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A consortium approach to molecular genetic services

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Abstract

The four Scottish university medical genetics centres formed a consortium in 1985 to provide a DNA based service in prenatal diagnosis, carrier detection, and predictive testing for a range of Mendelian disorders. Each centre took sole responsibility for laboratory analyses of an assigned set of disorders, while families continued to be investigated and patients counselled within their own areas. DNA was extracted from relevant tissues in the centre most convenient to the family member and then dispatched to the appropriate laboratory for analysis. Results were interpreted and risks assessed by discussion between laboratory staff and the clinical geneticist in charge of the case.

In the first three years of the consortium 92 prenatal diagnoses or exclusion tests were carried out, the majority being for cystic fibrosis (35), Duchenne muscular dystrophy (21), and Huntington's disease (11). Carrier testing was carried out in 271 X linked recessive disorders, the most common indications being Duchenne and Becker muscular dystrophies (198) and haemophilias A and B (48). Predictive testing was attempted in 41 consultands at risk for Huntington's disease, 37 at risk for myotonic dystrophy, and 32 at risk for developing adult polycystic kidney disease. The total of all carrier tests, including those for autosomal recessives, was 543.

A consortium or supraregional approach to molecular genetics services has a number of advantages. Constituent laboratories need hold only those probes and enzymes relevant to their assigned disorders and can gain maximum experience with these systems. Scattered families may often be linked into single kinships, thus allowing rapid confirmation of diagnosis when an urgent request is made for a prenatal diagnosis.

Regular meetings of members of the consortium enable responsibility for new probes to be assigned in a planned manner, and has created a de facto national molecular genetics committee that can argue for all aspects of funding in clinical genetics. Because each centre remains in close touch with its patients and the clinicians who serve it, it can continue to fulfil a local educational and consultative role.

By 1984 it had become clear that there was already an established need for laboratory diagnostic services based on the new DNA technologies. Three Scottish medical genetics centres submitted requests to the Scottish Home and Health Department (SHHD) for funds under the New Developments in Health Care programme. SHHD responded by asking all four university medical genetics centres in Scotland (Aberdeen, Dundee, Edinburgh, and Glasgow) to form a consortium, and thus to provide an integrated and flexible response to the new service need. Although a request was made to SHHD for an expansion of clinical support of DNA services, only laboratory staff, consumables, and some equipment were funded.

Organisation of the service

The principle was established by SHHD that there was to be no overlap of laboratory services, and that each centre was to be responsible for a set of genetic disorders for the whole of Scotland. Representatives of the four centres met in 1985 and decided on the assignments, which, after some readjustment and extension, are as shown in table 1. The two main principles guiding assignments are that each centre should have at least one disorder with a major potential workload, and that selection should, to some extent, be based on local research interests.

Each centre would continue to be responsible for investigating families and counselling patients within their own area, whatever the disorder. DNA would be extracted from blood and other tissues by the local laboratory before dispatch to the relevant diagnostic

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Table 1 Assignments to each centre.

Aberdeen	Dundee	Edinburgh	Glasgow
Antithrombin III deficiency	Adult polycystic kidney disease	Antitrypsin deficiency	Acute porphyrias
Charcot-Marie-Tooth disease (autosomal and X linked)	Collagen disorders	Choroideraemia	Adrenoleucodystrophy
Complement C3 deficiency	Growth hormone deficiency	Congenital adrenal hyperplasia	Haemochromatosis
DNA fingerprinting	Multiple endocrine neoplasias, I* and II	Cystic fibrosis	Haemoglobinopathies
Fragile X syndrome	Neurofibromatoses I and II*	Friedreich's ataxia*	Haemophilias A and B
Hyperlipidaemias	Osteogenesis imperfecta	Huntington's disease	Muscular dystrophies
Menkes' disease	Retinoblastoma	Phenylketonuria	Tuberous sclerosis
Mitochondrial disorders*	Wilson's disease*	Retinitis pigmentosa	Von Hippel-Lindau syndrome*
Myotonic dystrophy		Spinocerebellar ataxia, type I*	X linked ichthyosis
Norrie's disease			X linked immunodeficiency
Polyposis coli			

*Assignments made at most recent meeting.

centre. Interpretation of DNA results would involve discussion between laboratory scientists and the clinical geneticist in charge of the case.

