Beyond Boundaries: The Continuous Spectrum in FGFR3-Related Conditions

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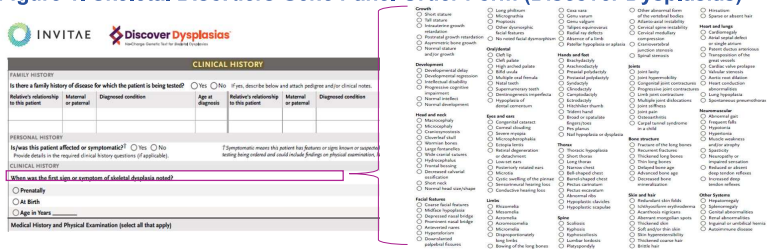
Background

- Prior to the era of molecular testing, conditions resulting from gain-of-function variants in the *FGFR3* gene (e.g., thanatophoric dysplasia, TD; achondroplasia, ACH; hypochondroplasia, HCH) were diagnosed primarily by clinical and radiological imaging.
- Across *FGFR3*-related conditions, there are shared clinical characteristics with varying prominence, including disproportionate short stature (short-limbed), craniofacial features (e.g., frontal bossing and midface hypoplasia), and other skeletal abnormalities.
- Despite having a shared molecular genetic etiology, these conditions continue to be considered distinct clinical diagnoses. This delineation can be clinically meaningful, but in practice an overlapping clinical spectrum is commonly noted.
- Although many disease-causing variants have been identified and continue to be discovered, a few specific variants account for the majority of diagnosed cases.
- Even within these well-characterized variants, there is a spectrum of phenotypes reported, challenging the lines between clinically defined categories.[1–5] This ambiguity can lead to diagnostic challenges and delays in accessing appropriate care.

Methods

- To characterize the spectrum of phenotypes associated with FGFR3, we analyzed de-identified data collected as part of the no-cost Discover Dysplasias gene panel testing program[6] for all patients who had one of the ACH or HCH "classic" genetic variants in *FGFR3*: p.Gly380Arg (ACH) and p.Asn540Lys (HCH).
- Data included 1) *FGFR3* variant, 2) clinical signs/symptoms as reported by ordering clinician on test order form (Figure 1), and 3) patient height/age.
- Collection of data was via test request form with clinical features outside of eligibility criteria being optional; only forms with ≥1 completed optional field were included.

Figure 1. Skeletal Disorders Gene Panel Order Form (Discover Dysplasias)



Results

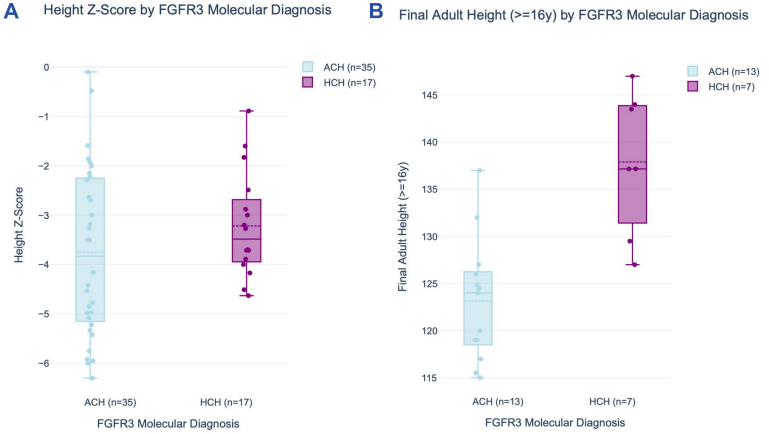
Population

- A total of 385 patient results were included: 296 with the most common ACH-associated variant (p.Gly380Arg) and 89 with the most common HCH variant (p.Asn540Lys), referred as ACH and HCH, respectively.
- Height Z-score was reported in 52 patients and final adult height in 20. The majority (93.2%, N=359) of patients had clinical features indicated on the order form.
- Of the clinical features assessed, the only one exclusive to ACH was spinal stenosis. All other clinical features of interest were represented in both groups (ACH vs HCH), including trident hand (36% vs 8%), macrocephaly (54% vs 51%), rhizomelia (64% vs 43%), and frontal bossing (41% vs 29%) (**Figure 2**).
- ACH and HCH had significantly decreased Z-scores, with more prominent deficits in the ACH group. Within both ACH and HCH, there was a high degree of variability in Z-score and a significant overlap between ACH and HCH groups (mean [std]: –3.8 [1.7] and -3.2 [1.1], respectively). A similar trend was observed when looking at final adult height (defined as height at ≥16y) (**Figure 3**).
  - Interpretation of these results may be limited by the small number of patients with reported height Z-score and final adult height

Figure 2. Prevalence of Clinical Signs & Symptoms by *FGFR3* Variant

	p.Gly380Arg (n=276)	p.Asn540Lys (n=83)
Narrow Chest	7.2%	2.4%
Spinal Stenosis	3.3%	0
Developmental Delay	11.2%	14.5%
Frontal Bossing	40.9%	28.9%
Macrocephaly	54.3%	50.6%
Midface Hypoplasia	32.6%	19.3%
Short Stature	80.4%	95.2%
Rhizomelia	64.1%	43.4%
Trident Hand	35.9%	8.4%

Figure 3. Height by *FGFR3* Variant: A) Z-score and B) Final Adult Height



Conclusions

There is a phenotypic and clinical spectrum within and between disease-causing variants

- Both patients with ACH and those with HCH present on a phenotypic spectrum.
- The clinical spectrum of ACH and HCH overlap with one another.

Suggesting that these FGFR3-related conditions may be genetically distinctive they also can be conceptualized as part of a shared disease spectrum.

References

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Disclosures

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