with milder forms where their stature 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 hypochondroplasia compared with the average-stature population, with clear differentiation apparent from birth[8]. For both of these reasons, the ratio of sitting height to standing height warrants inclusion both as a component of a major criterion for defining disproportionate short stature, and as a separate minor criterion when disproportion is present alone without short stature.

Relative macrocephaly is another core feature. Although absolute macrocephaly shows strong predictive value for hypochondroplasia[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 HCH-I (published in February 2026) formalizes head–height disproportion as height *z* score − half head circumference *z* score[6]. The HCH-I discriminates people with hypochondroplasia from population controls with good sensitivity and specificity in infants and children. Indeed, when applied to a large average-stature cohort of children ($n = 4{,}620$), only 2.4% of this cohort had an HCH-I score below −2 compared with 78% of children with hypochondroplasia ($n = 364$). The efficacy of the HCH-I is improved for children over 12 months of age, where 1.9% of the average-stature children compared with 90% of children with hypochondroplasia had an HCH-I score below −2 (ref. 6). These findings support the use of the HCH-I 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-to-humeral length ratio greater than two 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].

Box 1 | Scenarios leading to a diagnosis of hypochondroplasia

Scenarios leading to a definitive diagnosis of hypochondroplasia

- Pathogenic variant in *FGFR3* plus at least one major criterion
- Pathogenic variant in *FGFR3* plus at least three minor criteria
- Likely pathogenic variant in *FGFR3* plus at least two major criteria
- Likely pathogenic variant in *FGFR3* plus one major criterion and at least three minor criteria

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:

- Likely pathogenic variant in *FGFR3* with no major criteria but at least six minor criteria
- Variant of uncertain significance (VUS) in *FGFR3* plus at least two major criteria
- VUS in *FGFR3* plus one major criterion and at least three minor criteria
- No variant detected in *FGFR3* and at least four major criteria

In addition to the signs and symptoms of hypochondroplasia classified as major and minor criteria, additional phenotypic characteristics are present in some individuals with hypochondroplasia. These characteristics can 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 people with hypochondroplasia)[2,20]. Symptoms of spinal stenosis can require intervention in adults with hypochondroplasia more commonly than in children with hypochondroplasia, in whom spinal stenosis rarely causes problems[1].

Radiographic features of hypochondroplasia. Radiographically, failure of the normal craniocaudal increase in lumbar interpedicular distance, secondary to short lumbar pedicles, is recognized as the most characteristic spinal feature of hypochondroplasia and underpins the major radiographic criterion in children aged 12 months or older[2,3,15,26] (Table 1). This spinal feature 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. When interpreting radiographic assessments of neonates, infants or young children with suspected hypochondroplasia, it should be noted that findings meeting the major criterion can develop as the child ages. Because of this fact, in individuals who fail to meet the major criterion, or where equivocal results are observed, radiographic assessment can be repeated 1 year later, or after the child's third birthday (whichever is later).

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 hypochondroplasia diagnosis. However, a separate set of radiographic signs has been proposed, all of which showed sufficient discriminatory performance in neonates with hypochondroplasia-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, although individually nonspecific, comprise the minor radiographic criteria[1–3,15,26].

Brain MRI and neurocognitive features of hypochondroplasia. The major criterion related to brain MRI findings reflects accumulating evidence that temporal lobe malformations are common in people with hypochondroplasia. In a series of 13 patients with hypochondroplasia 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 of the patients who had undergone MRI assessments[20]. Brain MRI is not required for a diagnosis of hypochondroplasia 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 hypochondroplasia and are therefore included as a minor criterion[2,20]. Although hydrocephalus has been reported in patients with hypochondroplasia with the p.N540K substitution[2,20], this is a rare complication.

Across several cohorts of patients with hypochondroplasia, 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 attention deficit hyperactivity disorder, diagnosed learning difficulties or executive dysfunction.

Additional diagnostic evaluations. R3: if a patient does not meet the criteria for a diagnosis of definitive hypochondroplasia, 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 can be clinical, radiographic or genetic. In the case of clinical and radiographic assessments, it should be noted that some signs of hypochondroplasia can become more apparent as children age (see R7 and associated discussion). In individuals where certain diagnostic assessments have not previously been performed, such as brain imaging or comprehensive radiological evaluation, additional assessments might help to confirm a diagnosis, either of hypochondroplasia or of another skeletal dysplasia. Identification of an alternative diagnosis might occur where initial diagnostic assessments are performed outside specialist centres and the initial interpretations missed important diagnostic criteria.

