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Earlier detection of hypochondroplasia: A large single-center UK case series and systematic review

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Abstract
Hypochondroplasia (HCH) is a rare autosomal dominant skeletal dysplasia condition caused by FGFR3 mutations leading to disproportionate short stature. Classically, HCH presents in toddlers or school-age children, as limb-to-trunk disproportion and is often mild and easily overlooked during infancy. We report experiences from a single-center UK HCH-cohort of 31 patients, the rate of antenatal HCH detection in our cohort (13/31, 41.9%) and describe relevant case-data for this subset of 13 patients. Inclusion criteria were patients with confirmed molecular HCH diagnosis (by age 3 years) and presenting with short long-bones or large head size on antenatal ultrasound scan. We then conducted a systematic literature review using PUBMED and MEDLINE, analyzing patients with HCH and related antenatal findings. Antenatally suspected (with subsequent molecular confirmation) HCH has been reported 15 times in the literature (2004–2019). Key markers (consistent in both groups) included reduced; femur length, humeral length and increased; biparietal diameter and head circumference. HCH is increasingly detected both antenatally and in infancy, contrary to previous descriptions. This is likely due to greater HCH awareness, improved imaging, and easier molecular testing. Thus, one should consider HCH outside the classical presenting period. Studying the natural history of younger patients with HCH is important with the advent of several targeted FGFR3 therapies currently in trials for Achondroplasia, that may soon be trialed in HCH.

KEYWORDS
FGFR3, hypochondroplasia, prenatal diagnosis

1 | INTRODUCTION

Hypochondroplasia (HCH), although a rare genetic disorder, is a relatively common skeletal dysplasia (SD) condition (some authors suggest the prevalence to be 1 in 33,000) caused by activating heterozygous mutations of the fibroblast growth factor receptor (FGFR3) gene (Bober, Bellus, Nikkel, & Tiller, 1999). The N450K variant accounts for around 70% of all reported patients (Rousseau et al., 1996). HCH is characterized by disproportionate short stature with limb rhizomelia, sometimes with facial dysmorphism (macrocephaly, frontal bossing, mid-facial hypoplasia) though often without and characteristic radiological features on skeletal survey (the commonest being; rhizomelic long bones with mild metaphyseal flare; lack of widening of the inferior lumbar interpediculal distances; mild-to-moderate brachydactyly;
short, broad femoral necks; and squared, shortened ilia. (Bober et al., 1999) Diagnosis is based on clinical and radiographic grounds but is challenging due to often subtle features and phenotypic overlap with other SD conditions; thus, molecular confirmation is key. HCH has similar skeletal features to achondroplasia (ACH) but milder presentation with less severe medical complications.

Classically HCH presents in toddlers or school-age children (with decreased growth velocity leading to short stature) since limb-to-trunk disproportion is often mild and easily overlooked during infancy (Stoll, Manini, Bloch, & Roth, 1985). The recent literature, however, demonstrates that HCH is clinically detectable earlier, even antenatally. Yet, this literature is often biased by patients with HCH with family history, priming clinicians to look for clinical features, rather than reflecting the earliest HCH detection in an unselected population. Thus, it does not reflect the unselected HCH presentation in the background population. Further bias includes patients reported without molecular confirmation of HCH, which considering the phenotypic overlap with other short stature conditions, creates doubt about the diagnostic accuracy or "purity" of the reports.

Documenting the earlier presentation (as compared with classical texts) of HCH in the unselected population is important, to prevent clinicians unduly discounting HCH diagnosis in infancy or antenatally. We report experiences from a single UK center, HCH-cohort (n = 31) and systematically review the literature to explore antenatal detection of HCH.

In the systematic review, we identify all patients with antenatally detected HCH and highlight common detection themes. On analysis of the local cohort, we further identify patients with HCH that are both molecularly confirmed and clinically diagnosed ante-natally and report the antenatal detection rate of HCH for the first time.

2 | BACKGROUND

HCH can be detected antenatally via sonography, based on short long-bone findings with or without increased biparietal diameter (BPD) and subsequent molecular confirmation (Stoll et al., 1985).

