Achondroplasia (ACH) is an autosomal dominant disorder characterised by 12micromelic short stature and a unique facial appearance.1,2 Recent reports have confirmed that more than 98% of patients with ACH have an identical glycine-to-arginine substitution at residue 380 (G380R) of fibroblast growth factor receptor 3 (FGFR3)3-6. This exceptional genotypic homogeneity is likely to contribute to the phenotypic homogeneity of ACH. Hypochondroplasia (HCH) is another disorder with short-limbed short stature and autosomal dominant inheritance. Many of its features resemble those of ACH, but the abnormalities are less severe overall and the face is almost completely normal. About 60% of patients with HCH have been reported to have an asparagine-to-lysine substitution at residue 540 (N540K) of FGFR3.10,11 Although the genotypic background of the remaining cases of HCH has not been clarified, the N540K substitution seems to be responsible for a significant proportion of cases of this condition.12-14 In spite of a long history of 50 observations suggesting allelism between ACH and HCH15, it has been claimed that the clinical and radiological features of ACH and HCH overlap.16,17 We have compared the phenotype of genotyped populations to clarify whether or not each of these two genotypes has a distinctive phenotype.

Patients and Methods

Blood samples were collected from patients clinically diagnosed as having ACH and HCH, and the FGFR3 genotype was determined as previously described. There were 23 patients with ACH and the G380R mutation of FGFR3 and eight with hypochondroplasia and the N540K mutation. Both conditions share the classical pathological features of micromelic short stature, reduced or unchanged interpedicular distances in the lumbar spine, disproportionately long fibulae, and squared and shortened pelvic ilia. These were significantly more severe in the G380R patients than in the N540K patients. Our findings have shown a firm statistical correlation between the genotype and the phenotype, although there were a few exceptional cases in which there was phenotypic overlap between the two conditions.
first and fourth lumbar vertebrae (L1/L4 ratio) irrespective of whether they were reduced or not. We also determined the ratio of the length of the fibula to that of the tibia (F/T ratio) to ascertain whether the fibular length was disproportionate. Lastly, we measured squaring and shortening of the pelvic ilia by calculating the ratio of the interteardrop distance to the pelvic width (pelvic index). The first two indices have already been reported 17,22 and we devised the third to quantitate the skeletal changes. Statistical analysis used the unpaired t-test for the height standard deviation score and the span to height ratio percentage or analysis of variance and Scheffe’s post-hoc test for the three radiological indices.

Results

Both groups of patients had severe short stature. The mean height standard deviation score of the G380R patients was -5.3 ± 1.2 which was lower than that of the N540K patients (-4.2 ± 1.5) although there was no statistical significance (p = 0.0502;f). The mean span to height ratio percentage of the G380R patients was 90.4 ± 3.6 which was significantly lower than that of the N540K patients (96.9 ± 2.4; p < 0.0001;f).

The lumbar interpedicular distance was considerably reduced in both groups in comparison with the normal controls.23 In the G380R patients the mean L1/L4 ratio was 1.18 ± 0.10 which was significantly higher than that of the N540K patients (1.02 ± 0.09; p = 0.0006;), but the latter was itself significantly higher than that of the normal group (0.89 ± 0.05; p = 0.0032). The mean F/T ratio in the G380R patients was 1.12 ± 0.03 which was significantly higher than that of the N540K patients (1.07 ± 0.03; p = 0.0002), but again the latter was significantly higher than that of the control group (1.01 ± 0.02; p = 0.0002;). The mean pelvic index of the G380R patients was 0.42 ± 0.03 which was significantly higher than that of the N540K patients (0.37 ± 0.03; p = 0.0026;). There was no significant difference in the pelvic index between the N540K patients and the control group (0.37 ± 0.03; p = 0.8908).

Discussion

We have shown that patients with ACH (G380R genotype) and HCH (N540K genotype) shared the classical skeletal changes (i.e., phenotype) to different degrees. According to the height standard deviation score and the span to height ratio percentage, the micromelic short stature was present in both conditions, but was more severe in ACH. Measurement of the L1/L4 ratio, the F/T ratio, and the pelvic index showed that the reduction of the interpedicular distances in the lower lumbar spine, the disproportionally long fibulae, and the squared iliac bones were more pronounced in ACH than in HCH. Both conditions carry a distinct mutation of FGFR3, which is a negative regulator of bone growth.24 25 Different levels of activation of FGFR3 should account for the differences in phenotypic severity between ACH and HCH.26–28 Statistical analysis of our results clearly separated the two conditions, showing that the skeletal changes in the G380R patients were more severe than those in the N540K patients. There were, however, four exceptional patients with the G380R mutation (a 5-year-old girl, a 7-year-old girl, and two 12-year-old boys) who showed milder phenotypes in all of the three radiological indices than the most severe case of the N540K mutation, demonstrating a phenotypic overlap between the two genetically distinct conditions. In these patients the radiological measurements may fail to distinguish the genotype and therefore genotyping is required for the differential diagnosis.

A short and broad femoral neck is another characteristic of ACH and HCH.19–20 In spite of our efforts to quantitate the deformity of the femoral neck, none of the radiological measurements could represent the appearance of the films. The hip sustains more mechanical loading than other joints and thus the coxa planovalvarus becomes more severe as growth continues. Comparison of the uniformity of the femoral neck in young G380R patients with that in older N540K patients would therefore confuse the clinical diagnosis. The L1/L4 and F/T ratios were less affected by the age of the patients. Genetically diagnosed ACH and HCH share common skeletal changes to different degrees, with a firm statistical correlation between the genotype and the phenotype. A few exceptional cases showed phenotypic overlap between the two conditions.

References