The genetic testing of children

I am happy to have the opportunity to comment on the response from the Genetic Interest Group (GIG) Working Party to the Report of the Clinical Genetics Society's (CGS) Working Party on the genetic testing of children. I was chairman of the CGS Working Party, but here I am presenting my own views.

I am very pleased that the CGS report has stimulated discussion among families and the GIG, and the five statements of principle set out in the GIG document will provide a most useful reference for future debate. I would like to comment on these principles.

2.1 CHILDHOOD ONSET CONDITIONS

The CGS report clearly states that testing for childhood onset disorders was excluded from consideration, because the ethical and practical concerns that abound in relation to testing for late onset disorders simply do not apply. There do remain problems of definition (what is a childhood onset condition?) but as a general policy I fully endorse the GIG approach. Their concern that the CGS report equivocates on this is misplaced. When predictive testing in childhood for an adult onset disorder is being considered, and if the medical benefits of presymptomatic diagnosis in childhood are unclear, then the results of pyschosocial evaluations of childhood testing may well be critical for certain medically "borderline" cases. This statement was never intended to apply to childhood onset conditions, and I feel that the GIG criticisms reflect a simple misunderstanding on this point.

2.2 TESTING FOR CARRIER STATUS

This principle concerning carrier testing is problematical. The phrasing suggests that parents only have a right to have the carrier status of their child determined "after suitable counselling" and after making an "informed choice". These qualifications, however, require a clear understanding of "suitable counselling" and "informed choice". And if a professional sincerely believes that testing a particular child would place them at risk of harm, do they have an obligation nevertheless to carry out the test? If not, what force does the word "right" carry? If counselling is to be a hoop through which a determined parent has to jump in order to have their child tested, then the counselling is being enforced and will be worthless.

I would endorse the second sentence in the principle 2.2 and would wish to strengthen it by deleting the word "ideally" and inserting the word "fully", thus: "Children should only be tested when of an age to be fully involved in the decision." Does not this sentence in fact contradict the preceding one?

2.3 ADULT ONSET CONDITIONS

The GIG statement of this principle is a shade stronger than the working party recommendation. It is difficult to reconcile the GIG wording with the notion that each case should be considered individually, a notion which both working parties seem to respect, and the laying down of such a firm principle could be legally vulnerable.

2.4 ADOPTION

The CGS Working Party report does not "leave loopholes" for adoption, but simply states that judgements of a child's best interests may be more complex if the child is being considered for adoption. The discussion in the report puts this very properly into context. The report is clearly opposed to the idea that genetic testing could be used to judge the suitability of a child for adoption.

As regards children in care, their position is legally the same as any other child; parental responsibility may not be held by the biological parents, but this does not alter the moral or legal responsibilities of the "parents". Adoption is quite different because of an imminent change in identity of the "parents".

2.5 PRENATAL TESTING

The meaning of this principle is not entirely clear, although I sympathise with the GIG working party in stating it. Should carrier status for a genetic disorder be imparted to parents undergoing prenatal diagnosis for a recessive condition, or should they simply be told that the child will or will not be affected? Principle 2.2 does not help. Should parents only be offered prenatal testing for a late onset disorder on the condition that they terminate an affected fetus? Principle 2.1 does not help. I understand the points made in the GIG document but the applications of the principle would appear somewhat opaque.

The statement of these five principles will prove most useful in providing a focus for future discussion. It is certainly interesting that the GIG working party took a very firm stand against predictive testing for adult onset disorders, but took a much less clear position in relation to carrier testing.

Perhaps this reflects the differences of opinion among parents on this issue, as the CGS report reflected differences of opinion among professionals.

Finally, let me turn to section 1 of the GIG report. I have read and re-read the relevant sections of the CGS report (section 5 and appendix 3) relating to the questions that the CGS Working Party sent around GIG member organisations. I remain mystified why the GIG response states that the CGS report is partronising towards GIG members, that the consultation with them was poor, and that GIG and its members were badly represented. The questions sent around GIG were very straightforward, and our reporting of the various responses was also straightforward. It was also quantified as far as the data permitted. Perhaps someone needs to take me to one side and point out (gently, please) just how patronising the report was.