Prenatal HCH diagnosis, based exclusively on fetal sonographic measurements, is difficult. In 1985, Stoll et al. proposed that it may be possible to diagnose HCH antenatally with the assistance of the presence of family history (Stoll et al., 1985). Five years later, Jones et al. reported the first patient with HCH that was diagnosed prenatally in the absence of family history. However, this was deemed difficult to replicate, attributing to the unremarkable family history and mild features when compared with other SD conditions (Jones, Robinson, & Sperrazza, 1990). Distinct HCH antenatal sonographic measurements were first reported in 1999 by Huggins et al., on a 25 weeks gestation fetus with HCH, born to a mother with ACH and a father with HCH (Huggins, Mernagh, Steele, Smith, & Nowaczky, 1999). The long-bones appeared shorter than expected, whilst the head measurements (BPD and head circumference [HC]) remained normal. The commonest skeletal dysplasia condition to consider antenatally when short long bones and macrocephaly are present is ACH. It is presumed short long-bones in the absence of increased head measurements could suggest HCH. Huggins et al. concluded that HCH may be distinguished based on sonographic measurements solely (Huggins, Smith, et al., 1999). More recently, Saito et al., reported two patients with HCH where the diagnosis of HCH could have been made based on previous antenatal sonographic measurements, despite the actual diagnosis being made at 3 years (Saito et al., 2016).

3 | METHODS

3.1 | Editorial policies and ethical considerations

Ethics committee review for the local cohort was obtained (approval number 08/H0810/14). The systematic review aspect of the article by its nature is not subject to ethics review. Patient privacy and confidentiality have been protected where nonidentifiable local cohort data has been used.

3.2 | Cohort

The HCH MDT service/clinic at Evelina Children's Hospital (ECH) has an active cohort of 31 patients with molecularly confirmed HCH (April 2020), 13 of whom met the inclusion criteria for this study (with confirmed FGFR3 mutations—12 N540K and one R200C—and antenatal findings consistent with HCH). Inclusion criteria were patients with confirmed molecular HCH diagnosis (by age 3 years) and presenting with short long-bones or large head size on antenatal ultrasound scan (US). We chose to only include patients with a molecularly confirmed HCH diagnosis as a clinical diagnosis of HCH (without molecular confirmation) have historically been mislabeled.

Exclusion criteria were patients with an immediate family member suspected/diagnosed with ACH or HCH (so that any antenatal detection or suspicion of HCH was made without a priori knowledge, enabling determination of an “antenatal HCH detection rate” [AHDR] in its purest form without bias) and patients that were suspected with HCH but the pregnancy was terminated without molecular confirmation and absence of clinical postmortem findings (as such information is important to confirm that the diagnosis of HCH is secure).

3.3 | Systematic review

A systematic, retrospective search for reviews and primary research studies (short reports and case reports/series) was conducted using PubMed and MEDLINE databases, as shown in Figures 1 and 2. The specific search terms are shown in Table 1. Research articles dated from 2004 to 2019. Identified reviews and primary research studies were "title and abstract" screened, and results were merged from PubMed and MEDLINE. A full-text screen was undertaken by three independent assessors and any discrepancies settled by group discussion.
The inclusion and exclusion criteria for patients with HCH in the systematic review were the same as in the ECH cohort. All 15 patients with HCH identified through the systematic review were clinically suspected as having HCH based on antenatal US findings and had molecular confirmation by age 3 years. Age three was used as a cut-off as before this is uncommon for patients to present with clinical HCH. Terminated pregnancies were only included when there was clinical documentation of molecular confirmation of HCH. Patients with intermediate ACH-HCH were excluded (to ensure an unambiguous cohort). Intermediate ACH–HCH cases are defined as:

1. those cases where the variant is not the classical variant for ACH (G380R) or HCH (N540K) and the variant itself has been reported in the literature with a phenotype of "severe HCH/mild ACH" by expert clinicians as with S348C (Bengur, Ekmekci, Karaozlan, Guroz, & Alanay, 2020). In the case of S348C, the variant was reported three times with the same phenotype.