If there is a strong clinical suspicion of hypochondroplasia, but previous genetic assessments have not identified a hypochondroplasia-associated variant within *FGFR3* (Table 2), a clinician should consider the possibilities of technical and/or laboratory error affecting the initial genetic findings or incomplete genetic testing. Relevant *FGFR3* variants might 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, or 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 can be considered. These additional investigations should also include the confirmation that genetic testing for hypochondroplasia differential diagnoses has been performed. This genetic testing could include *SHOX*-deletions testing, or skeletal dysplasia multigene next-generation sequencing panel and/or whole-exome or whole-genome sequencing to confirm whether variants are present in non-*FGFR3* genes that might have overlapping phenotypes with hypochondroplasia (for example, *SHOX*, *ACAN*, *GNAS*, *NPR2*, *COL2A1* and *IHH*)[1,29–31].

R4: a diagnosis of suspected hypochondroplasia can be made based on a combination of genetic and phenotypic criteria (detailed in Box 2) (mean score: 96; proportion scoring ≥70: 100%).

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

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

Table 1 | Major and minor radiographic criteria for hypochondroplasia diagnosis by age group

Age group	Major radiographic criterion for hypochondroplasia diagnosis	Minor radiographic criteria for hypochondroplasia diagnosis
Neonates and infants (<12 months old)	No major criteria	(1) Short sciatic notches (2) Short, relatively broad long bones (3) Broad femoral necks (4) Horizontal acetabular roofs (5) Small iliac bones, with reduced diameter in craniocaudal and transverse directions
Individuals ≥12 months old	Radiological signs of progressive lumbar canal stenosis (L1 to L4), defined as: On anteroposterior view of lumbar spine: lack of normal widening of the L1 to L4 interpedicular distance; and 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)[a] (2) Small iliac bones, with reduced diameter in craniocaudal and transverse directions (3) Short and/or broad femoral necks (4) Short, relatively broad long bones; metaphyses can appear flared (5) Prominent sites of muscular insertion, e.g., at deltoid insertion in humeral diaphysis

[a]In children 3 years and older, to qualify for minor radiographic criteria, minor criterion (1) must always be met.

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

R6: individuals with a suspected hypochondroplasia 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 hypochondroplasia typically become more pronounced as the child ages; in some less severe cases, first presentation can be in late childhood or adulthood (mean score: 94; proportion scoring ≥70: 95%).

Clinical features of hypochondroplasia 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 individuals, 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 hypochondroplasia 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 fact is reflected in observational cohorts documenting individuals first diagnosed in late childhood or in adulthood, often during evaluation of short stature, back or limb symptoms, or when a relative is diagnosed[1,15,19,24].