When the consortium was first established there was some anxiety that assignment of a disorder to a particular centre might inhibit research on the same disorder in another centre. It was therefore decided to limit assignments to service needs, so that any centre was free to investigate any genetic disorder in which it was interested. However, as time has passed there has been a natural tendency within the consortium to focus research activities on those disorders for which centres have service responsibilities, and to offer service in disorders where centres have a research interest.

Work of the service

Laboratory work of the consortium is an integral part of the more general responsibilities of the four regional genetic centres and depends heavily upon support of clinical geneticists and their ancillary staff. However, in each centre the molecular genetics service draws upon the support of research groups often working in the same city. The importance of the interrelationship between research and service cannot be overemphasised; many technical problems in establishing a particular diagnostic service have been solved by access to experienced research colleagues.

RECEIPT AND WORK UP OF SAMPLES

When blood or other samples containing DNA are received by the laboratory, the first task is to validate the pedigree supplied, ideally by cross referencing to family data held in the local genetic register. It is often possible in X linked recessive and autosomal dominant conditions to confirm that a particular disorder is segregating in a family by connecting a local part of a pedigree to a larger national one.

Once the disorder and family are identified, the nature of the service request is established and assigned to a degree of urgency coding. Unfortunately, in many cases referred for prenatal diagnosis, the patient is already pregnant before anyone realises that establishing her suitability for DNA analysis may take several weeks of intensive laboratory effort and will involve tracing and counselling other members of the family. The disruptive nature of these unplanned emergencies to the smooth working of the laboratory has been a dismaying feature in the early years, but may now be declining in frequency.

In most centres DNA is extracted on the same day from any sample received. Until very recently, none of the four centres had automated equipment for extraction, and all samples were dealt with using manual, multistep extraction processes. As recommended by the Clinical Genetics Society Report,[1] every effort is made to obtain and store DNA from key members of families before they die. Moves are afoot in some centres to put DNA banking onto a formal basis and to store all samples as two separate aliquots in different freezers.

Table 2 shows DNA samples extracted and stored for each of the disorders covered by the consortium over the first three years of service. The large number of samples in the 'other' row in table 2 reflects the consortium's policy of ensuring that when new DNA probes for other diseases become available, some of the basic work for the relevant family will have been completed.

Since analyses are only carried out in one laboratory, each centre does a considerable amount of work extracting DNA from blood and other tissue samples and packaging them for transport to the correct laboratory. In 1988/1989 over 450 samples were exchanged between centres, or about one-fifth of those extracted. However, this gives no indication of another essential part of sample dispatch, namely the preparation of an appropriate pedigree to give a clear indication of the number of samples that may need to be analysed, and further samples that may need to be collected, in order to make a diagnosis possible.

ANALYSIS OF SAMPLES

During the first three years, virtually all the genetic disorders listed in table 2 were diagnosed by means of linked restriction fragment length polymorphisms (RFLPs). Since the informativeness of a polymorphism and the linkage phase relationship of the RFLP and the gene causing the disease must be approached in an ad hoc fashion, this is a somewhat cumbersome and inefficient process. This is shown by comparison of tables 3 and 4. Table 3 shows the

Table 2 DNA samples extracted and stored by the consortium.

