ABSTRACTS OF THE MEETING OF THE CLINICAL GENETICS SOCIETY HELD ON 5 AND 6 OCTOBER 1989 AT MIDDLESEX HOSPITAL MEDICAL SCHOOL

Hereditary motor and sensory neuropathy type I is linked to chromosome 17
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Early reports suggested that the disease locus for HMSN1, the commonest type of inherited neuropathy in the UK, might be on chromosome 1, near the Duffy blood group locus. Subsequent work from many groups, including ours, failed to confirm this, suggesting that the earlier results arose by chance or that HMSN1 is genetically heterogeneous. Vance et al (Exp Neurol 1989;104:186–9) have reported linkage of HMSN1 to the pericentromeric region of chromosome 17. We have confirmed this linkage in eight families. D17S58 (EW301) gave a maximum lod score of 5.89 at θ=0.08 and D17S71 (pA10-41) a maximum lod score of 3.22 at θ=0.08. EW301 is on 17p, 5.5 cM from the centromere. One family, previously reported as showing linkage to the Duffy blood group locus on chromosome 1, was included in the study and now provides a positive lod score for chromosome 17 markers (lod 1.80 at θ=0 D17S58). There was no evidence of heterogeneity.

Predictive testing for Huntington’s disease (HD) in Scotland: the first 50 cases
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Using DNA probes at the D4S10, D4S43 and D4S95 loci, we have carried out predictive testing on 50 subjects at high risk of inheriting the HD gene, identified through the Consortium arrangements. Six of these were on first trimester chorionic villus biopsy specimens and resulted in two prenatal exclusions and four non-exclusions. The remaining 44 tests were on adults, 19 of whom had a greatly increased risk and 25 a substantially decreased risk of inheriting the HD gene. Family structures in Scotland are suitable for testing about 75% of would-be consultands, while the new generation of DNA markers makes virtually all cases informative. However, even with closely linked markers, residual risks of HD in many consultands are less than ideal. This does not appear to deter those who embark on predictive testing.

Statistical analysis of the two stage mutation model in von Hippel-Lindau disease, sporadic cerebellar haemangioblastoma, and renal cell carcinoma
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Analysis of the age incidence curves for unilateral and bilateral retinoblastoma led Knudsen (Proc Natl Acad Sci USA 1971;68:820) to propose that hereditary tumours may arise by a single event and sporadic tumours by a two stage mutation process. Recently Erlandsson et al (Cancer Genet Cytogenet 1988;36:197) have suggested that sporadic renal cell carcinoma (RCC) arises from a two stage mutation process. We analysed the age incidence curves for symptomatic RCC (n=26) and cerebellar haemangioblastoma (CHB) (n=68) in 109 patients with VHL disease, and compared them to 104 patients with sporadic RCC and 43 patients with sporadic CHB. The age incidence curves for RCC and CHB in VHL disease were compatible with a single mutation model, whereas the age incidence curves for sporadic RCC and CHB suggested a two stage mutation process. These data are compatible with the VHL gene functioning as a recessive tumour suppressor gene. Sporadic CHB and some RCC may arise from somatic mutations inactivating both alleles at the VHL locus.

Molecular genetic studies of Angelman’s syndrome
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Thirty-seven typical cases of Angelman’s syndrome have been studied. Cytogenetic deletions in the region 15q11–q13 were observed in 18/24 isolated cases. No deletions were observed in 13 cases from six families with more than one affected child. DNA probes from the region (D15S24 and D15S13), which detect RFLPs, were used to confirm the deletion in four cases. In other deletion cases the same probes are present in two copies, showing variable deletion breakpoints. In 11 cases it has been possible to elucidate the parental origin of the deleted chromosome and these have been shown to be predominantly of maternal origin. Cytogenetics have shown a de novo deletion of a maternal chromosome in five cases and paternal in two. Molecular genetics have shown a maternal origin in four cases (including confirmation of one cytogenetic result). Flow karyotyping has shown one maternal deletion. This is in contrast to the overwhelmingly paternal origin of an apparently similar deletion in Prader-Willi syndrome. Linkage studies in affected sibs make straightforward autosomal recessive inheritance unlikely.
Lethal osteogenesis imperfecta: a family with 6 affected sibs heterozygous for a type I collagen mutation

