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Chromosome 1 in relation to human disease

S POVEY AND J M PARRINGTON

From the MRC Human Biochemical Genetics Unit, The Galton Laboratory, University College London, Wolfson House, 4 Stephenson Way, London NW1 2HE.

SUMMARY Chromosome 1 is thought to represent about 6% of the total human genome and the 85 loci so far identified may constitute about 1% of the genes present on this chromosome. The existence of at least 22 loci sufficiently polymorphic in Europeans to be useful as genetic markers has allowed the construction of an elementary genetic map. This permits comparisons with physical and chiasma maps and has demonstrated striking homologies between different regions of chromosome 1 and mouse chromosomes 1, 3, and 4. The existence of a map should be of great help in developing a more systematic approach to further mapping studies.

A wide range of disease can be attributed to allelic variation on chromosome 1 and the homologies with the mouse may be useful in predicting the position of other genes involved in human disease. Rearrangements of this chromosome are a common finding in many different types of malignancy. Loss of material from the short arm and activation of one or more of the four oncogenes in this region may play an important role in the later stages of tumour development. Polymorphic markers of all kinds will be useful in the future for investigating the somatic events which have occurred during the malignant process.

The assignment of a gene to its appropriate autosome by family studies is even today a formidable undertaking. Initially it was only possible by observing segregation of the marker in question with a visibly altered chromosome. The first success in this highly labour intensive approach was on chromosome 1, with the finding of linkage between the Duffy blood group (Fy) and an unusually large variant of centromeric heterochromatin, visible without banding and designated 'uncoiler', now called 1qh.¹ This result also assigned chronic pulverulent cataract (CAE) to chromosome 1, because of its previously described linkage to Fy.² Assignment of the amylase 2 locus by linkage to 1qh was made independently.³ By this time a number of workers had contributed to knowledge of the linkage relations of the Rh blood group (for a review see Renwick⁴) but only in 1972 did work on somatic cell hybrids permit the assignment of these loci to chromosome 1.⁵ In a review in 1973 Hamerton and Cook⁶ were able to present a list of 16 loci on chromosome 1 (15 of which have stood the test of

time), information coming equally from family studies and somatic cell hybrids. The list of loci was not far short of the total list for all other autosomes combined and provided a basis for much of the pioneering work in human autosomal mapping, developed over the years by Peter Cook until his untimely death in 1982.

The current list of genes on chromosome 1 contains 85 loci, 14 of which were initially assigned by family studies, 11 by *in situ* hybridisation, and 60 by somatic cell genetics. In many cases the regional assignment of loci has depended on several of these techniques. For a full list of loci the reader is referred to Human Gene Mapping 8.⁷ Only seven of the loci are anonymous DNA segments, which will not be considered further except with regard to their potential contribution to a linkage map. The remaining loci will be discussed in general terms with some emphasis on their interest to a clinical geneticist.

'Disease loci'

Table 1 shows a list of those loci where clinical

TABLE 1 *Loci on chromosome 1 where different alleles may cause clinical disease.*

	Locus	McKusick number	Method
<i>Dominant disorders</i>			
Elliptocytosis	ELI	13050	F
Haemolytic disease of newborn	Rh (RH)	11170	F
Erythrokeratoderma variabilis	EKV	13320	F
Porphyria cutanea tarda	UROD*	17610	S
Chronic pulverulent cataract	CAE	11620	F
Antithrombin deficiency	AT3*	10730	F
Charcot-Marie-Tooth disease (HMSN type 1)	CMT 1	11820	F
<i>Recessive disorders</i>			
Hypophosphatasia	ALPL	24150	S
Complement C8 deficiency	C8A C8B	12095	F
Fucosidosis	FUCA*1	23000	S
Gaucher disease	GBA*	23080	S
Glycogen storage disease type VII	PFKM	23280	S
Respiratory infection ? immunodeficiency	UMPK	19171	S

*Cloned gene.

F=family studies.