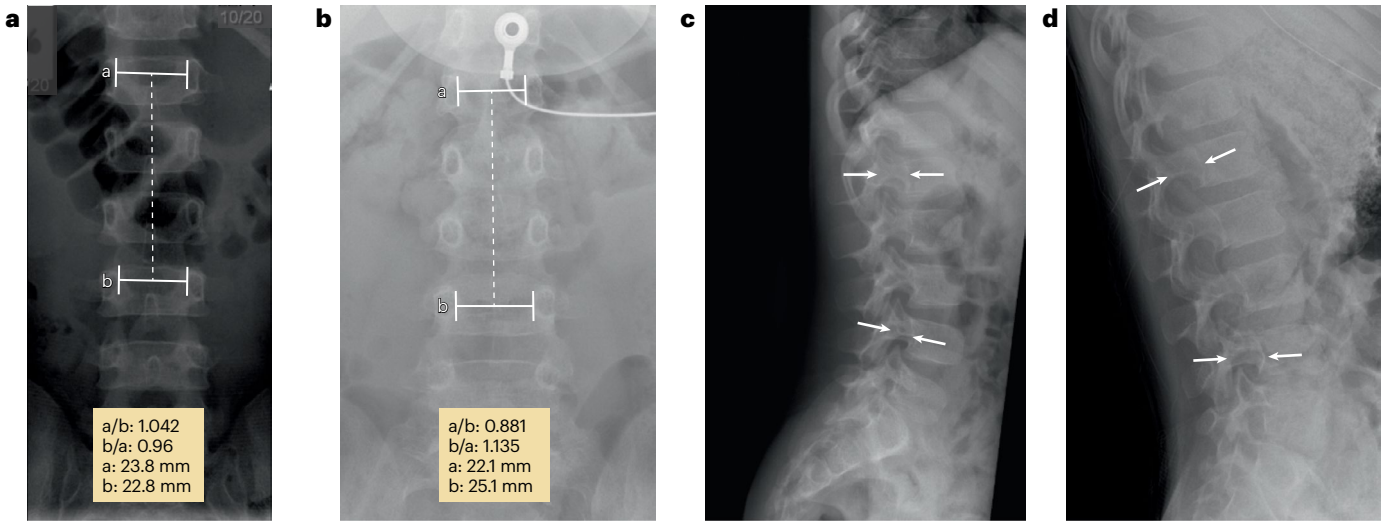

Fig. 2 | Radiographs showing key features of hypochondroplasia. Anteroposterior view of lumbar spine (part **a**) in a 5-year-old boy with a c.1620C>A variant in *FGFR3* and corresponding view (part **b**) in a healthy 5-year-old boy without hypochondroplasia. Callipers highlight the lack of normal widening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

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

Prenatal diagnosis of hypochondroplasia

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

Features of hypochondroplasia most commonly identifiable prenatally by ultrasound are shortening of the long bones and relative macrocephaly[24]. Detection as early as 20 weeks of gestation has been documented[24]. Although many countries do not schedule routine ultrasound assessments after 20 weeks, signs of hypochondroplasia become more pronounced in assessments performed at 24–28 weeks[32].

Although prenatal detection is possible, there are many cases where hypochondroplasia is not detected antenatally[10]. This later detection can be due to the variable presentation of hypochondroplasia — 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 hypochondroplasia could lead to higher levels of prenatal diagnosis or earlier postnatal referral and evaluation of individuals with hypochondroplasia. Indeed, when retrospectively examining ultrasonography images in individuals diagnosed antenatally, it is not unusual to see prenatal signs of hypochondroplasia 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 hypochondroplasia (mean score: 93; proportion scoring ≥70: 94%).

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

NIPS of cell-free fetal DNA (that is, of placental trophoblast origin) is being increasingly used in routine prenatal care[33,34], starting from around 10 weeks gestation. In some settings, this includes single-gene screening for variants in *FGFR3*, including those associated with hypochondroplasia. 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 hypochondroplasia 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 hypochondroplasia, chorionic villus sampling can 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[1,35]. How these are used in the diagnostic process will be guided by the clinical situation and established processes within individual health-care systems with appropriate pre-test genetic counselling.

R11: infants with a clinical suspicion of hypochondroplasia 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 hypochondroplasia 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 hypochondroplasia or other

Table 2 | Selected pathogenic and likely pathogenic *FGFR3* variants related to hypochondroplasia