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We describe a family with unrelated, normal parents in which six pregnancies have been affected with thin boned osteogenesis imperfecta (OI). There have been no normal children. The first affected infant, delivered at 39 weeks’ gestation, died after 10 hours. The index case and two other pregnancies were terminated after ultrasound diagnosis. Histological and radiological findings confirmed OI. Skin fibroblast cell lines were established from the index case and from both parents. Collagen was metabolically labelled in cell culture and analysed by SDS-PAGE. The index fetus synthesised and secreted overloaded type I collagen. The use of α1-dipirydyl and one dimensional cyano- gen bromide peptide mapping showed excessive post-translational hydroxylation throughout the triple helical portion of the molecule. However, once formed, the collagen melted at the normal temperature. Protein from the parents appeared normal. The presence of overhydroxylated α chains was also shown in cells taken by chorionic villus biopsy from a subsequent pregnancy. Ultrasonography confirmed the diagnosis of an affected fetus, which was then terminated. The biochemical profiles of these two affected subjects were identical. Two dimensional cyanogen bromide peptide mapping has now indicated that both the affected fetuses are heterozygous. We suggest that the mutation is dominant and that it may illustrate gonadal mosaicism.

POSTERS

Origin of the X chromosome in a patient with the 49.XXXXY syndrome

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The results of X chromosome RFLP studies undertaken on a 36 year old male with the 49.XXXXY syndrome are presented. Chromosome analysis from cultured lymphocytes showed a 49.XXXXY constitution in 45 (90%) out of 50 cells examined, with a 48.XXXY constitution in the remaining five (10%) cells. Parental chromosomes were normal. X chromosome RFLP analysis using the pERT87-1 and 87-15 probes with XmnI enzyme indicated that all of the patient’s X chromosomes were maternally derived and that he possessed two copies of each of his mother’s pERT alleles.

Carriers of the Tay–Sachs disease (TSD) gene have a reduced percentage of hexosaminidase A (Hex A), which can be differentiated from the other Hex isoenzymes by its relative lability. We have developed an automated assay for Hex A using a centrifugal analyser. After a manual heat inactivation step, Hex A levels are measured in serum. Assay on leucocytes is used to follow positive or borderline serum results and when serum results are unreliable, especially during pregnancy. The advantage of the centrifugal analyser over continuous flow systems in current use is its relative simplicity of operation and its versatility in also handling leucocyte samples, as we receive many samples from antenatal clinics. We have defined our normal range from testing the sera of 30 obligate TSD carriers and 184 non-Jewish blood donors using 4–MU–β–N-acetylglucosaminide as substrate. Four per cent of people initially tested on serum give borderline results which can be resolved on leucocyte testing. Use of the highly Hex A specific substrate 4–MU–β–GlcNAc–6–sulphate avoids the need for the three hour heat inactivation step and provides better discrimination when the data are analysed as a two dimensional plot of Hex A versus Hex A/total Hex. The data we have obtained from screening 2556 members of the Jewish community in Britain so far indicate a carrier frequency of 1 in 27.

A genetic study of ataxia telangiectasia: what benefit to the families?

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A genetic study of families with ataxia telangiectasia in the UK was conducted. We were interested to know why families had participated and if they had found the study of any help. Fifty-two families were contacted by letter, introducing the genetic study. Four did not respond, one declined to participate, and 47 agreed and were subsequently visited at home. When visited almost all families spoke of isolation, rarely knowing another affected family. After completion of the genetic study an anonymous questionnaire was sent to the 47 families: 43 replied. Most had participated because “it would help in the future”. None objected to blood samples being taken from all family members. All wanted to know study results. Two families, who were put in touch during the study, started an ataxia telangiectasia parents support group. In human terms, this genetic study of a rare disorder was of great benefit to the families involved.

Strategies for detection of single base changes in subjects heterozygous for alleles of the apolipoprotein B gene

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Apolipoprotein B (apo B) is the sole apoprotein on the low density lipoprotein (LDL) particle and the ligand through which this particle is cleared via the LDL receptor. As such, apo B plays a central role in cholesterol metabolism and thus the apo B gene is a candidate for the development of atherosclerosis. It has been shown that several subjects have reduced clearance rates of LDL cholesterol that are not the result of defects in the LDL receptor. We have been developing PCR related techniques of direct sequencing, mismatch analysis, and
allele specific oligo (ASO) melting, in order to detect mutations affecting the putative receptor binding domain of apo B, which may be the cause of the reduced clearance.