Disorder	1986/87	1987/88	1988/89	Total
Adrenoleucodystrophy	0	15	0	15
Adult polycystic kidney disease	364	38	26	428
Antithrombin III deficiency	6	14	0	20
Antitrypsin deficiency	10	27	122	159
Charcot-Marie-Tooth disease	36	33	6	75
Choroideraemia	38	41	26	105
Collagen disorders	0	0	88	88
Cystic fibrosis	383	176	574	1133
Fragile X syndrome	7	21	20	48
Haemoglobinopathies	27	0	17	44
Haemophilias A and B	201	229	95	525
Huntington's disease	710	494	418	1622
Hyperlipidaemias	25	1	13	39
Multiple endocrine neoplasia	0	32	66	98
Muscular dystrophy—Duchenne	588	344	238	1170
Muscular dystrophy—Becker	121	28	52	201
Myotonic dystrophy	92	146	68	306
Neurofibromatosis	0	14	32	46
Norrie's disease	0	8	0	8
Phenylketonuria	8	14	9	31
Polyposis coli	0	0	36	36
Retinitis pigmentosa	237	292	44	573
Retinoblastoma	21	27	29	77
Tuberous sclerosis	14	9	20	43
X linked immunodeficiency	0	45	13	58
Other (all)	201	713	521	1435
Total	3089	2761	2533	8383

Table 3 Samples analysed by the consortium.

Disorder	No of subjects	Samples analysed			
		1986/87	1987/88	1988/89	Total
Adrenoleucodystrophy	4	60	0	0	60
Adult polycystic kidney disease	44	0	154	153	307
Antithrombin III deficiency	9	42	9	0	51
Antitrypsin deficiency	159	0	108	170	278
Charcot-Marie-Tooth disease	75	0	850	0	850
Choroideraemia	105	150	161	157	468
Collagen disorders	37	0	0	310	310
Cystic fibrosis	1028	870	1260	1758	3888
Fragile X syndrome	48	0	0	288	288
Haemoglobinopathies	4	8	0	0	8
Haemophilias A and B	148	464	353	536	1353
Huntington's disease	671	443	989	944	2376
Hyperlipidaemias	7	0	21	0	21
Multiple endocrine neoplasia, IIa	72	0	150	242	392
Muscular dystrophy—Duchenne	492	2209	2835	2065	7109
Muscular dystrophy—Becker	131	1422	378	336	2136
Myotonic dystrophy	174	384	445	335	1164
Neurofibromatosis	21	0	2	157	159
Norrie's disease	6	0	24	0	24
Phenylketonuria	31	0	45	48	93
Polyposis coli	28	0	0	134	134
Retinitis pigmentosa	573	620	845	496	1961
Retinoblastoma	50	0	300	208	508
Tuberous sclerosis	5	4	4	0	8
X linked immunodeficiency	5	0	0	15	15
DNA fingerprinting	118	0	0	260	260
Other	203	68	838	982	1888
Total	4248	6744	9771	9594	26 109

Table 4 Service requests completed by the consortium.

Disorder	Prenatal diagnoses/carrier detections			
	1986/87	1987/88	1988/89	Total
Adrenoleucodystrophy	0/1	—	—	0/1
Adult polycystic kidney disease	—	0/22	0/10	0/32
Antithrombin III deficiency	—	0/9	—	0/9
Antitrypsin deficiency	0/10	0/40	8/0	8/50
Charcot-Marie-Tooth disease	—	—	0/3	0/3
Choroideraemia	1/3	2/5	1/1	4/9
Cystic fibrosis	10/8	12/15	13/50	35/73
Haemoglobinopathies	1/0	—	—	1/0
Haemophilias A and B	2/5	1/27	1/16	4/48
Huntington's disease	—	2/1	9/40	11/41
Hyperlipidaemias	0/1	—	—	0/1
Multiple endocrine neoplasia	—	0/5	0/11	0/16
Muscular dystrophy—Duchenne	4/31	5/55	12/63	21/149
Muscular dystrophy—Becker	0/15	0/16	0/18	0/49
Myotonic dystrophy	0/5	0/25	0/7	0/37
Norrie's disease	—	0/1	—	0/1
Phenylketonuria	—	1/0	—	1/0
Polyposis coli	—	—	0/4	0/4
Retinitis pigmentosa	1/2	2/8	2/2	5/12
Tuberous sclerosis	—	1/0	—	1/0
X linked immunodeficiency	—	—	0/2	0/2
Other	1/0	0/6	—	1/6
Total	20/81	26/235	46/227	92/543*