The GIG response also states that the tone of the CGS report is patronising to parents. I deeply regret this, if this is a widespread perception. I would not be so surprised if medical colleagues in paediatrics or haematology regarded the report as patronising, because it does suggest that there is a real danger of inappropriate genetic testing of children becoming widespread as access to such tests becomes simpler and bypasses clinical geneticists, perhaps becoming available commercially. No doubt these professional groups will learn from their mistakes, as geneticists have done, but a lot of harm could be done by inappropriate testing during this learning process. I would hope that these medical colleagues will find the report to be helpful rather than patronising, but I could understand some of them regarding it in that light. In so far as recommendations need to be framed so as to protect children from genetic testing by anyone, it is from testing carried out without adequate previous consideration or discussion by a professional who may not be alert to the complexity of the issues until too late. I will be disappointed if GIG interprets this caution on the part of the CGS Working Party as an indication that we are patronising towards parents. When the GIG working party's "principles" are somewhat more prescriptive than our "recommendations" I am not sure that this attribution is entirely fair.

In conclusion, this document from GIG is a very helpful contribution to the debate on these issues. It is striking how similar the GIG statements of principle are to the CGS document's recommendations, although there are some differences. It is also striking how much common ground there is between both documents and the reports from Wertz *et al*[1] and Andrews *et al*.[2]

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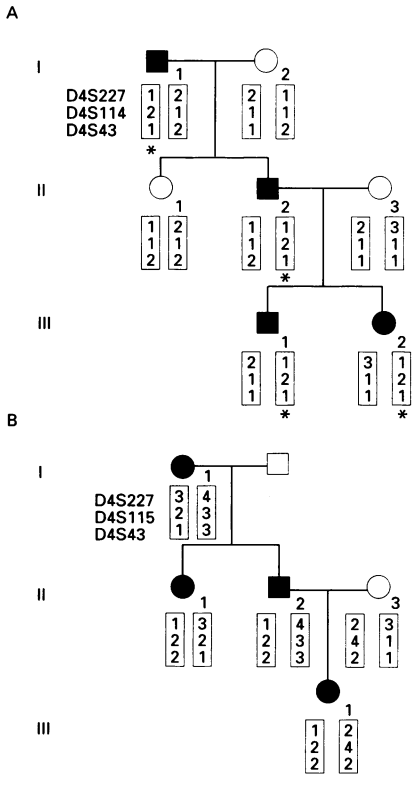
Possible genetic heterogeneity in hypochondroplasia

Segregation analysis in families with hypochondroplasia indicates that at least some cases of the condition result from mutations in a gene other than FGFR3 and suggests that hypochondroplasia is genetically heterogeneous. Mutation analysis shows that the G380R substitution in the FGFR3 is not the underlying cause in hypochondroplasia.

Hypochondroplasia is an autosomal dominant disorder characterised by short limbed dwarfism (rhizomelic type), lumbar lordosis, short and broad bones, and caudad narrowing of the interpediculate distance of the lumbar spine.[1] The phenotype of hypochondroplasia is similar to that of achondroplasia but milder. The two conditions have been thought to be allelic.[2] Recently, achondroplasia was localised on the short arm of chromosome 4 (4p16.3)[3–5] and its molecular basis was elucidated.[6,7] A G→A transition at nucleotide 1138 of the gene encoding fibroblast growth factor receptor 3 (FGFR3) was identified in 58 of 62 achondroplasia chromosomes studied.[6–8] This mutation results in a G380R substitution in the transmembrane domain of the FGFR3. This remarkable phenotype-genotype correlation and the assertion by Le Merrer *et al*[4] that hypochondroplasia maps in the same chromosome region as achondroplasia prompted us to investigate further the relationship between hypochondroplasia and FGFR3.

