Abstracts of the meeting of the Clinical Genetics Society held on 20 and 21 November 1987 at St George’s Hospital Medical School, London (joint meeting with the Skeletal Dysplasia Group)

The association of Angelman syndrome and deletions within 15q11-13
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Ten additional children with Angelman (happy puppet) syndrome have had their karyotypes reassessed following the observation in two patients of a deletion within 15q11-13, one of which was initially regarded as a polymorphic variant. Four out of 10 showed a deletion within 15q11-13, one showed an apparent pericentric inversion with breakpoints at 15q11 and q13 inherited from his mother, and five showed no discernable abnormality. These figures are compared with a 1985 survey of 93 consecutive cytogenetic referrals by MG and MF, in which 11 small, 14 medium, three extensive, and one total (including band 15q12) deletion of band 15q11-2 were found. The six children with deletions were in the case family and of four parent sets studied three had normal chromosomes and in one the mother had a deletion of 15q11-2 but not 15q12. Of the five children without discernable chromosome change, one had a definitely affected sib and one a possibly affected sib. These observations coupled with the reported sib recurrence risk of about 5% point to a combination of autosomal recessive inheritance and dominant ‘de novo’ chromosomal deletions involving a locus (loci) within 15q11-13.

Linkage analysis of X linked hypohidrotic ectodermal dysplasia: implications for carrier detection and prenatal diagnosis
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Accurate carrier detection for X linked hypohidrotic ectodermal dysplasia (EDA) has previously been imperfect based on clinical examination, and prenatal diagnosis has not been available. Recently the disorder has been localised to the general region of the proximal long arm (Clarke et al, Hum Genet 1987;75:378), and we have extended that study to a total of 36 families, British and American, and have used six new RFLPs for a total of nine marker loci. Three loci show tight linkage: DXS1591 (θ=0-01, Z=14-8), PGK1 (θ=0-02, Z=13-4), and DXS72 (θ=0-02, Z=11-4), while four others show looser linkage within 14 cM of the disorder (DXS146, DXS14, DXYS1, DXYS2), and could be used as flanking markers. Risks calculated for the offspring of our 90 obligate and manifesting carriers should be significantly improved, since 81% of the carriers are heterozygous for at least one of the three loci within 2 cM of the disorder, and 93% of them for a marker within 5 cM. Seventy two percent of carriers are informative for flanking markers, one third of them bracketed by a total distance of 0 to 5 cM. Linkage analysis using RFLPs can provide relatively accurate carrier detection and prenatal diagnosis for at risk families.

A survey of neural tube defect pregnancies in the northwestern region
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The North West Regional Working Party on Neural Tube Defects is undertaking a prospective study aimed at complete ascertainment of neural tube defect affected pregnancies throughout the region. This is combined with an investigation of support and counselling received by parents once such a diagnosis is made, particularly regarding the use of periconceptional vitamins for subsequent pregnancies. These pregnancies are then being followed up. The preliminary results of the first year of our study show that 94 neural tube defect pregnancies were notified, 45 anencephalic, four encephaloceles, and 45 spina bifida. Fifty-nine resulted in a termination of pregnancy, eight were stillborn, and 27 born alive. At present 24 mothers are pregnant again. Detailed interviews with these parents identified that the advice they received was variable. One third had been counselled by clinical geneticists and a further third by other clinicians involved in their care generally the obstetrician, but 15 couples could not recall being told anything regarding recurrence risks or vitamin supplementation for subsequent pregnancies.

Prospects for preimplantation genetic diagnosis of hypoxanthine-phosphoribosyl transferase (HPRT) activity and sexing using biotinylated Y specific probes in human pre-embryos
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Despite the availability of first trimester sampling, high risk prenatal diagnosis can be associated with repeated pregnancy loss and some patients who fail to achieve a healthy family feel unable to continue. An alternative, now under investigation, which would be acceptable to a proportion of such couples involves making the diagnosis on cells removed from the pre-embryo before implantation, either after IVF or after recovery from the uterine cavity (Penketh and McLaren, 1987, Ballieres Clinical Obstetrics and Gynaecology; Whittingham and Penketh, 1987, Human Reproduction 2, No 3, 267–70). Rapid diagnostic techniques applicable to very few cells will allow biopsy of the embryo during cleavage, continued culture of the biopsy, diagnosis, and the return of unaffected embryos to the uterus at the early blastocyst stage during the cycle of egg collection, avoiding the need for cryopreservation. We report activities of HPRT in human pre-embryos and single blastomeres indicating the feasibility of diagnosis of Lesch–Nyhan syndrome during cleavage. Sexing of pre-embryos using in situ hybridisation of radiolabelled Y specific probes to interphase nuclei has been achieved (West et al. Lancet 1987;i:1386–7). Biotinylated probes detect by the streptavidin linked alkaline phosphatase system (Garson et al., Nucleic Acids Res 1987;4761–70) allow sexing of interphase nuclei in less than 24 hours. We report the sexing of embryos using these techniques which may be of future benefit to carriers of X linked conditions.