2. or those cases where the infant is compound heterozygote for N540K and G380R as one parent has ACH and one parent HCH, resulting in a blended phenotype and such patients were excluded (Huggins, Mernagh, et al., 1999).

4 | RESULTS

4.1 | Local cohort

The earliest confirmed molecular diagnosis of a patient with HCH was at 20 weeks (gestation) and latest at 3 years old. From those where data was recorded, the average age of genetic confirmation was 31 gestation weeks for those detected prenatally (n = 7: patients A1, A2, A6, A9, A10, A11, and A12; see Table 2). For those detected post-natally (n = 6: patients A3, A4, A5, A7, A8, A13), the average age of detection was 70.7 weeks, see Table 2 (range 1 month to 3 years).

All patients' reports documented antenatal US findings indicative of HCH: short long-bones and large HC. The earliest anomaly was detected at 20 weeks and the latest at 35 weeks. The most common sonographic feature of HCH was short long-bones (especially femurs), followed by large HC. Eleven patients with HCH documented short long-bones, of which three reported short femur length (FL) specifically. Three patients had a large head size. Both short long-bones and large HC, as well as a large abdominal circumference (AC), was reported for Patient A12. This patient's records demonstrated these features became more pronounced with gestational age.
There were 15 patients with HCH identified from the systematic review of eight different studies. These patients showed different \( \text{FGFR3} \) mutations: 12 had the N540K mutation, 1 L324V, 1 Y278C, and 1 S351C mutation. We have presented the \( \text{FGFR3} \) alterations as amino acid substitutions rather than gene variants as not all articles reported the gene variants. The earliest molecular confirmation was

**TABLE 1** Literature search terms

| Search                          | Database          | Search terms                                                                 | Limits applied |
|---------------------------------|-------------------|------------------------------------------------------------------------------|----------------|
| Review                          | PubMed            | Hypochondroplasia                                                           | Review         |
|                                 | MEDLINE           | Hypochondroplasia                                                           | Review         |
| Primary research studies        | PubMed            | Hypochondroplasia AND natural history OR phenotype OR antenatal OR prenatal OR detection OR trimester OR anomaly scan OR growth parameters OR growth curve OR birth length OR occipitofrontal circumference OR head circumference OR weight OR on ultrasound | None           |
|                                 | MEDLINE           | Hypochondroplasia AND natural history OR phenotype OR antenatal OR prenatal OR detection OR trimester OR anomaly scan OR growth parameters OR growth curve OR birth length OR occipitofrontal circumference OR head circumference OR weight OR on ultrasound | None           |

**4.2 Systematic review**

There were 15 patients with HCH identified from the systematic review of eight different studies. These patients showed different \( \text{FGFR3} \) mutations: 12 had the N540K mutation, 1 L324V, 1 Y278C, and 1 S351C mutation. We have presented the \( \text{FGFR3} \) alterations as amino acid substitutions rather than gene variants as not all articles reported the gene variants. The earliest molecular confirmation was...
made at 22 weeks (gestation) and latest at 3 years. All reports of patients demonstrated initial antenatal US findings suggestive of HCH (such as increased FL, humeral length [HL], and increased BPD/HC); the earliest detected anomaly was at 22 weeks and the latest at 37 weeks.

From those where data is available, the average age of molecular confirmation was 26 weeks for those detected prenatally (n = 6: patients B2, B3a, B3b, B4a, B4b, B6; see Table 3). For those detected postnatally (n = 9: patients B1, B5a, B5b, B7, B8a, B8b, B8c, B8d, B8e), the average age of detection was 48.9 weeks, see Table 3.