Nucleotide change (exon number) NM_000142.5	Protein change (protein domain) NP_000133.1	ACMG classification	Key citations	Comments (genotype–phenotype, ClinVar ID, variant frequency)
c.251C>T (exon 3)	**p.Ser84Leu** (IgI)	**P**	Heuertz et al.[40] Hasegawa et al.[5] Andrade et al.[41] Plachy et al.[42] MacCarrick et al.[43]	16358 Moderate phenotype[40]
c.598C>T (exon 5)	**p.Arg200Cys** (IgII)	**LP**	Heuertz et al.[40] Almeida et al.[18] Hasegawa et al.[5]	287276
c.667C>T (exon 6)	**p.Arg223Cys** (IgII)	**LP**	Mejia et al.[44] Andrade et al.[41] MacCarrick et al.[43]	838879
c.791C>T (exon 7)	**p.Thr264Met** (IgII–IgIII linker)	**LP**	Song et al.[3] MacCarrick et al.[43]	1680030
c.802G>T (exon 7)	**p.Gly268Cys** (IgII–IgIII linker)	**LP**	Heuertz et al.[40]	1680033
c.833A>G (exon 7)	**p.Tyr278Cys** (IgIII)	**P**	Heuertz et al.[40] Song et al.[3] Chen et al.[45] Xue et al.[17] Li et al.[46] Zhao et al.[47] Chandler et al.[48] Cheung et al.[9]	16357 Severe phenotype, overlapping with achondroplasia in some patients[45,46]
c.835A>T (exon 7)	**p.Ser279Cys** (IgIII)	**LP**	Heuertz et al.[40] Friez et al.[49]	16356 Severe skeletal phenotype overlapping with achondroplasia at birth, then evolving to mild–moderate hypochondroplasia[49]
c.970C>G (exon 7)	**p.Leu324Val** (IgIII)	**LP**	Saito et al.[50] Ishii et al.[51] MacCarrick et al.[43]	1680048
c.971T>A (exon 7)	**p.Leu324His** (IgIII)	**LP**	Nagahara et al.[52] Ishii et al.[51]	No ClinVar ID
c.983A>T (exon 7)	**p.Asn328Ile** (IgIII)	**LP**	Winterpacht et al.[53] Heuertz et al.[40]	65916
c.1043C>G (exon 7)	**p.Ser348Cys** (IgIII)	**LP**	Couser et al.[54] Bengur et al.[55] Hasegawa et al.[56] Chaudhry et al.[57]	1526266 Severe hypochondroplasia phenotype, overlapping with mild achondroplasia, acanthosis nigricans
c.1052C>T (exon 7)	**p.Ser351Phe** (IgIII)	**LP**	Yao et al.[58] MacCarrick et al.[43]	649812
c.1052C>G (exon 7)	**p.Ser351Cys** (IgIII)	**LP**	Ishii et al.[51] MacCarrick et al.[43]	372751
c.1075+95C>G (intron 8)	p.A359delinsG TGFCCCCCSAL SGGRWLGTR QSCQDGRESS (TM)	**LP**	Xu et al.[28] Ouedraogo et al.[39]	2664079
c.1138_1139GG>AA (exon 10)	**p.Gly380Lys** (TM)	**LP**	Almeida et al.[18] Santos et al.[59]	No ClinVar ID
c.1612A>G (exon 13)	**p.Ile538Val** (TK1)	**P**	Grigelioniene et al.[60] Plachy et al.[42] MacCarrick et al.[43]	16345

Table 2 (continued) | Selected pathogenic and likely pathogenic *FGFR3* variants related to hypochondroplasia

Nucleotide change (exon number) NM_000142.5	Protein change (protein domain) NP_000133.1	ACMG classification	Key citations	Comments (genotype–phenotype, ClinVar ID, variant frequency)
c.1618A>G (exon 13)	**p.Asn540Asp** (TK1)	**LP**	–	374828
c.1619A>C (exon 13)	**p.Asn540Thr** (TK1)	**P**	Deutz-Terlouw et al.[61] Barbour et al.[62] MacCarrick et al.[43]	16344
c.1619A>G (exon 13)	**p.Asn540Ser** (TK1)	**P**	Mortier et al.[63] Thauvin-Robinet et al.[64] MacCarrick et al.[43]	16349
c.1620C>A (exon 13)	**p.Asn540Lys** (TK1)	**P**	Bellus et al.[65] Prinos et al.[66] Xue et al.[17] MacCarrick et al.[43]	16337 Most common hypochondroplasia causative variant. Variable phenotypes, but often severe and can overlap with achondroplasia[17]
c.1620C>G (exon 13)	**p.Asn540Lys** (TK1)	**P**	Bellus et al.[65] Prinos et al.[66] Xue et al.[17] MacCarrick et al.[43]	16338 Most common hypochondroplasia causative variant. Variable phenotypes, but often severe and can overlap with achondroplasia[17]
c.1948A>C (exon 15)	**p.Lys650Gln** (TK2)	**P**	Bellus et al.[37] Blomberg et al.[67] Ishii et al.[51] Xue et al.[17]	16348 Acanthosis nigricans Mild–moderate skeletal phenotype
c.1949A>C (exon 15)	**p.Lys650Thr** (TK2)	**P**	Berk et al.[68] Castro-Feijoo et al.[69] Muguet Guenot et al.[70] Xue et al.[17] MacCarrick et al.[43]	65855 Acanthosis nigricans Mild–moderate skeletal phenotype
c.1950G>T (exon 15)	**p.Lys650Asn** (TK2)	**P**	Bellus et al.[37]	16346 Mild–moderate skeletal phenotype
c.1950G>C (exon 15)	**p.Lys650Asn** (TK2)	**P**	Bellus et al.[37]	16347 Mild–moderate skeletal phenotype
c.2005C>G (exon 16)	**p.Arg669Gly** (TK2)	**LP**	Spurna et al.[71] Patani et al.[72]	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 hypochondroplasia were not included in this table when evidence thus far was insufficient to declare them as pathogenic (P) or likely pathogenic (LP), or phenotypic data were not available. Examples of this include p.Asn262His[40], p.Ser269Cys[73], p.Leu326Trp[74], p.Gly342Cys[75], p.Glu360Lys[18], p.Val381Glu[40] and p.Gly382Asp[76]. Variants considered causative for hypochondroplasia 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 hypochondroplasia can be found on the IAF website at achondroplasiaforum.com/resources. If ambiguity persists, multidisciplinary expert opinion, including clinicians and molecular geneticists with experience in skeletal dysplasia genetic studies, is encouraged. ACMG, American College of Medical Genetics.