S=somatic cell hybrids.

effects can definitely be associated with different alleles. As expected, those assigned by family studies tend to be relatively mild dominant conditions. There are several cases, for example, elliptocytosis⁸ and Charcot-Marie-Tooth disease,⁹⁻¹¹ where linkage studies have clarified the classification of the underlying defect by the demonstration of heterogeneity. Rhesus haemolytic disease has been included as a dominant because of its manifestation in heterozygotes, although it is unusual in depending on a different genotype in another subject. The three severe autosomal recessive disorders, infantile Gaucher disease,¹² fucosidosis,¹³ and hypophosphatasia,¹⁴ were all assigned by analysis of the appropriate enzymes using somatic cell hybrids. α fucosidase can also be studied in families because of a common genetic polymorphism which has been shown to be allelic to the 'silent' gene or genes causing the disease.¹⁵ Four of the genes involved in major disease have been cloned, α fucosidase (*FUCA1*),¹⁶ glucocerebrosidase (*GBA*), uroporphyrinogen decarboxylase (*UROD*),¹⁸ and antithrombin 3 (*AT3*).¹⁹ In one family, deletion of the *AT3* locus was found²⁰ and in another family with *AT3* deficiency, restriction fragment length polymorphisms have shown close linkage to the disease.²¹ For the other diseases the defects have not yet been identified at the DNA level. Although there is some controversy over the regional assignment of β glucocerebrosidase,^{12 22 23} it seems probable that all the variants of Gaucher disease are

mutant alleles at the same locus.²³ Recently a DNA polymorphism of *GBA* was demonstrated in several racial groups. A number of Jewish Gaucher type 1 patients were found to be heterozygous for this polymorphism, implying that the Gaucher disease mutation in Jews has occurred independently on more than one occasion.²⁴ Prenatal diagnoses of fucosidosis and Gaucher disease are routinely available from enzyme assay of cultured amniocytes. Pregnancies at risk for Gaucher disease have been monitored by chorion villus biopsy²⁵ and work on levels of α fucosidase in chorion samples suggests that this would also be applicable to fucosidosis.²⁶ First trimester diagnosis of hypophosphatasia using a monoclonal antibody has been reported.²⁷

In the case of *UMPK* (uridine monophosphate kinase) the relationship to disease is not entirely clear. The allele *UMPK*2* codes for a less active or less stable enzyme, and in the first report two sibs of phenotype *UMPK2* were found to have frequent severe respiratory illness, suggesting that immunodeficiency might be associated with *UMPK* deficiency.²⁸ Recently, an association between the *UMPK*3* allele and invasive *Haemophilus influenzae* type B infection has been described in Eskimos.²⁹

There are several genes where either the assignment to chromosome 1 or the relationship to disease was not thought strong enough to be included in table 1. An autosomal form of retinitis pigmentosa has shown small positive lod scores with Rh, but insufficient to establish linkage.³⁰ Other possible linkages to Rh include that of a single gene causing familial cutaneous malignant melanoma/dysplastic naevus syndrome^{31 32} and a form of breast cancer found in families in which ovarian cancer also occurred.³³ Pooled data from families with Köbner and Weber-Cockayne types of epidermolysis bullosa simplex gave a maximum lod score of 1.8 with Fy.³⁴

A variety of different abnormalities of α spectrin have been demonstrated in spherocytosis, elliptocytosis, and in pyropoikilocytosis,^{35 36} but it is not entirely clear which of these result from primary abnormalities of the α spectrin gene. The recent assignment of α spectrin (*SPTA*) to 1q³⁷ suggests that the elliptocytosis which shows some hint of linkage with Fy³⁸ may result from such a defect. It is not clear if Fy itself has any clinical effects, but it has been suggested that the Fy determinant is the receptor for *Plasmodium vivax* and that the high incidence of Fy(a-b-) in some areas of high malaria prevalence may be the result of natural selection.³⁹

The gene coding for the β subunit of nerve growth factor (*NGFB*), firmly assigned to p22.1, seemed a likely candidate as a cause of disseminated neurofibromatosis, but this disease has been virtually excluded from the whole of 1p by family studies.^{40 41}

Analysis using restriction fragment length polymorphisms in *NGFB* has also excluded abnormality of this gene as a cause of familial dysautonomia.⁴²

An intriguing gene on chromosome 1 which may have some relationship to disease is *CFAG*, coding for an antigen which is increased in the serum of patients with cystic fibrosis and also in their parents.⁴³ Extensive family studies on this disease excluded detectable linkage with several DNA probes on chromosome 1,⁴⁴ as well as with classical markers,⁴⁵ and have recently been followed by the discovery of a linkage which assigns cystic fibrosis to chromosome 7.⁴⁶⁻⁴⁸ Thus, abnormalities of *CFAG* are presumably not the primary cause of the disease, but the abnormality of the protein in heterozygotes may throw some light on the pathways involved in cystic fibrosis.

