Table 2 Combinations of mutant alleles in patients with glycogen storage disease type II

	Infantile	Juvenile	Adult	α glucosidase activity*
IVS1(-13T→G)/IVS1(-13T→G)	-	-	-	?
Δ T525/ Δ T525	5	-	-	<1
Δ exon18/ Δ exon18	2	-	-	<1
Δ exon18/ Δ T525	4	-	-	<1
IVS1(-13T→G)/ Δ exon18	-	-	5	11.3-16.0
IVS1(-13T→G)/ Δ T525	-	1	10	9.1-20

* α -glucosidase activity in cultured fibroblasts as % of the mean of normal controls.

*et al.*⁵ respectively. To identify the IVS1(-13T→G) mutation, two PCR primer sets were designed, based on the amplification refractory mutation system (ARMS) described by Newton *et al.*⁶ The first set amplifies specifically the wild type allele, the second set the IVS1(-13T→G) allele (figure). The frequencies of the three mutant alleles are given in table 1.

Our data confirm those of Huie *et al.*² who found that IVS1(-13T→G) is a frequent mutation in adult GSD II, but is not associated with infantile GSD II. Further, we have shown the IVS1(-13T→G) mutation in juvenile GSD II. The mutation was not encountered in a total of 54 unrelated controls. The other two mutations are not restricted to certain phenotypes and are more frequent in the Dutch than in other patient populations. This could be the result of a founder effect.

By screening for these three mutations, we succeeded in identifying one mutant α glucosidase allele in 42 of 121 patients (35% of the total and 49% of the Dutch patient population). In an additional 27 patients, both alleles were identified (22% of the total and 39% of the Dutch patient population) allowing a genotype-phenotype correlation to be made (table 2).

Homozygotes for Δ exon18 or Δ T525 and compound heterozygotes for these mutant alleles have the infantile form of GSD II and no α -glucosidase activity. In contrast, patients with either Δ exon18 or Δ T525 in combination with IVS1(-13T→G) have the juvenile (one patient) or the adult (15 patients) phenotype and have 10 to 20% of the mean α -glucosidase activity in normal controls, suggesting that IVS1(-13T→G) is a mild mutation allowing α -glucosidase synthesis and function at 20-40% of the normal level. Homozygotes for IVS1(-13T→G) were not encountered, possibly because the residual activity in these subjects prevents clinical signs.

We propose that these data are good evidence of genotype-phenotype correlations in GSD II and suggest that genotype analysis may complement routine (prenatal) diagnosis, particularly when common mutations can be identified. Further, carrier detection in couples at risk becomes a practicable option.

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M A KROOS
M VAN DER KRAAN
O P VAN DIGGELEN
W J KLEIJER
A J J REUSER
Department of Clinical Genetics,
Erasmus University,
PO Box 1738,
3000 DR Rotterdam,
The Netherlands.
M J VAN DEN BOOGAARD
M G E M AUSEM
H K PLOOS VAN AMSTEL
Clinical Genetics Centre,
Utrecht, The Netherlands.

L POENARU
M NICOLINO
Department of Genetics and Lysosomal Pathology,
CHU Cochin,
Université René Descartes,
Paris, France.
R WEVERS
Department of Clinical Genetics,
Academic Hospital,
Nijmegen, The Netherlands.

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Partial trisomy 3q and the mild Cornelia de Lange syndrome phenotype

The article published by Holder *et al.*¹ described two children whose facial features

were very similar to children with mild de Lange syndrome. Cytogenetic analysis showed them to be trisomic for the region 3q25.1-26.2 as a result of inheriting an unbalanced interchromosomal insertion from their father who was a balanced insertion carrier. Fluorescence in situ hybridisation (FISH) studies using chromosome 3 paint confirmed that the insertion on chromosome 10 had originated from chromosome 3.

We were particularly interested in these children both because their phenotypes overlapped with that seen in mild de Lange syndrome and because they were duplicated for a very small region of chromosome 3. We had previously reported a child with Cornelia de Lange syndrome and a de novo translocation, t(3;17)(q26.3;q23.1)². Before the identification of this patient it had been thought that the de Lange gene may map to 3q because of phenotypic overlap with subjects who were trisomic for variable regions of 3q. These people are usually trisomic for large regions of 3q and also monosomic for other variable regions of the genome. However, the common region of overlap in all cases is 3q26.3.

Chromosome 3q has two prominent Giemsa bands near the end of the q arm which are similar in size and vary only in the intensity of staining. The children described in the report of Holder *et al.*¹ were thought to be trisomic for the more proximal Giemsa band in 3q26, 3q26.1, whereas the translocation breakpoint in the patient with the de novo translocation disrupts the more distal band, 3q26.3. Using a non-chimeric yeast artificial chromosome (YAC) clone (CEPH 886e7) positive for microsatellite marker AFM164tc7 (D3S1548), which is known from somatic cell hybrid data to map to 3q26.3,³ we were able to show that the children are trisomic for the more distal of the two Giemsa bands on 3q26, that is, 3q26.3. The figure shows metaphase chromosome spreads from one of the children hybridised with the biotinylated YAC DNA that has been detected with FITC. In addition to two signals from distal 3q there is an additional signal on 10q. The fact that these children are trisomic for 3q26.3 further confirms that 3q26.3 is the 3q duplication critical region and that the de Lange syndrome gene maps in this area.