There is no single clinical or radiological feature unique to HCH since there is much overlap with ACH; thus several parameters were used to make a clinical diagnosis (Bengur et al., 2020; Bober et al., 1999). Saito et al. reported that abnormal FL and BPD in the third trimester is highly indicative of HCH, though not specific as would be seen in ACH too (Saito et al., 2016). The typical phenotype of HCH is

| Code | Genetic confirmation | Age of Genetic confirmation | Pregnancy history and information | Ultrasound scan information | Last seen |
|------|---------------------|-----------------------------|----------------------------------|----------------------------|-----------|
| A1   | N540K               | 38/40 weeks                 | Gestation: 40 weeks             | Short limbs                | 2 months  |
| A2   | N540K               | 22/40 weeks                 | First child                     | 20 weeks—short long legs   | 8 months  |
|      |                     |                             |                                  | W: 6 lb 6 oz               |           |
| A3   | N540K               | 18 months                   | Five older siblings             | 20 weeks—abnormally large head | ND³       |
| A4   | N540K               | 21 months                   | First child                     | 20 weeks—short femur       | 4 years 2 months |
|      |                     |                             | Gestation: 38 weeks             |                             |           |
|      |                     |                             | BW: 3.175 kg                    |                             |           |
| A5   | N540K               | 10 months                   | First child                     | Increase in HC             | 10 years 6 months |
|      |                     |                             |                                  |                             |           |
| A6   | N540K               | 28/40 weeks                 | First child                     | 28 weeks—reduced long bone length | ND        |
| A7   | N450K               | 1 month                     | ND                               | (CT scan at 30 weeks—short long-bones) | 11 years 11 months |
|      |                     |                             |                                  |                             |           |
| A8   | N450K               | 14 months                   | Gestation: 39 weeks             | 20 weeks—Y-short long bones | 3 years 11 months |
|      |                     |                             | BW: 2.96 kg                     |                             |           |
| A9   | N540K               | 20–32/40 weeks              | Gestation: 37 + 5 weeks         | 20 weeks—short limbs       | 1 years 6 months |
|      |                     |                             | BW: 2.66 kg                     |                             |           |
| A10  | N540K               | 34/40 weeks                 | Gestation: 38 weeks             | 29 weeks—significant shortening of long bones, all <3rd | 9 months |
|      |                     |                             | BW: 3.365 kg                    |                             |           |
|      |                     |                             | OFC: 35 cm                      |                             |           |
| A11  | N540K               | 33/40 weeks                 | Gestation: 39 weeks             | 29 weeks—short long limbs  | 8 months 3 weeks |
|      |                     |                             | BW: 3.365 kg                    |                             |           |
|      |                     |                             | HC: 35 cm                       |                             |           |
| A12  | R200C               | 34/40 weeks                 | Gestation: 39 weeks             | 29 weeks—short femur, large HC.34 weeks—features more pronounced: Increased HC and an increased AC | 3 months 2 weeks |
|      |                     |                             | BW: 4.73 kg                     |                             |           |
|      |                     |                             |                                  |                             |           |
| A13  | N540K               | 3 years                     | Gestation: 41 weeks             | 35 weeks—short femur       | 11 years 7 months |
|      |                     |                             |                                  |                             |           |