Use of PCR to genotype a polymorphic dinucleotide repeat within the PAI-1 gene in patients with a recent MI

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Plasminogen activator inhibitor (PAI -1) has been identified as an independent risk factor for myocardial infarction (MI). An eight allele dinucleotide CA repeat polymorphism was identified within the PAI-1 gene using PCR. Allele frequencies were estimated in 44 random subjects and ranged from 0-02 to 0-37. Inheritance was followed in an extended family and was according to Mendelian rules. Genotypes were determined for two populations: one healthy and one of patients with a recent MI. These data were compared with similar experiments with a previously reported HindIII RFLP using standard Southern blotting techniques. The HindIII 2-2 genotype was significantly associated with raised PAI levels in the control population and the same association was found in the patient population but at a non-significant level. The HindIII and CA repeat genotypes are in linkage disequilibrium. Routine use of PCR to type these highly informative polymorphic dinucleotide repeats provides a rapid method for following the inheritance of genetic markers.

Presymptomatic detection and prenatal diagnosis for myotonic dystrophy by means of linked DNA markers

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The close genetic linkage between the loci for apolipoprotein CII (apo CII) and myotonic dystrophy makes presymptomatic detection and prenatal diagnosis feasible. We report three years' experience of providing presymptomatic detection and prenatal diagnosis for myotonic dystrophy in 99 families. Careful clinical study of older family members remains important. The introduction of new probes (CKMM and BCL4) has helped to solve the problem of uninformativeness owing to unhelpful genotype distribution in a family. Nevertheless informativeness cannot be guaranteed and families should be studied before pregnancy is undertaken whenever possible. Presymptomatic testing and prenatal diagnosis for myotonic dystrophy are soundly based. All affected subjects should have DNA banked for future use when other family members may require genotype information.

Lethal bowing syndrome in two sibs

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Two sibs with skeletal changes similar to a patient reported by R E Stevenson (Proc Greenwood Center 1982;1:47) are presented. The first affected female child of the family was born at 33 weeks of pregnancy. She had very short, curved limbs with flexion contractures in the arms, club feet, small chin, low set ears, and dimples on the knees and buttocks. The radiographs showed sharply angulated radii, ulnae, femora, tibiae, and fibulae. The child died of respiratory difficulties after 10 hours. No additional abnormalities were found at necropsy. Before the birth of a normal child fetal death was found by ultrasound at 15 weeks of the following pregnancy. The male fetus had skeletal changes identical to the first affected child. This suggests autosomal recessive inheritance of this condition.

Clinical application of haplotype frequencies in cystic fibrosis families in Wales

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The DNA markers pXV2c and pKM19 show strong linkage disequilibrium with the cystic fibrosis (CF) mutation on chromosome 7. Our data show that in Welsh families, CF segregates predominantly (85-3%) with haplotype B (pXV2c allele 1/pKM19 allele 2) whereas this haplotype occurs in only 11-4% of normal chromosomes. Based on this information we have been able to help families where material from an index case is not available for DNA analysis; we have also adjusted the risks of carrier status for partners of CF patients and for partners of known CF carriers. In addition knowledge of haplotypes may be used to strengthen or weaken a possible diagnosis of CF: these situations have arisen when diagnostic criteria have been borderline, or when the death of an infant with suggestive symptoms has occurred early in the neonatal period before a confirmatory sweat test can be carried out.

Cystic fibrosis DNA probe anomalies: crossover, misdiagnosis, non-paternity or sample error

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During the routine DNA analysis of 83 cystic fibrosis families in Northern Ireland, we identified four families in which there appeared to have been one, or more, recombination events between the probes Met H, Xv–2c, KM19, or pJ3.11 and the CF gene. The affected subjects had been diagnosed either by uncreased levels of immunoreactive trypsin and sweat testing or by sweat testing alone after referral on clinical suspicion. Family 1 (three affected) showed an apparent crossover with Xv–2c but on further investigation a diagnosis of ectopic eczma was made. The affected subject from family 2 showed several anomalies with the probes Xv–2c and Met H and, when examined with the VNTR probe YNH24, appeared to have no maternal alleles. The results did suggest, however, that the samples from the affected girl and her father had been mixed up and this was confirmed using an X linked VNTR probe M27. Both family 3 (two affected, one unaffected) and family 4 (four affected, two unaffected) showed a potential crossover between KM19 and CF with no evidence of non-paternity or misdiagnosis. Family 5 (two affected) showed multiple cross-
overs including Xv–2c, KM19, and pJ3.11. Testing with the VNTR probes did not suggest sample error or non-paternity and the diagnosis of CF was confirmed. Further analysis of these families with the probes D9 and C67 will be necessary.

