

LETTER

Novel FGFR3 mutations in exon 7 and implications for expanded screening of achondroplasia and hypochondroplasia: a response to Heuertz *et al*

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We read with great interest the study by Heuertz *et al*¹ in *European Journal Human Genetics* presenting novel FGFR3 mutations causing achondroplasia (ACH) and hypochondroplasia (HCH). We agree with the authors' recommendation to expand the screening for patients with the clinical features of ACH or HCH who lack the most common variants of the disorders. Specifically, the presence in exon 7 of four out of seven mutations (S279C, Y278C, G268C, and N262H) has particular relevance because exon 7 is routinely sequenced for mutations indicative of craniosynostosis and thanatophoric dysplasia. Therefore, expanded screening of exon 7 is straightforward using existing protocols.

It should be noted that one of the mutations Heuertz *et al* deemed novel has previously been reported. Our laboratory identified the S279C mutation in a newborn male diagnosed with ACH.² The phenotype appears to be somewhat variable in these cases. Since our report in 2001, the phenotype of the patient with the S279C variant has evolved from features of ACH noted at birth toward a milder HCH phenotype in early childhood. We were interested to learn that the clinical manifestations

observed by Heuertz *et al* in patient 2, a female with mutation Y278C and an ACH phenotype at birth, had similarly changed to a milder HCH phenotype by the age of 3.5 years. Unlike our S279C patient, however, patient 1 in Heuertz *et al*, a male who also harbours the S279C variant, has maintained a more typical ACH phenotype. This apparent clinical heterogeneity of S279C patients still supports the increased severity of phenotypes associated with cysteine residues, as suggested by Heuertz *et al*.

Our laboratory has tested approximately 400 patients for ACH and/or HCH since January 2001. Samples were submitted by our own clinics or from a variety of outside sources. They represent the full range of sample types commonly received at a large, full-service molecular diagnostic laboratory, and consequently, the certainty of each clinical diagnosis and the precise reason for testing may vary substantially. Our facility has banked DNA samples from many of the patients for whom an FGFR3 mutation has not been discovered. To test the practicality of the expanded screening recommended by Heuertz *et al*, we selected those samples that tested negative for the most common mutations for ACH and/or HCH for further testing of FGFR3 exon 7. Some of those were then excluded for obvious reasons, for example they had already been referred for additional FGFR3 testing that included exon 7 or were presumably unaffected family members of patients with known common mutations. The resulting cohort consisted of 222 samples collected between January 2001 and February 2007. Of these, 78 had previously tested normal for ACH only, 85 tested normal for HCH only, and 59 tested normal for both disorders (see Table 1). We were particularly interested in the 59 patients referred for both HCH and ACH testing who, therefore, might possess overlapping phenotypes. Heuertz *et al* suggest that such phenotypes would increase the likelihood of finding novel mutations, as compared with those having classical HCH phenotypes who would most likely be referred for HCH testing only.

None of the patients originally tested for HCH were found to have any pathogenic changes in exon 7. One patient (a newborn female) originally tested for ACH only was found to have the S279C variant, bringing the total reported cases to three. No other patient was found to have

Table 1 –FGFR3 exon 7 screening results

	Negative for ACH only	Negative for HCH only	Negative for ACH & HCH	Total
Total patients	78	85	59	222
Abnormal for S279C	1 (1.3%)	0	0	1 (0.5%)
Abnormal for R248C	2 (2.6%)	0	0	2 (0.9%)
Total abnormal	3 (3.8%)	0	0	3 (1.4%)

ACH, achondroplasia; HCH, hypochondroplasia.

any of the four mutations reported by Heuertz *et al*; however, we did find the R248C mutation which is associated with thanatophoric dysplasia type 1 in two of the samples. One was a prenatal sample and the other was from a newborn male. Both samples had been tested for ACH only.

These findings seem to further indicate that the routine screening of exon 7 in newborns and patients diagnosed prenatally with ACH is advisable, where it is practical to do so. Indeed, it is especially worth considering in cases diagnosed prenatally after 26 weeks of gestation. Thanatophoric dysplasia is unlikely to be overlooked during routine ultrasound screening in the second trimester, but the signs of ACH are typically subtle into the third trimester. We concur with Heuertz *et al* that FGFR3 hot spots should be tested first, but that follow-up testing of additional exons, especially exon 7, is appropriate. However, detection rates likely will vary depending on how samples were selected for initial testing. For example, samples sent simply to reassure an anxious parent that their child really is unaffected can be assumed negative, whereas those suspected by an experienced clinician to be affected should produce a significant yield. Thus, it might

be cost-effective for laboratories that have little control over the samples or the accompanying clinical information they receive to first contact the referral source for more detailed information.

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References

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