The Schinzel-Giedion syndrome: clinical features and natural history
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We report three more children with the multiple malformation syndrome originally described by Schinzel and Giedion of which the prominent dysmorphic features are mid-face retraction, hypertrichosis, hypoplasia of dermal ridges, congenital hydrocephalus, genital abnormalities, talipes, and characteristic skeletal findings. The latter include a steep, sclerotic base of the skull, wide cranial sutures and fontanelles, broad ribs, and hypoplasia of the distal phalanges. Two of the seven children reported died in the neonatal period and the remainder developed intractable epilepsy and spasticity along with profound growth and developmental retardation. Three of the affected children were male, and although five of the cases were sporadic and there are no reports of consanguinity, autosomal recessive inheritance has been suggested on the basis of one pair of affected sibs of unlike sex.

Genetic aspects of tuberous sclerosis in the west of Scotland
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Complete ascertainment of tuberous sclerosis (TS) was attempted in the west of Scotland (population 2 745 000). A total of 103 subjects with TS was identified living in the region on 30 June 1986. Overall minimum prevalence was 1 in 27 000, but for children under 10 years prevalence was 1 in 14 000. In 80 cases both parents were assessed. Assuming complete penetrance, 60% of these cases were new mutations. The mutation rate (based on live births in the last 25 years) was 1.6 x 10^-6 (SE 2.7 x 10^-7). In 12 of the 76 families the trait was inherited. In two families, four generations were affected, in four families three generations, and two generations in the remainder. Variable expression was marked in these families. In two further families non-penetrance or gonadal mosaicism resulted in affected sibs with normal parents. One previously published report (Primrose, 1975) of non-penetrance was shown by DNA fingerprinting to be a single mutation in monozygotic twins. Linkage has been established in these families between TS and a Taq1 restriction fragment length polymorphism detected by v-abl (J Med Genet 1987; 24:544–6) and in one family first trimester prenatal exclusion has been performed using this marker.

Autosomal recessive osteogenesis imperfecta: excess post-translational modification of collagen not linked to either COL1A1 or COL1A2
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We have studied a family with first cousin parents and three sibs affected with osteogenesis imperfecta. One affected sib died in the neonatal period, the second has survived for >five years, and the third was detected in utero and the pregnancy terminated. The parents also have three normal children. The clinical and radiological picture of the affected children suggest Sillence type III OI. Investigations of collagens synthesised by fibroblasts cultured from the two affected children, both parents, and two grandparents showed that the children were homozgyous for the production of an overmodified type I collagen whereas that of the parents was normal. Further evidence from peptide mapping and thermal stability measurements suggested the mutation was likely to be at the extreme C-terminal end of the molecule. However, genetic linkage analysis using RFLPs and probes for the collagen α(1) [COL1A1] and α2(I) [COL1A2] genes excluded both as the disease locus. At present the molecular abnormality in these patients is unknown but we suggest a defect in a post-translational modification enzyme that is specific for type I collagen molecular assembly and that the disease results from the integration of the overmodified collagen molecules into fibrils.
In vitro studies of chondrocyte differentiation in the human chondrodysplasias
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The chondrodysplasias (CDX) are a genetically heterogeneous group of disorders of linear bone growth, that is, disorders of endochondral ossification or of the skeletal growth plate. Despite the large number of morphological and biochemical abnormalities of growth plate cartilage that have been observed, the basic defects remain poorly understood. Probably the most important hindrance to elucidating these defects has been the inability to culture differentiated human growth plate chondrocytes and thereby investigate the defective bone growth process in vitro.

We have recently developed a method to accomplish this. Human chondrocytes are first allowed to dedifferentiate in monolayer culture. They are subsequently cultured in an agarose gel system which promotes their sequential redifferentiation over three to four weeks to typical chondrocytes and then to hypertrophic chondrocytes. A combination of light and electron microscopy, immune and lectin histochemistry, polyacrylamide gel electrophoresis of labelled collagens and proteoglycans, and dot blot analysis of mRNAs is employed to assess the differentiation process. At initiation of agarose culture, dedifferentiated normal cells are round with no pericellular matrix. They synthesise types I, III, and V collagens and contain mRNAs for type I but not type II collagen. By two to three weeks of culture the cells have doubled in size, exhibit the ultrastructural features of typical chondrocytes, including a pericellular matrix rich in proteoglycan and type II collagen, produce type II but not types I, III, and V collagens, and accumulate mRNAs for type II but not type I collagen. At three to four weeks the cells have enlarged four fold; they contain many vacuoles and secretory vesicles and exhibit alkaline phosphatase activity, all of which are characteristic of hypertrophic chondrocytes.

Thus, normal human chondrocytes appear to progress in vitro through a differentiation scheme comparable to that which occurs during normal endochondral ossification. Chondrocytes from patients with thanatophoric dysplasia, achondroplasia, achondrogenesis type II, and other CDX are now being studied in this system. Preliminary results show abnormalities in the rates at which the CDX cells progress through the differentiation scheme and in their ability to express particular chondrocyte phenotypes. Studies to define these abnormalities at the ultrastructural, biochemical, and mRNA levels are now in progress. It is anticipated that this in vitro approach to investigating chondrocyte differentiation in the human CDX will provide many new insights into the pathogenetic mechanisms and basic defects of the disorders.