¹Not documented.
**TABLE 3**  HCH patients from systematic review search

| Patient code | Author                     | Journal                | No. of patients (n = 15) | Age of detection | Pathogenic variant | Age at ultrasound (weeks) | Head circumference (cm) | Biparietal diameter (cm) | Femur length (cm) | Humeral length (cm) |
|--------------|----------------------------|------------------------|--------------------------|------------------|--------------------|--------------------------|------------------------|-----------------------|-------------------|-------------------|
| B1           | Kataoka et al., 2004        | Prenat Diagn           | 1                        | 39 weeks         | N540K              | 37 (equivalent to 39 weeks) | 9.15 (equivalent to 28 weeks) | 5.0 (equivalent of 28 weeks) | ND                | ND                |
| B2           | Bonnefoy et al., 2005       | Fetal Diagn Ther       | 1                        | 32/40 weeks      | N540K              | 32 (equivalent to 40 weeks) | ND                     | 5.3 (equivalent to 28 weeks) | 4.7 (equivalent to 28 weeks) | ND                |
| B3a          | Karadimas et al., 2006      | Am J Med Genet         | 2                        | 23/40 weeks      | N540K              | 23 (normal)             | 6.3 (normal)           | ND                   | <5th centile     | <5th centile     |
| B3b          |                            |                        | 22/40 weeks               | Normal            | ND                 | 10th to 5th centile     | 10th to 5th centile     | ND                   | <3rd centile     |
| B4a          | Hatzaki et al., 2011        | Am J Med Genet         | 2                        | 23/40 weeks      | N540K              | 23 (normal)             | 6.30 (normal)          | 7.8 (upper limits)    | 4.3 (<3rd centile) | 4.2 (3rd centile) |
| B4b          |                            |                        | 23/40 weeks               | ND                | ND                 | ND                       | 3.79 (<5th centile)    | 3.79 (<5th centile)    | ND                |
| B5a          | Saito et al., 2012          | Am J Med Genet         | 2                        | 3 years          | L324V              | 32 (normal)             | 8.2 (normal)           | 5.14 (persistent shortening, −2.1 SD) | 4.59 (<2.5th centile) |
| B5b          |                            |                        | 3 years                   | ND                | ND                 | ND                       | 9.3 (<2.5 SD)          | 5.78 (persistent femoral shortening, −2 SD) | ND                |
| B6           | Chen et al., 2013           | Taiwan J Obstet Gynecol| 1                        | 30/40 weeks      | Y278C              | 30 (normal)             | 7.38 (normal)          | 3.97 (<5th centile)    | 3.64 (<5th centile) | ND                |
| B7           | Cesaretti et al., 2014      | Prenat Diagn           | 1                        | At birth, 38 weeks | N540K              | 23 (Postnatal HC−33.4 cm (10th–25th centile)) | ND | <5th centile  | ND                |
| B8a          | Saito et al., 2016          | Pediatr Radiol         | 5                        | 1 month          | N540K              | LT                       | ND                     | ND                   | ND                | ND                |
| B8b          |                            |                        | 2 years                   | LT                | ND                 | +3.3 SD                 | −3.3 SD                | ND                   | ND                | ND                |
disproportionate short limbs, with FL being the most common (and earliest detected) radiological finding (Bober et al., 1999) which correlates with all studies that reported FL (FL was low in all 14 patients where FL was documented). HL was low in six and high in one of the seven patients in which it was documented, thus a useful marker for HCH. Alongside this BPD, as a marker of head size, was increased in five out of 13 reported patients with HCH, along with HC which was not reported as often as BPD. BPD was larger than normal in five patients with HCH, normal in seven patients, and it was not documented for three patients. These patients had larger BPD for gestational age, and their heads appeared larger to their body and limbs.

AC and FL/AC were infrequently reported, and measurements were inconsistent, preventing any association. The facial appearance was noted in several patients with HCH but this reporting was not consistent enough to draw conclusions, this may be due to a normal facial appearance which is associated closely with HCH and one of the differentiating factors between HCH and ACH. It should be noted that when craniofacial deformities were present, HC is a better measurement than BPD for assessing the head size, since BPD is dependent on head shape whereas HC is independent. Where craniofacial abnormalities are present and distort the head shape the BPD may under or overestimate the head size (Loughna, Chitty, Evans, & Chudleigh, 2009). Digits and fetal weight were not consistently reported, as they are not parameters suggestive of HCH antenatally.

5 | DISCUSSION

Knowing how early and in what way HCH presents in the unselected population is important, as some clinicians may discount the possibility of HCH in a child aged less than 2–3 years old based on the classical reported age of presentation. In this article, we have tried to ascertain those patients with molecularly confirmed HCH in both the reported literature and our large cohort of HCH patients, where HCH was detected antenatally or soon after birth, without a prior family history. We identified 15 patients with HCH in the reported literature with suggestive antenatal findings (molecular confirmation occurring between age 22 weeks gestation to 3 years of age) and an additional 13 patients with HCH in our 31 patient cohorts (molecular confirmation occurring between age 20 weeks gestation to age 3 years). Thus, in total, 28 patients with antenatal HCH findings are reported having molecular confirmation by age 3 years. Therefore, HCH as a potential diagnosis should not be dismissed lightly in children under age 3 years, where there is decreasing growth velocity, short stature (even if mild)/skeletal disproportion/macrocephaly/suggestive antenatal or radiological findings.