A molecular study to identify a subject homozygous for the myotonic dystrophy gene

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We have studied a large multigenerational pedigree in which two third cousins, both affected with myotonic dystrophy (DM), have married. They have four children who are affected with DM, and are therefore possibly homozygous at the DM locus. All four children have been examined by one of us (EJI) and a clinical summary will be presented. We have used the polymorphic DNA probes BCL3, APOC2, and CK-MM, shown to be within 2 cM of the DM gene, as well as some recently isolated probes, also closely linked to DM, in order to follow the inheritance of the DM haplotype in the family. This information has been used to determine if any of the four subjects in question is homozygous at the DM locus and to determine if severity of the DM phenotype is subject to a dosage effect.

Chromosomal translocation t(8;10)(q22.3;p13) associated with dominantly transmitted cleidocranial abnormalities

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An apparently balanced translocation, 46,XX,t(8;10)(q22.3;p13) was detected in a mother and daughter who presented with identical craniofacial abnormalities. The dysmorphic features consisted of hypoplastic clavicles; large anterior fontanels in the daughter with suggestion of wormian bones on skull x ray; broad forehead; marked hypertelorism; micrognathia with class II occlusion in the mother; high palate; and relative short stature (10th centile). The mother is of normal intelligence and her daughter is making normal developmental progress. The mother's parents and her other child have normal karyotypes and no craniofacial abnormalities. Chromosome abnormalities have not previously been reported in cleidocranial dysostosis, although the dysmorphic features present in this family may represent a new clinical entity. The presence of the chromosomal translocation in the affected mother and daughter suggest localisation of a dominant gene causing cleidocranial abnormalities at either 8q22.3 or 10p13.

Types of albinism in the Black populations of Southern Africa

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Oclocutaneous albinism (OCA) occurs in 1 in 3900 births in Southern Africa. This study aimed to identify and describe the local types of OCA. Subjects were ascertained during a community survey and types were identified by clinical examination, hair bulb incubation tests, tyrosinase (ty) assays, and visual evoked potential testing. Results showed that in 96 albinos 82% had ty-pos OCA, 11.5% brown, and 6% rufous albinism. None had ty-neg albinism (mapped to 11q11) or the allelic yellow mutant type. The ty-pos subjects comprised both those with pigmented patches and those without, the latter being at significantly greater risk for skin cancer. The brown albinos had more pigment than the ty-pos and fewer visual problems. The rufous had the most pigment and the least visual problems. The decoussation defect of the optic tract detected in three ty-pos albinos was not apparent in three rufous subjects. Homogeneous OCA groups have to be identified before results from molecular studies can be interpreted.

Linkage study of F8 in the fragile X syndrome

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The genetic distance of F8 from FRAXA remains undetermined and pulse field gel electrophoresis data (Patterson et al, 1987) showing its proximity to G6PD rather than to the cluster (DXS52, DXS15) suggested that it should be investigated as a potential flanking marker for carrier detection in the fragile X syndrome. Families segregating for fragile X syndrome were studied with an informative intragenic F8 polymorphism but a peak lod score of 0·63 at θ = 0·27 suggested insufficient meioses had been available to estimate the precise recombination fraction. A multipoint linkage analysis using the LINKMAP component of LINKAGE 4·7 excluded FRAXA from the interval DXS32–F8 with a peak lod score of −2·0 being observed for that test interval. A multiply informative phase known family supports the order in distal Xq of: FRAXA–(DXS52, DXS15, probe 1A1)–F8–telomere. Thus in the families studied F8 appears to be too loosely linked to be a useful flanking marker in fragile X syndrome and is likely to be the most telomeric of the distal interval markers used.