Cytoplasts derived from normal human fibroblasts⁴⁹ or from human-hamster hybrids containing chromosome 1⁵⁰ were able to complement the defect in cells from xeroderma pigmentosum group A patients, after fusion with UV irradiated XPA cells. This allowed assignment of a gene *XPAC*, concerned with DNA repair, to chromosome 1. However, the relationship of this gene to the defect in xeroderma pigmentosum group A is not clear because cytoplasts from human-hamster hybrids containing chromosome 1 were able to correct the defect in XPA cells even if the chromosome 1 had been derived from the same patient.⁵⁰ Another gene, *ERCC2*, can complement DNA repair deficiency in Chinese hamster fibroblasts, but whether this is related to any of the many human diseases involving defects in DNA repair is unknown.⁵¹

The locus for the B chain of CIQ, a complement subcomponent, has been mapped to chromosome 1 using a cDNA probe,⁵² but this has not been included as a disease locus as it is not certain which chain is involved in CIQ deficiency*.⁵³

Chromosome 1 and malignancy

Chromosome 1 abnormalities have been found in many different types of tumour⁵⁴ and about half of the breakpoints occur in or around the centromeric heterochromatin.⁵⁵ Rearrangements giving rise to trisomy of all or part of 1q are a common finding in haematological disorders,^{56 57} childhood tumours,⁵⁸ colorectal tumours,⁵⁹ and breast cancer.^{60 61} Deletions of 1p are also found. They are the most frequent abnormalities in neuroblastoma^{62 63} and are also found in malignant melanoma.⁶⁴ A recent study in our laboratory on newly established cell lines from testicular teratomas has shown evidence

in three cases for deletion of 1p in one homologue as a result of a rearrangement giving rise to duplication of 1q. Two apparently identical copies of the other homologue were also present.⁶⁵

The frequent and non-specific occurrence of chromosome 1 rearrangements in human tumours suggests that they are important during the later stages of tumour development. It has recently been shown that a human chromosome 1 is essential for suppression of carcinogen transformed BHK cells,⁶⁶ indicating that loss of normal genes on this chromosome may be important in allowing a malignancy to become established. Loss of normal genes in somatic cells can arise as a result of mutation, chromosome rearrangement, or mitotic recombination. There is now evidence from a number of sources that chromosome 1 C band heteromorphisms are more frequent in cancer patients,^{67 68} and it is possible that this heterochromatic variation could promote the formation of both mitotic chiasmata and chromosome aberrations.

Five oncogenes have been assigned to chromosome 1 (table 2), as well as the gene coding for the β subunit of nerve growth factor already mentioned. Activation of *N-ras* has been reported in many tumours and tumour cell lines. It was first found in the neuroblastoma line SK-N-SH⁷⁷ and in the fibrosarcoma cell line HT1080. In the latter, activation was shown to be due to a specific amino acid substitution Glu→Lys at position 61 of the P21 RAS gene product.^{78 79} Activated N-RAS genes have subsequently been reported in rhabdomyosarcoma⁷⁴ and different clinical types of acute myeloblastic leukaemia (AML).⁸⁰ In AML the amino acid substitution is at position 13 and can be either Gly→Asp or Gly→Val.⁸⁰ N-RAS activation has also been shown in a small proportion of malignant melanoma cell lines⁸¹ and in late but not early passages of an ovarian teratocarcinoma cell line.⁸² Recently the oncogene *MYCL* has been found to be amplified in several cases of small cell lung cancer.⁷³

A direct relationship between oncogene activa-

TABLE 2 *Oncogenes on chromosome 1.*

Name	Derivation	Position	Reference
SRC-2	Avian sarcoma viral gene homologue	p36-1→36.2	69 70 71
BLYM	Avian lymphoma oncogene homologue	p32	72
MYCL	MYC gene family from lung carcinoma	p32	73
NRAS	Neuroblastoma oncogene(s)	p22 and/or p11→p12	74 75*
SKI	SK-77 avian sarcoma oncogene homologue	q12→qter	76

*See also reference 7 for more extensive list of references and discussion.