Our findings strengthen the previous reported antenatal sonographic findings suggestive of HCH, that is, decreased FL and or HL and increased BPD and or HC, illustrated by Figure 3a,b. The inverse relationship between FL and BPD in HCH is more marked as the gestational age increases. Short FL is the most useful of these parameters for HCH detection, and its detection should include a complete assessment of the patient to consider multiple SD conditions, as well
as consideration for molecular testing of not only chromosomal imbalances but FGFR3 testing. In light of our findings, we suggest that when antenatal short bones are detected one should not look for ACH hotspot mutations alone (i.e., G380R hotspot; c.1138G>A (p.G380R) is identified in approximately 98% of individuals with ACH; c.1138G>C (p.G380R) in 1%) but also HCH hotspot mutations [i.e., N540K hotspot: c.1620C>A and c.1620C>G (p.N540K) in 70% of patients with HCH] and consider investigating for rarer variants as outlined by Chen et al. (Bober et al., 1999; Pauli & Legare, 1996). Ideally, FGFR3 sequencing should be performed if possible, as there are now many more mutations known to cause HCH than the well-known N540K hotspot (Jones et al., 1990).

The data discussed in our literature search pertains to US findings in the main, as opposed to radiological changes. The medical literature surrounding the radiological detection of HCH has emphasized the association of lack of interpedicular widening in the lumbar region with HCH (Panda, 2014; Sargar, Singh, & Kao, 2017). Diagnostic measures for HCH should include imaging of the anterior–posterior spine, which is of importance in identifying interpedicular distances, the decrease of which is more apparent with age (Bober et al., 1999; Panda, 2014). A lumbosacral spine radiograph taken of a 28-month-old child with HCH, referred for assessment of short stature and genu varum, was reported to show normal interpedicular distances (Ahn, Kim, Baek, Bae, & Lee, 2016). Further study, consisting of an 8-year-old boy and his 32-year-old mother showed unchanged interpedicular distances in L1–L5 regions for both patients (Chen et al., 2018). Therefore, despite this radiological feature being commonly reported, there has been no mention of its presence in the postnatal or under 3 years age group. This may be due to the subtlety of radiological features during this period. This information would be vital in establishing whether these radiological findings may be diagnostic at an earlier date.

In the future, with advances in CT technology and reduced radiation dosing, CT fetal scanning may become an adjunct tool in fetal SD diagnosis if skeletal sonographic findings are abnormal.

Though the overall total number of patients with HCH is small, it is still useful to explore the rate of patients that are antenatally detected with HCH in comparison to a large current cohort of patients with HCH. Considering the 31 patients in our single-center UK cohort, all with molecular confirmed HCH, antenatal findings suggestive of HCH were detected in 13 (49.1%). The cohort is pediatric, with ages ranging from 14 months to 17 years 8 months old, with most patients under 13 years old. This means that all our patients were born after 2004, and most after 2010 at a time when genetic testing became more widespread and significant advances in knowledge and antenatal sonography occurred.

In the six patients from our cohort where molecular confirmation occurred postnataally, reasons for later detection included: antenatal measurements were mild and when born there was no clinical suspicion of SD conditions or testing was offered prenatally but was refused by parents.

Making an earlier diagnosis of HCH is important for many reasons, including the possibility of administering emerging therapies. C-natriuretic peptide (CNP) analogues and drugs that modify the FGFR3 pathway are increasingly being trialed in younger patients, including under 6 months of age (BioMarin Pharmaceutical, 2020). It is expected that the same drugs being trialed in ACH will be efficacious in HCH. Some experts predict that earlier treatment will be more beneficial in terms of long-term growth and prevention of possible complications. Thus earlier detection of HCH is key. Additionally, detection in the antenatal period allows improved assessment and monitoring through the preambulant years, a period where current data is lacking.