Metaphase chromosomes from one of the children, hybridised with probe 886e7 from 3q26.3. Note three signals are visible, two from 3q26.3 and one from chromosome 10.

M IRELAND
C ENGLISH
I CROSS
S LINDSAY
T STRACHAN
Department of Human Genetics,
University of Newcastle upon Tyne,
19/20 Claremont Place,
Newcastle upon Tyne
NE2 4AA, UK.

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Response to GIG's response to the UK Clinical Genetics Society report "The genetic testing of children"

The Genetic Interest Group (GIG) based their response to the Clinical Genetics Society (CGS) report on their perspective "informed by the experience of families directly affected by genetic disorders". GIG's main focus is to argue for the right of parents to have their children tested, except in the case of adult onset conditions. They criticise the CGS for being too negative about testing for childhood onset conditions and for carrier status and insufficiently negative about testing for adult onset conditions.

The arguments given for testing include: "possible freedom from anxiety; facilitating open relationships; and the parents' need to secure the best environment they can for themselves, the child who will develop the disorder, and other children in the family." "Although the vast majority would prefer there not to be a genetic disorder in their family, knowledge comes to be accepted as a fact of life in the same way that other issues are recognised to be individual and integral to any family. It is also our experience that children can cope with information about themselves from an early age and that it is much more often the adult who has a problem in giving information." "Early knowledge of carrier status could help the child adapt to the consequences of being a carrier over a period of time, rather than having the in-

formation presented at puberty, when s/he is going through a time of emotional adjustment and may not best handle the information. ... Facts of life are best absorbed slowly and when the moment is right rather than during a crisis over pregnancy."

The arguments given for testing could also apply to adult onset conditions. Differentiating so markedly between child and adult onset raises questions of "what is a child and what is an adult?" and "how should conditions with variable age of onset be dealt with?" It is not clear why arguments are used for children to have knowledge of carrier status which only becomes relevant in adulthood (as defined by age at which reproduction is possible) but not to knowledge of adult onset conditions.

GIG cites one argument against testing for adult onset conditions: that testing takes away the child's right as an adult to make an informed decision. This completely ignores the other side of the coin. Not testing takes away the right of the adult to have been brought up with the knowledge that they will or will not develop a genetic condition in adulthood.

GIG criticises the CGS for being patronising and overly preoccupied with the harm that knowledge of genetic disorders can cause within families. They consider that CGS gives insufficient credit to families: "parents are responsible for the welfare of their children and at the end of the day most of them are better equipped to decide what is in the best interest of a particular child, and the family as a whole, than are outsiders. Denying them the right to cope in the way that they see as best may have the opposite effect to that intended."

It is unclear why parents should be seen as having this responsibility for childhood onset, but not adult onset, conditions. Parenting is about building the basis for happy and fulfilled adult lives, not just about doing the best within childhood.

We agree with GIG that "it is both possible to draw up standard, basic, guidelines for testing, and also necessary to do so if best practice is to survive the extra burdens that will result from the expansion of the field." However, this raises the question of the basis upon which such guidelines are to be developed. One key element is the contribution of all relevant perspectives, which should include affected families, voluntary organisations such as GIG, and the general public as well as professionals. But all of these perspectives should be informed by data beyond personal experience.

One of the best ways to resolve these questions is to collect evidence through systematic studies.¹ While we have, as yet, no ex-

perimental or large scale studies to draw upon, we have access to children undergoing predictive genetic testing for late onset conditions as part of routine genetics services. In order to document the perspectives and experiences of these families, we are completing the follow up of a single case study² and initiating a multiple single case study. Just as debates about clinical and social policy should shape the research that is carried out, so research findings should be available to inform these debates.

SUSAN MICHIE
THERESA M MARTEAU
Psychology & Genetics Research Group,
UMDS,
Guy's Campus,
London SE1 9RT, UK

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- 2 Marteau TM, Michie S. Genetic testing of newborns: the need for evidence. *BMJ* (in press).

This letter was shown to GIG who reply as follows:

The Genetic Interest Group is pleased that its Letter to the Editor in the June issue on "The genetic testing of children" has aroused interest and possibilities for further debate. We would like to answer a couple of points made by Drs Michie and Marteau.

First, we believe that there is a profound difference in the knowledge that you are a gene carrier with implications for reproduction, and the knowledge that you are at some point in your adult life going to be personally affected by a genetic disorder.

Second, not testing in childhood for adult conditions for which there is no treatment does not of course mean that children should not be aware of their risk status. Experience with Huntington's disease has shown that most people at risk and their partners who have not been informed generally feel angry and deprived of making their own decision in the light of that knowledge. The low take up of the test, however, shows that testing is often not desired.

We welcome the idea of further research and debate from a variety of perspectives. We are currently in conversation with the BMA in the hope of holding a conference on the subject in 1996.

SHIRLEY DALBY
Genetic Interest Group,
Farringdon Point,
29-35 Farringdon Road,
London EC1M 3JB, UK