*Footnote added in proof. Abnormality of *CIQB* gene has been shown in one case of CIQ deficiency (McAdam *et al.* *Complement* 1985;2:52).

tion and the rearrangements on chromosome 1 already discussed is not yet established but is being actively investigated. Rearrangements of chromosome material can result in specific repositioning of oncogenes, as in chronic myeloid leukaemia⁸³ and Burkitt's lymphoma,⁸⁴ or loss of normal alleles, as in retinoblastoma and Wilms' tumour.⁸⁵ Both these somatic events are thought to play an important part in the process of tumourigenesis. Rearrangements of chromosome 1 or oncogene activation or both may play a role in the two hereditary cancers tentatively mapped to chromosome 1, familial cutaneous malignant melanoma and breast cancer, mentioned previously.

Mapping studies on chromosome 1

Table 3 shows markers on chromosome 1 which have been or could be used for family studies, listed

in approximate order along the chromosome from p to q. The usefulness of each marker is indicated by its polymorphism information content, or 'pic', number, a statistic introduced by Botstein *et al.*⁸⁶ This figure indicates the probability that a nuclear family segregating for a disease or a new marker of interest will give some linkage information with the marker listed. The 'pic' depends, of course, on the frequency of heterozygosity and the number of different alleles. The most informative locus is *DNF15S1*, defined by an interesting DNA sequence which was originally thought to be derived from chromosome 1, but turns out to have come from chromosome 3. With *StuI* a polymorphism is found on chromosome 1 (table 3), but the same probe used with different restriction enzymes defines a polymorphism on chromosome 3.⁸⁹ However, there are several 'classical' markers on chromosome 1 which are very useful, both Rh and PGM1 being informa-

TABLE 3 Genetic markers on chromosome 1 which have been or could be useful in linkage analysis.

Marker (symbol)	Name	Tissue	Method*	'pic'†	Region‡
GDH	Glucose dehydrogenase	WBC	IEF	0.30	pter→p36.13
ENO1	Enolase	RBC	Starch	<0.01	pter→p36.13
PGD	Phosphogluconate dehydrogenase	RBC	Starch	0.04	p36.2→p36.13
ELI	Elliptocytosis	RBC	Haematological/clinical	<0.01	pter→p34
DNF15S1	Random probe (formerly D1S1)	DNA	R/ <i>StuI</i>	0.67	p36
RH	Rh blood group	RBC	Immunological	0.58	p36.2→p34
FUCA1	α fucosidase	WBC	IEF	0.31	p34
EKV	Erythrokeratoderma variabilis		Clinical	<0.01	p
UMPK	Uridine monophosphate kinase	WBC (better) or RBC	Starch	0.09	p32
MYCL	Oncogene	DNA	R/ <i>EcoRI</i>	0.37	p32
RD	Radin blood group	RBC	Immunological	<0.01	pter→p22.1
SC	Scianna blood group	RBC	Immunological	0.02	p36.2→p22.1
C8A§	α/γ subunit of C8	Serum or plasma	IEF	0.36	p34→p22.1
C8B	β subunit of complement C8	Serum or plasma	IEF	0.1	p34→p22.1
PGM1	Phosphoglucomutase 1	RBC	Starch	0.29	p22.1
			IEF	0.53	
NGFB	Nerve growth factor	DNA	R/ <i>BglII</i>	0.29	} 0.46 p22.1
			R/ <i>TaqI</i>	0.24	
AMY1	Salivary amylase	Saliva	Agar	<0.01	} 0.46 p22.1
		Saliva	IEF	0.1	
AMY1/AMY2		DNA	R/ <i>PstI</i>	0.22	
			R/ <i>PstI</i> / <i>BamHI</i>	0.37	
AMY2	Pancreatic amylase	Serum	Agar	0.17	p22.1
1qh	Centromeric heterochromatin	Lymphocytes	C banding	0.14	q11
Fy	Duffy blood group	RBC	Immunological	0.37	p21→q23
CAE	Chronic pulverulent cataract		Clinical	<0.01	p21→q23
APOA2	Apolipoprotein 2	DNA	R/ <i>MspI</i>	0.26	p21→qter
REN	Renin	DNA	R/ <i>HindII</i>	0.36	p21→qter
AT3	Antithrombin 3	Serum	Deficiency	<0.01	
		DNA	R/ <i>PstI</i>	0.38	} 0.45 q23→25
			R/ <i>BamHI</i>	0.30	
CMT1	Charcot-Marie-Tooth disease		Clinical	<0.01	q
PEPC	Peptidase C	RBC	Starch	0.005	p25 or
		WBC	Starch	0.05	q42
GBA	β glucocerebrosidase	DNA	R/ <i>PvuII</i>	0.37	q21 or q31
DNF10	Random probe	DNA	R/ <i>SstI</i>	0.32	q23→qter
FH	Fumarate hydratase	WBC	Starch	<0.01	q42.1
DIS2	Random probe	DNA	R/ <i>BglII</i>	0.27	No regional
DIS4	Random probe		R/ <i>BglII</i>	0.15	assignment