*92/543 indicates 92 prenatal diagnoses and 543 carrier detections.

numbers of subjects and the samples analysed, each analysis representing an RFLP or dot blot. It can be seen that for each subject the average number of RFLPs was six with a range of 1·7 (α_1 antitrypsin deficiency) to 16·3 (Becker muscular dystrophy). Primarily this reflects attempts to find informative probe and enzyme systems for particular disorders, but it also includes the work done when new probes came on stream during the work up of a family. The number of samples analysed per subject should begin to fall once the optimum system is established for each disorder.

Table 4 shows service requests completed by the consortium. In this table predictive tests for late onset, dominantly inherited disorders, such as myotonic dystrophy and Huntington's disease, are listed as 'carrier detections', even though the amount of work involved is usually much greater than for a carrier test in a recessively inherited condition. The labour intensive nature of RFLP based diagnosis is illustrated by comparing the number of subjects tested (table 3, 4248) with the number of prenatal diagnoses and carrier detections (table 4, 92 and 543) actually completed. The ratio of subjects tested to diagnoses made is likely to begin to reduce in X linked recessive and autosomal dominant conditions, since the working up of individual samples in a family is not necessarily restricted to a diagnosis in a single subject. Furthermore, many of the analyses carried out in table 4 were part of setting up exercises for new probe/enzyme combinations.

In the most recent year of this service, the polymerase chain reaction (PCR) has been used to facilitate diagnoses of cystic fibrosis,[2] α_1 antitrypsin deficiency,[3] phenylketonuria,[4] and Huntington's disease.[5] Each dot blot following a PCR is recorded as an analysis in table 3.

Outreach of the service

An important measure of the success of a service is found in whether it reaches a substantial proportion of families who need prenatal diagnosis, carrier detection, or predictive testing. This issue can only be addressed for those disorders which are sufficiently common for reliable prevalence and incidence figures to exist.

DUCHENNE AND BECKER MUSCULAR DYSTROPHIES

From data in our genetic registers, it is known that there are 254 families in Scotland in which either Duchenne (DMD) or Becker (BMD) muscular dystrophies are segregating. Currently, 198 women known to be at risk of being carriers have had their genetic status investigated by DNA typing. Of the 66 carriers found, 54 were detected by means of linkage analysis and 12 by molecular pathology (66% of affected males in these families have a dystrophin gene deletion). Approximately 12% of the women investigated could be offered no carrier risk reduction by DNA analysis, the most common reason being that key family members were not available to allow unequivocal establishment of phase.

Twenty-one first trimester prenatal diagnoses have already been carried out and this number is rising

(table 4) as those subjects diagnosed as carriers take advantage of the molecular genetics service. In addition, DNA has been banked for 130 of the known affected males, including 22 of the 23 patients who have died since 1983.

CYSTIC FIBROSIS

The birth incidence of cystic fibrosis (CF) is 1 in 2500.[6] There are approximately 68 000 births per year in Scotland, of which 109 will be to couples where each partner is a CF heterozygote. Assuming that each couple has an average of two children, half of these pregnancies will be second pregnancies, and in one quarter (13·6/year) of the second pregnancies, prenatal diagnosis of CF will be possible. Thus, in the absence of reproductive compensation,[7] we would have expected to provide a maximum of 41 prenatal diagnoses of CF in the three year period. The actual number was 35, of which 22 were to Scottish couples. This represents about 54% of expectation.

MYOTONIC DYSTROPHY

The prevalence of myotonic dystrophy in the UK is of the order of 5·5 per 100 000,[8] or a total of 275 living affected patients in Scotland. To date, 52 affected subjects (19% of the theoretical total) have been DNA tested and a majority of the families found to be informative for prenatal testing.