skeletal dysplasia. This consideration can help to inform the diagnostic process, based on current understanding of relevant autosomal dominant inherited conditions[1].

R13: hypochondroplasia 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 hypochondroplasia that lack a variant within *FGFR3*[4,5,18]. It had previously been reported that this figure was approximately 30% of patients with hypochondroplasia[17]. However, a study from 2014 of 29 patients with hypochondroplasia found that only two lacked a hypochondroplasia-associated variant within *FGFR3*; the authors suggested that incomplete genetic screening of *FGFR3* in previous studies could account for this apparent disparity[17].

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

R14: although the most common hypochondroplasia-causing variants are those leading to the p.N540K (p.Asn540Lys) substitution, several other variants causing hypochondroplasia 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[36], primarily driven by missense variants. Although 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 syndrome (OMIM#616482) whereas p.Lys650Asn, p.Lys650Gln and p.Lys650Thr cause milder phenotypes fitting a diagnosis of hypochondroplasia[37]. The diagnostic criteria refer to heterozygous pathogenic or likely pathogenic variants (per American College of Medical Genetics and Association for Molecular Pathology guidelines)[38] specifically linked to hypochondroplasia, for which Table 2 provides a selection. Variants should be annotated using the 'standard' Matched Annotation from the NCBI and EMBL-EBI (MANE) transcript (NM_000142) to avoid misinterpretation.

Hypochondroplasia 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[28,39]. No deletions or duplications involving *FGFR3* have been reported to cause hypochondroplasia[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 substantial number of variants that should be classified as variants of unknown significance (VUS), not only the ones affecting previously unreported amino acid residues[38]. Difficulties in interpretation derive from lack of detailed phenotypic descriptions or functional studies in the literature, making it difficult to apply American College of Medical Genetics criteria confidently even when one identifies some of the previously reported variants (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 versus inherited). We anticipate additional hypochondroplasia-associated variants will continue to be identified and, because of this, genetic analysis of *FGFR3* in individuals with suspected hypochondroplasia should refer to online resources (for example, ClinVar and Leiden Open Variation Database) for the latest data, and expert consultation might be required.

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

Depending on the care pathways within the health-care system, this assessment and (if appropriate) the subsequent genetic counselling can be undertaken by a variety of specialists. Where possible, these specialists should have previous experience with hypochondroplasia and skeletal dysplasia. As previously mentioned, it is not uncommon for a diagnosis of hypochondroplasia to lead to further diagnoses within a family. Multiple family members carrying the same variant can 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

Box 2 | Major and minor criteria for hypochondroplasia diagnosis

Major criteria for hypochondroplasia diagnosis

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

Minor criteria for hypochondroplasia diagnosis

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

Family history: a first-degree relative who meets the suspected hypochondroplasia diagnostic criteria (Box 1).