*Starch=starch gel electrophoresis, agar=agar electrophoresis, IEF=isoelectric focusing, R/=restriction endonuclease.

†'Pic'—for DNA polymorphisms taken from Willard *et al.*⁸⁷ except for MYCL⁷³ and GBA.²⁴ For other markers, calculated as described in Botstein *et al.*⁸⁶ from published frequencies in North Europeans.

‡In some cases deduced from gene order.

§Assignment of C8A is controversial as one report⁸⁸ found C8A and C8B to be unlinked.

tive in over half the families and FUCA1 and Fy in more than one-third. Included in table 3 are a number of loci for which only rare variants have been found, and also those diseases on which linkage studies have actually been performed.

Although these could form the basis of further linkage studies they cannot be regarded as generally useful markers.

The extent of variation seen in the heterochromatic region 1qh depends on the investigative

FIGURE Male genetic map of chromosome 1 with some physical regional assignments. The position of cloned genes which are thought to express functional proteins and have not so far been used in linkage studies is also shown. Regions showing homology with mouse chromosomes are indicated on the right. Dotted lines indicate some doubt about the region or extent of the homology. In each case the genes are listed under the human nomenclature, and no attempt is made to give gene order in the mouse. Loci in parentheses may not be truly homologous to mouse genes. Abbreviations for those loci not listed elsewhere are as follows. RNU1=small nuclear RNA. PND=pronatriodilatin. TSHB= β subunit of thyroid stimulating hormone. ACTA=skeletal muscle α actin. CRP=C reactive protein. APCS=serum amyloid P component. H4F2=histone gene. AK2=adenylate kinase 2.

technique used, and the 'pic' value given represents the average from a large number of surveys.^{90 91} Magenis *et al*⁹² followed the inheritance of 1qh in 42 families and found no indication of non-Mendelian inheritance, so it seems reasonable to regard it as a genetic marker. Some of the earliest successes in autosomal gene assignment resulted from studies of unusually large 1qh regions detectable on orcein staining. Nevertheless, a significant amount of the heterogeneity found in linkage data on chromosome 1 arises from studies of 1qh.⁹³ It is unclear whether this is an interesting biological phenomenon or a technical problem. Angell and Jacobs⁹⁴ have described a refinement of classification of 1qh which involves compound lateral asymmetry of fluorescence of chromatids when treated with 5-bromodeoxyuridine and Hoeschst staining. Twenty of 44 unrelated subjects were unequivocally identified as heterozygotes and inheritance was shown to be Mendelian. This technique has not so far been used extensively in linkage analysis but has proved very useful in ascertaining the origin of a particular homologue of chromosome 1 in abnormal conceptions, such as hydatidiform moles and tetraploids.^{95 96} C band heteromorphism and isozyme markers on chromosome 1 were also used to demonstrate diverse modes of origin of ovarian teratomas.^{97 98}

The number of markers available on chromosome 1 (22 having a 'pic' of more than 0.05) has allowed the construction of a genetic map, a summary of which is shown in the figure. This also shows the position of all the cloned genes which are known to express a functional product and which have not yet been used for linkage studies. The genetic map is largely the work of Dr Stephanie Sherman and is based on lod scores published in 1984,⁹⁹ together with subsequent information presented at HGM8. The map has been constrained only by gene order from known physical regional assignments and is the 'best' male map obtainable from two point data. The position of some of the less variable markers (for example, Radin and Scianna) is at variance with that suggested by three point data, and awaits further typing of flanking polymorphisms in critical families. The position of *FY* and *CAE* in relation to 1qh, a matter of some controversy,¹⁰⁰ is still not certain. The map is calculated on the basis that female map distances are $1.8 \times$ those of the male and give a good fit with the data, but there is some suggestion of variation in the sex difference in different regions of the chromosome, the ratio of female to male map distance decreasing on moving from Rh towards the centromere.^{101 102} The reason why *PGMI* and *NGFB*, although physically in the same band, show no linkage is not clear, but a high frequency of

recombination in this area would fit quite well with the chiasma map, which is otherwise difficult to reconcile with the genetic map.¹⁰³