Prenatal diagnosis of the fragile X syndrome

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Prenatal diagnosis has been undertaken for 50 pregnancies in women who are at risk for the fragile-X or Martin-Bell syndrome. Owing to the invasive nature of the procedure, the majority of pregnancies undergoing cordocentesis had been previously selected as male, either by CVS or ultrasound. Of the 50 mothers, 34 were considered to be carriers of the syndrome either because they themselves carried the fragile X (26 subjects) or because they had a previous affected child (18 subjects) or both. There were 43 male outcomes of which 11 were positive for the fragile X. Of these, nine were terminated and two were liveborn. (One was missed prenatally and the other mother refused a termination.) Seven female pregnancies resulted in two fragile X positive (one terminated, one liveborn) and five fragile X negative outcomes. Of the 23 fragile X positive mothers with male pregnancies, 14 had boys without fragile X, while nine
males were fragile X positive showing an expected deficiency. Recently, early detection of the fragile X in CVS samples has resulted in the identification of two affected pregnancies obviating the need for fetal blood sampling.

Clinical problems associated with predictive testing for Huntington's disease

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Experience with nearly 300 applicants for predictive testing for Huntington's disease has shown that apart from the expected problems, such as those related to possible misuse of the test, there were several less foreseen difficulties. These may be divided into those occurring before, during, and after the test. Examples of problems occurring before testing are inappropriate referrals, lack of clear family history, and counselling of the affected applicant and the applicant with equivocal symptoms. Problems during testing concern collection of blood samples (inadequate labelling, use of pseudonyms) and unintentional risk alteration. Problems after testing include requests from third parties for results of the test and refusal of follow up by applicants. More of the problems involve clinical and counselling aspects rather than laboratory procedures.

X linked retinitis pigmentosa: recombinational analysis and carrier estimation with the proximal Xp markers XJ1.1, OTC, and M27β

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X linked retinitis pigmentosa (RP2) is a hereditary retinal degenerative disorder which has been localised to the proximal short arm of the X chromosome. Recent evidence suggests that the disorder is heterogeneous with two possible loci for the disease mutation. Recombinations observed on DNA analysis of the family presented in this paper show that the mutation is mapped to the more distal loci (RP2α), between OTC and M27β. This enabled flanking markers to be used for the detection of female carriers in this family. In none of the females was a tapetal reflex (metallic sheen) observed, suggesting that this phenotypic feature is not a reliable marker for mutations at the more distal RP2α locus.

Linkage of Watson’s syndrome to chromosome 17 markers

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Watson's syndrome was first reported in 1967 and is characterised by café au lait spots, freckling, pulmonary stenosis, and short stature. We have analysed a three generation family with Watson’s syndrome using 12 chromosome 17 pericentromeric markers, of which eight were informative. Close linkage with DNA marker D17S33 was noted (θ=0.00, Z=3.20). This marker is also the closest marker to NF1. Watson’s syndrome may be allelic to NF1. Linkage analysis for other variant forms of NF and for pulmonary stenosis is indicated.

Paternal origin of new mutation in Von Recklinghausen neurofibromatosis (NF1)

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Von Recklinghausen neurofibromatosis is one of the most frequent autosomal dominant disorders with a prevalence of about 1 in 5000. The mutation rate is very high and about 50% of affected cases result from a new mutation. Linkage analysis has recently mapped the disease to chromosome 17 and the identification of two NF1 patients with balanced translocations has allowed the location of the disease to be narrowed to 17q11.2. With the availability of the closely linked DNA markers to NF1, it is now possible to determine directly the parental origin of new mutation by genetic linkage in three generation families, in which a new mutation is identified in the middle generation. We have analysed five families with 12 chromosome 17 DNA markers and the new mutation is of paternal origin. It has been possible to infer the chromosome on which the new mutation originated from the haplotypes in each family. Paternity was confirmed in each family using hypervariable DNA probes. NF1 resembles retinoblastoma in that both show a predominance of paternal new mutation but little or no paternal age effects.