Our study provides interesting data on the relative presentation of HCH as compared with ACH in a single UK center. HCH is a relatively common skeletal dysplasia, though accurate prevalence data is not readily available. Some authors suggest the prevalence to be 1 in 33,000 or close to that of ACH (1 in 20,000–25,000 live births) (Bober et al., 1999; Pauli & Legare, 1996). In the ECH HCH–ACH MDT (one of, if not the, largest UK single-center ACH and HCH patient-cohorts) cohort of 198 patients, 31 patients had HCH. Outwardly this suggests HCH is a lot less prevalent than ACH, but the figure is heavily biased and not reflective of the actual prevalence, which is probably a lot higher. This is because; firstly the HCH–ACH MDT clinic at GSTT attracts patients nationwide and since it runs several key trials for ACH (and currently none for HCH), it disproportionately attracts patients with ACH; secondly, HCH is milder than ACH, so many patients are unlikely to be referred for quaternary level input and lastly HCH can be a difficult diagnosis to make (especially since height ranges can overlap with those in the unaffected population,
and many affected patients have no symptoms except short stature, thus do not seek medical intervention) making case-ascertainment challenging. Considering this, the patients with HCH that present to our center are naturally biased toward patients where the phenotype was clearer and perhaps more striking and thus more amenable to molecular confirmation. In our cohort of patients, all but one patient had the classic N540K mutation. No genotype–phenotype correlation could be drawn concerning antenatal detection of HCH based on genotype.

The earlier detection of known rare disorders (sometimes with a milder presentation) is becoming more apparent as imaging modalities improve, and our knowledge of rare disorders/genetic testing improves, so what we find in HCH is a paradigm for other rare disorders.

We believe the threshold for undertaking exome or genome sequencing upon the detection of fetal anomalies will lower. In the UK, the national fetal rapid exome sequencing service (R21) (launching late 2020) has five eligible categories for testing including "suspected skeletal dysplasia conditions," demonstrating increasing access to testing and lowering of the testing threshold (UK Genetic Testing Network, 2019). The R21 service is born out of research from the prenatal assessment of genomes and exomes (PAGE) study, which showed fetal exome yields of 8.5% in unselected cases of fetal anomalies, though further work and other studies showed that in selected cases (after genetics reviews) yields can increase to over 30% (Normand et al., 2018). Specifically the highest yield in any subcategory of fetal exome testing occurred in SD conditions (after case selection post genetics review) with rates of over 80% (Yang et al., 2020). Therefore, detection of SD conditions in the prenatal period will increase. We believe the identification of short FL in the presence of other markers suggestive of SD will lead to more genetic testing and likely increased pick up of SD conditions, that is, HCH and ACH at an earlier stage. This will no doubt be useful for parents and clinicians since ACH in particular, can have very serious consequences in the infant period requiring monitoring and surveillance, for example, foramen magnum stenosis. With HCH, earlier detection, not only avoids protracted diagnostic investigations later in life but may also lead to an incidental diagnosis in any affected parents, so they can get the right help (as has been seen in our clinic). Again with the advent of several different FGFR3 targeted therapies, earlier detection will allow for earlier treatment which we hope will not only improve vertical growth but decrease potential complications.

In conclusion, this article supports the previous literature and strengthens it specifically by analyzing unselected patients with molecularly confirmed HCH. It reaffirms the increasing antenatal detection of HCH, along with the key sonographic parameters and highlights patients that were detected with HCH at an even earlier gestation (20 weeks) than previous. The increasing detection of HCH, both antenatally and in infancy is contrary to classical texts and is likely due to greater HCH awareness, improved imaging, and greater molecular testing. Thus, one should consider HCH outside the classical presenting period. Studying the natural history of earlier patients with HCH is important with the advent of several targeted FGFR3 therapies as such therapies may soon be trialed in HCH and are likely most efficacious during the earliest skeletal maturation.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Ataf H Sabir: Manuscript prepared, conceptualized, and researched; Ataf H Sabir, Jameela Sheikh, Ananya Singh, and Elizabeth Morley cohort data researched and analyzed; and conducted systematic review; Moira Cheung, Alessandra Cocca, Melita Irving, Ataf H Sabir clinical care and phenotyping of local cohort. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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