[a]Standard deviation of appropriate unaffected background population distribution. [b]HCH-I is defined as height *z* score minus half the head circumference *z* score[6]. [c]If the patient meets major criterion 1 (disproportionate short stature), minor criteria 1 and 2 should not be used.

need for real-world testing and validation of these recommendations. This validation will provide data to further strengthen and develop our understanding of the diagnostic process for hypochondroplasia, and to inform future recommendations. There is also a need for testing, implementation and validation of the various grading and/or classification systems that have been developed to assess different aspects of hypochondroplasia[3,6,9,25]. This work 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 the past 5 years to improve our understanding of the effect of the various identified variants within *FGFR3*, further work is needed to help characterize the potential effects of VUS. It is also expected that, with rigorous genetic analysis more widely available than in the past, additional variants within *FGFR3* will be identified. Research is needed into the ways these variants affect individuals with hypochondroplasia and genotype–phenotype correlations. With the increasing availability of massively parallel sequencing customizable gene panels, and the sharing of resulting data, it is also important to characterize the proportion of individuals with suspected hypochondroplasia, or hypochondroplasia '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 that neuroimaging can play in the diagnosis of hypochondroplasia; for example, how neuroimaging findings are associated with neurological clinical findings and what these associations can tell us about the true prevalence of neurological complications in hypochondroplasia.

Strengths and limitations

The main strengths of this Consensus Statement are that it builds on the findings of multiple studies in hypochondroplasia and combines these findings with the experience from a broad international panel of hypochondroplasia experts from a variety of relevant fields (endocrinology, genetics and 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. Owing to this, statements are often based on findings from small cohort studies and prevalence estimates of specific criteria could be biased based on the setting in which these small cohort studies were recruited. 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 recognizes that access to molecular diagnostics varies globally. These recommendations are intended to be flexible and applicable across diverse health-care settings, with clinical and radiographic criteria remaining central to diagnosis when genetic testing is unavailable.

Conclusion

These expert guidelines provide a practical framework to help guide the diagnosis of hypochondroplasia in both general and expert clinical settings. These guidelines 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.

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Author contributions

R.S., A.D., M.S.C., J.H.-F., S.O.F., A.D.C. and A.C.O. researched data for the article. All authors contributed substantially to discussion of the content. R.S., A.D., M.S.C., J.H.-F., S.O.F., A.C., M.M., A.C.O. and S.B.S. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

This work was supported by an unrestricted educational grant from BioMarin. A.D. has served as a consultant for BioMarin, Ascendis Pharma, QED, Novo Nordisk, Pfizer, Sandoz, and Eton Pharmaceuticals and received grant funding from BioMarin and Pfizer. M.S.C. 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 and BioScientifica. M.S.C. is also an unpaid member of the Drug Medical Committee for a trial in achondroplasia for Ascendis Pharma, and holds unpaid leadership or fiduciary roles in the Skeletal Dysplasia Group, Skeletal Dysplasia Management Consortium and the Achondroplasia Network Meeting. J.H.-F. has received grants and contracts for clinical trials from BioMarin, BridgeBio Pharma and Pfizer, has received consulting fees from BioMarin, BridgeBio Pharma, Ascendis Pharma, 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. S.O.F. has participated in advisory boards and given presentations for BioMarin, Sanofi, Ascendis Pharma, BridgeBio Pharma and Novo Nordisk, honoraria have been paid to his institution, and he is principal investigator in ongoing clinical trials for BridgeBio Pharma and Ascendis Pharma. M.A. 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. S.B., A.C., V.C.-D. and P.K. report no competing interests. V.F. has participated in hypochondroplasia and achondroplasia clinical research at the Garrahan Hospital on BMD with QED. T.K. has received lecture fees from Kyowa Kirin and Novo Nordisk, consulting fees from BioMarin and Kyowa Kirin and grants from BioMarin and Kyowa Kirin. J.L.J. 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 Pharma, and is a medical consultant for the Brazilian Achondroplasia Patient Organization (ANNABRA). M.M. 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 Pharma, and BioMarin; and has participated on a data safety monitoring board/advisory board for Pfizer. G.M. has received consulting fees and payment for lectures or presentations and financial support for attending meetings from BioMarin, Pfizer and Sanofi. N.N. has received consultancy/advisory board honoraria from BioMarin, Kyowa Kirin, Ascendis Pharma 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 Pharma, and Teijin. A.C.O. has received grant funding from Alexion, and honoraria from Alexion and BioMarin. K.O. has received fees for lectures and brochure production from BioMarin, and lecture fees from Alexion and Sanofi Japan. S.B.S. has received honoraria for lectures, advisory board

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International Achondroplasia Forum (IAF): https://achondroplasiaforum.com/
Leiden Open Variation Database (LOVD): https://www.lovd.nl/

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