Identification of candidate genes for cardiac malformations using RNA from first trimester human hearts

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The complex congenital cardiac malformation 'atrioventricular septal defect' shows a strong association with human trisomy 21 and murine trisomy 16 (the genetic homologue of Down’s syndrome). In addition, Mendelian inheritance of the defect has been reported in several pedigrees. It was therefore hypothesised that the inherited genetic lesion in these families involves a gene which maps in the Down’s syndrome region of chromosome 21 and plays an important role in the process of atrioventricular septation. To isolate possible chromosome 21 specific candidate genes, RNA was extracted from 61 human embryonic and early fetal hearts obtained from the products of 109 routine suction terminations of pregnancy. Total RNA preparations were electrophoresed in agarose gels containing formaldehyde and transferred to nitrocellulose membranes by northern blotting. DNA sequences previously isolated from the Down’s syndrome region of chromosome 21 were radio-labelled and used as gene probes for specific mRNAs. Of 13 sequences tested, four were found to be expressed in early cardiac tissue. This study provides four candidate sequences which can be used to analyse possible
cosegregation of particular restriction fragment length polymorphisms with the defect in a number of pedigrees. Such an approach may permit the aetiology and pathogenesis of familial atrioventricular septal defect to be determined by identifying the underlying gene defect.

The use of 'ARMS' primers for the detection of the mutation causing cystic fibrosis and a rapid and simple technique for paternity testing

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Until recently cystic fibrosis (CF) carrier testing has been performed using linkage disequilibrium data generated from haplotype data obtained using closely linked probes. Useful sequence data from these probes have made it possible for the majority of haplotypes to be generated using polymerase chain reaction. The mutation causing cystic fibrosis has now been cloned and sequenced, enabling the precise detection of the most common CF abnormality. Three methods for the detection of the mutation are being developed in our laboratory: looking directly at the mutation on a polyacrylamide gel; using radioactive allele specific oligonucleotides; using primer sequences specific for the presence and absence of the mutation. It is now possible to detect the three base pair deletion using alternative primers, reading in different directions from the mutation.

Community attitudes to carrier screening for cystic fibrosis

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The mutation causing cystic fibrosis (CF) has been characterised and carrier testing in the general population will now be possible. A survey has been undertaken in north west London to assess knowledge of cystic fibrosis and attitudes to carrier screening and to ascertain what the demand for such a service will be. The survey has shown considerable interest from the general public, with most people indicating they would like to know their carrier status. CF relatives have expressed very strong feelings that screening should be introduced. General practitioners and medical staff at Family Planning Clinics within North West Thames Regional Health Authority have also indicated that they believe carrier testing for CF would be a worthwhile exercise. Possible strategies for the introduction of screening within the NHS have been explored.

Structural studies of the fragile site at Xq27.3

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Very little is known of the structure of the fragile sites on chromosomes at the molecular level. A common form of mental retardation (Martin–Bell syndrome) is frequently associated with a fragile site at Xq27.3. There are many theories as to the structure of this region at the DNA level, but little experimental evidence. Cytogenetically, the fragile site appears not to have condensed properly. Using fragile X and normal cell lines, chemical and enzymatic probes (which detect structural perturbations in the DNA) have been used to investigate the structure of the DNA in the region of the fragile site. Following treatment with the structural probe and removal of histones, the DNA was digested with rare cutting enzymes and the fragments separated using PFGE. Preliminary data show that DNA probes close to Xq27.3 detect different sized fragments in fragile X and normal cell lines. This suggests that this method of using chemical and enzymatic probes may help gain an insight into the structure of the region.

Linkage markers in schizophrenia in Wales

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Large or moderately large pedigrees containing multiple family members affected by schizophrenia have been sought throughout Wales. All available family members from pedigrees with a potentially informative structure have been interviewed using the Past History Schedule (PHS) (McGuffin et al, 1986) and an augmented version of the PSE (Wing et al, 1974). Additional information has been collected using the Operational Criteria Checklist for Psychotic Illness (OCCPI). Several DNA markers are being studied; however, for the purposes of this brief report we will focus on the 5q11–13 region where linkage to a putative schizophrenia susceptibility gene has been reported and we will present data on six pedigrees. We applied a 'near dominant' model of schizophrenia transmission as in the published report of Sherrington et al (1988), with some minor modifications. Two point linkage analysis with p105–599Hpa excluded close linkage. Although four families showed weakly positive lod scores with p105–153R0, on carrying out multipoint analysis with schizophrenia as the test locus and the two markers fixed at approximately 16 cM apart, we found that a gene for schizophrenia in this region in our Welsh pedigrees is improbable.
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