We studied a panel of eight two and three generation families in which hypochondroplasia segregated as an autosomal dominant trait. At least one affected person in each of the eight families was studied. The G380R mutation was not detected in any of the eight hypochondroplasia chromosomes tested. In addition we genotyped the hypochondroplasia families with the D4S227, D4S115, D4S114, and D4S43 markers which flank the FGFR3 gene and have been mapped to a 2·5 Mb distance in the telomeric region of



Genotyping of two hypochondroplasia families for markers in the 4p16.3 region. In family A, the phenotype cosegregates with the 1-2-1 haplotype. In family B the phenotype segregates independently of the markers.

chromosome 4p.[3 5] The map position and intralocus distances between the markers have been determined to be the following: telomere-0·7 Mb-D4S227-0·7 Mb-D4S115-0·8 Mb-FGFR3-0·1 Mb-D4S114-0·2 Mb-D4S43-centromere.[5] Haplotype analysis excluded the region between D4S227 and D4S43 and therefore FGFR3 in two families, suggested linkage in three families, and was uninformative in the remaining three families. The results of the haplotype analysis in two of the families are presented in the figure. In family A the disease phenotype cosegregated with the D4S227, D4S114, D4S43 haplotype, while in family B the hypochondroplasia phenotype segregated independently of the D4S227, D4S115, D4S43 haplotype. Our findings (1) indicate that at least some cases of hypochondroplasia are caused by mutations in a gene other than FGFR3; (2) suggest genetic locus heterogeneity in hypochondroplasia; and (3) exclude the G380R mutation as the underlying cause of hypochondroplasia. The possibility of genetic locus heterogeneity within hypochondroplasia had been raised by an earlier report.[9]

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UPD 13: no indication of maternal or paternal imprinting of genes on chromosome 13

We recently reported the first example of maternal uniparental isodisomy for chromosome 13.[1] This was found in a phenotypically normal male who inherited a t(13;13) in a balanced karyotype from his mother who also carried the same isochromosome. The transmission of the t(13;13) from mother to child was confirmed by analysis of dinucleotide repeat markers in the child and both his parents and we concluded that there were no maternally imprinted genes on chromosome 13.

Further analysis of the inheritance of this translocation in this family was not initially undertaken because the son's grandfather was not available for study. However, by recent analysis of the grandmother's DNA we found that there had been no transmission of two informative dinucleotide chromosome 13 alleles to her daughter (figure). By inference, the t(13;13) must have been transmitted by the grandfather either from a pre-existing constitutional or de novo translocation.

The first example of paternal UPD of chromosome 13 allows us to extend our original conclusion to suggest that there is no paternal or maternal imprinting of genes on chromosome 13.

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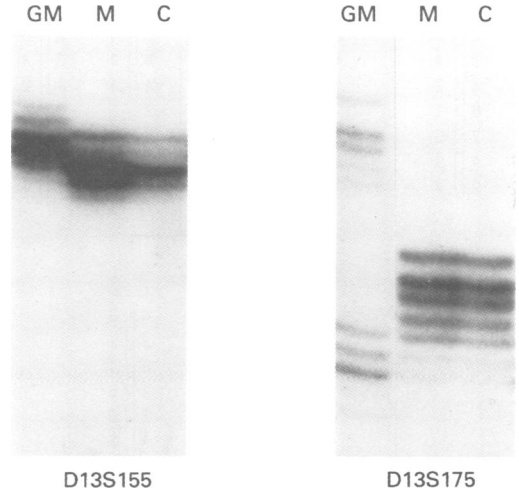
A family with autosomal dominant polycystic kidney disease linked to 4q21-23

We have previously reported a large kindred of southern Italian origin with autosomal dominant polycystic kidney disease, which is not linked to markers on 16p13.3.[1] Analysis of this family with microsatellites from 4q21-23 shows that the gene responsible for the disease



Allele segregation of CA repeat polymorphisms at D13S155 and D13S175 in the grandmother (GM), mother (M), and child (C). M and C are both carriers of an isochromosome 13 and show monoallelic patterns at both loci. GM shows biallelic polymorphisms for both loci, none of which is shared by M and C.