HUNTINGTON'S DISEASE

The prevalence of Huntington's disease in Grampian is estimated at 10 per 100 000,[9] giving about 500 living affected patients in Scotland. DNA has been stored for 204 of these (41% of the total). We are currently in the process of servicing 78 requests for presymptomatic testing in 56 Huntington's disease kinships.[10]

Discussion

There can be little doubt from the data shown here and elsewhere[11] that molecular genetic diagnosis is a rapidly growing field of service activity. The number of samples analysed by the consortium reached a peak during its second year (table 3) and is currently at a maximum level for existing staff. It is difficult to predict future developments with any degree of accuracy. On one hand, the 'catching up phase', during which a backlog of families with easily recognised, well known diseases like Duchenne muscular dystrophy and cystic fibrosis is cleared and serviced, may soon be completed. On the other hand, there are other quite common disorders, like myotonic dystrophy, adult polycystic kidney disease, and hypercholesterolaemia, where the demand for service is still uncertain and related to the perception of severity by both medical profession and patients. Furthermore, the rate of discovery of new DNA markers with linkage relationships to genes causing disease does not yet appear to have slowed. There is also the not too distant prospect of using molecular genetics in risk prediction for polygenic diseases, already becoming a reality with insulin dependent diabetes mellitus.[12]

There are, however, some hopeful signs. Although over 4000 different single gene defects are known, most of the higher frequency conditions are now diagnosable by DNA methodologies. As more genes responsible for genetic disorders are cloned and sequenced, there will be some shift from cumbersome indirect means of gene analysis, with involvement of extended families, to more direct, specific analyses. Gene amplification technologies, together with non-isotope detection systems, will both speed up and simplify the process of laboratory analysis.[2–5]

What are the particular advantages in a consortium or supraregional approach to molecular genetic services? The most significant lies in economy of scale, with each laboratory having to obtain and hold only those probes and enzymes for its assigned list of disorders. Equally important is the fact that laboratory staff gain maximum skill and experience with their systems and can provide a rapid and up to date response to service requests. For example, Edinburgh had to make an early investment in a thermal cycler, since a majority of prenatal diagnoses of both cystic fibrosis[2] and α_1 antitrypsin deficiency[3] are now carried out via the polymerase chain reaction.

A second advantage is that the close contact between the centres may enable scattered families to be linked quickly into a single pedigree. We have very complete information, for example, on the number of families in Scotland in which Duchenne and Becker muscular dystrophies are segregating. This type of information may be vital in confirming a diagnosis rapidly when an urgent prenatal diagnosis is requested. A linked family network is also more likely to provide sufficient members to enable gene tracking to be possible.

A single molecular genetics laboratory should be able to cope with a population the size of that of Scotland (5 million), but there are cogent reasons for the work to be geographically dispersed. Local populations, and the clinicians that serve them, need to have easy access to the laboratory personnel who can be expected to be closely in touch with new developments in this rapidly advancing field, and the laboratory thus fulfils both an educational and consultative role. By distributing the laboratory activities through four university medical schools, interaction and collaboration between the molecular genetics service group, the related regional cytogenetics service, and a wide range of local research groups is facilitated.

The existence of the consortium has been a potent factor in drawing together the staffs of the four genetics centres in Scotland at their semi-annual meetings. Assignments of probes, discussion of service problems,[13] and planning strategies to increase the funding of all aspects of genetics services provide the major topics at the meetings. Since the clinical and laboratory staff from each centre attend, a de facto national clinical genetics committee has developed. However, as argued in the report of the Working Group of the National Medical Consultative Committee,[14] the formal establishment of such a committee is most desirable.

The positive development of a consortium approach will avoid the danger of uncoordinated, costly, and ill judged forays into molecular genetics by inexperienced local laboratories. When this consortium was first established there was some disquiet among colleagues who felt that service molecular genetics should be provided by the speciality caring for the disorder. The challenge to this alternative approach has faded, largely because of the success of our integrated service. We therefore conclude that for a population the size of that of Scotland, the consortium is able to provide an efficient and effective service. This point has been recognised by the Scottish Home and Health Department, who have more than doubled the consortium's budget for the next service year.

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