The estimated male genetic length of chromosome 1p (115 cM) is in substantial agreement with the chiasma map which predicts 99 cM for 1p and 95 cM for 1q.¹⁰⁴ Laurie and Hultén¹⁰⁴ found significant interindividual differences in mean chiasma frequency both on 1p and 1q. Two genes which show polymorphisms but which are not in table 3 are the blood group INLU (inhibitor of Lutheran) and Dombrock. Both are undoubtedly polymorphic but their assignment to chromosome 1 is uncertain. INLU has a maximum lod score of about 2 with Rh.¹⁰⁵ The data on Dombrock are difficult to interpret and have been discussed elsewhere.⁹³

Other genes

Genes so far discussed are those which have some clinical interest or have been used in linkage analysis. Many of the other genes on chromosome 1 may, of course, move into these categories. There are 15 cloned 'functional' genes and 13 other cloned sequences in which polymorphism has not yet been reported and many genes coding for interesting proteins which may well be important in disease. For example, *F3*, coding for tissue thromboplastin, coagulation factor III, recently mapped to chromosome 1,¹⁰⁶ may well be involved in some coagulation defects but this has not been established. Cell surface proteins whose function is quite unknown can be of immediate practical use in the sorting of hybrids containing whole or part of chromosome 1 using a fluorescent activated cell sorter. This technique was used in the mapping of *ALPL*.¹⁴

Mouse homologies

Another striking feature of chromosome 1 is the conservation of three syntenic groups between man and mouse, shown in the figure.¹⁰⁷ On the highly conserved X chromosome it has been possible to predict, and subsequently confirm, the position of various human disease loci, for example, hypophosphataemia and anhidrotic ectodermal dysplasia, from the position of homologous loci in the mouse. Similar predictions from mouse to human might be useful on chromosome 1. One of these possibilities has already been discussed by Knott *et al*,¹⁰⁸ who propose that human genes determining the level of high density lipoproteins (but distinct from the structural locus *APOA2*) might be expected to lie in the region of the *PEPC-REN-APOA2* on chromosome 1. These workers have already presented preliminary evidence of linkage disequilibrium between one of the alleles at the *APOA2* locus and an unusually high level of high density lipoprotein.¹⁰⁹

The recent assignment of genes coding for the two light chains of laminin to this same linkage group in the mouse prompts speculation that the human laminin genes, which are probably of great importance in basement membranes and in neural tissue, may be in this region in man.¹¹⁰ In view of the involvement of 1p in malignancy discussed earlier, it may be of interest that a gene which was found to suppress malignancy in somatic cell hybrids mapped to the appropriate region of chromosome 4 in mice.¹¹¹

Inspection of the mouse map shows that genes for polysyndactyly, achondroplasia, and one form of diabetes also lie in the conserved region of mouse chromosome 4 and a gene for osteopetrosis close to amylase on mouse chromosome 3. However, a greater knowledge of comparative pathology than that possessed by the present authors will be needed to decide which of the many candidate mouse genes might be worth pursuing in man.

Conclusion

In the past, chromosome 1 has led the way in human autosomal gene mapping, being the first in which it was possible to integrate the results of many techniques to produce an elementary map. So far, no pattern has emerged, the genes on this chromosome coding for a wide variety of functions in many different tissues and being involved in a broad spectrum of diseases. Assuming that chromosome 1 contains approximately 2×10^8 base pairs, and that the average length of a gene might be about 20 kb, one can calculate that 1% of the genes on chromosome 1 may have been identified. If all expressed genes are in the lighter regions seen on G banding, this figure is probably an underestimate. As the gaps in the map are gradually filled in it should become of ever increasing theoretical interest and practical clinical value.

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Correspondence and requests for reprints to Dr S Povey, MRC Human Biochemical Genetics Unit, The Galton Laboratory, Wolfson House, 4 Stephenson Way, London NW1 2HE.