Dwarfism in antiquity: iconography and medical history
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Although literary evidence is very scanty, the iconography shows that in ancient Egyptian, Greek, and Roman cultures growth disorders always attracted attention and were carefully observed: the two main types of short stature are distinguished (disproportionate/proportionate). A few rare types are also depicted, such as diastrophic dwarfism and hypopituitarism. In the iconography of these three cultures, short limbed dwarfism (achondroplasia and hypochondroplasia) prevails. This preponderance may reflect reality since the incidence of achondroplasia and of hypochondroplasia is the highest of all types of dwarfism; affected newborn infants are also relatively strong. In each culture an iconographic model can be defined which depicts the most significant features of the disorder: the shortness of the limbs contrasting with the trunk of relatively normal length and the head which appears very large. Yet, each culture adopted a slightly different model; some real physical features are enhanced, as if they become more important, others are suppressed. Dwarfs are thus characterised essentially by normal faces associated with very short limbs in Pharaonic Egypt, but by snub noses associated with balding heads in Classical Greece, while an over large phallus is a common feature in the Hellenistic and Roman world. These iconographic choices cannot be explained by medical causes and they do not reflect the progress of scientific knowledge. More likely they express the different social roles given to that physical minority throughout centuries: dwarfs received a positive evaluation in Egypt (affinity with the Sun god) and in Greece (affinity with satyrs and the Dionysiac world), but in Rome only their apotropaic and entertaining qualities prevailed.

McCabe’s disease: hereditary expansile polyostotic ostetodyplasia
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We report 40 cases in one family of an autosomal dominant bone dysplasia, which, while exhibiting some histological similarity to Paget’s disease, is distinct enough in its features and natural history to be recognised as unique. There are both general and focal skeletal changes, the latter having a predominantly peripheral distribution and an onset from the second decade. Progressive osteoclastic resorption accompanied by medullary expansion leads to severe, painful, disabling deformity and a tendency to pathological fracture. The serum alkaline phosphatase and urinary hydroxyproline are raised to a variable degree, while other biochemical indices are normal. Most affected members of the family have an associated early onset deafness and loss of dentition as a result of unique middle ear and dental abnormalities. No previous description of this disease has been found.

Pelizaeus-Merzbacher disease: magnetic resonance imaging as a potential tool for carrier detection
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We have investigated two obligatory and four facultative
Carriers of the gene for Pelizaeus-Merzbacher disease from one family by magnetic resonance imaging (MRI). All six probands were adults and had normal neurological findings and mental status. The MRIs of five of the six, including both obligatory carriers, showed multiple signs of signal hyperintensity in the subcortical and periventricular white matter. The changes were more pronounced the older the subject was and had a frontal preponderance. They were indistinguishable from the findings common in MRIs of patients with multiple sclerosis. The sixth woman presented completely normal MRI findings. The significance of these abnormal MRI findings in carriers of the gene for Pelizaeus-Merzbacher disease has to be tested in other families, particularly in obligatory carriers at different ages.

Polymorphism of complement C4 and 21 hydroxylase genes in families with 21 hydroxylase deficiency
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We have used gene probes to investigate polymorphism at the duplicated C4 and 21-OH loci in 17 families with 21-hydroxylase deficiency. Our analyses show evidence for the occurrence of frequent gene deletion/duplication events which generally involve a compound unit of a C4 gene and a 21-OH gene, but which occasionally feature deletion of a single 21-OH gene. Additionally our analyses suggest that gene conversion of 21-OH and C4 genes may occur frequently. Although certain categories of mutational event are strongly associated with specific haplotypes, or individual HLA alleles, others, including defects in the 21-OH gene due to point mutation, are apparently not.

Carrier detection in X linked severe combined immune deficiency by X chromosome inactivation analysis
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Severe combined immune deficiency is a syndrome in which affected infants lack cellular and humoral immunity and die from overwhelming infection if bone marrow transplantation is not performed. With the exception of inherited deficiencies of adenosine deaminase and purine nucleoside phosphorylase, the autosomal and X linked forms cannot be distinguished clinically. Females carrying the X linked form are immunologically normal. The methylation pattern at the 5′ end of the PGK gene is different and constant between active and inactive X chromosomes. In females heterozygous for the PGK polymorphism it is possible to distinguish between a population of cells with random X inactivation and a population with non-random X inactivation using methylation sensitive restriction endonucleases. We have analysed the T cells of obligate and possible carrier women using this method. Two obligate carrier women have had a non-random population of T cells. Three potential carrier women in X linked families have been shown to have random T cell populations; one of these women had been predicted to be at low risk using the linked probe DXS159. The sister of one woman who had had two affected sons was found to have non-random X inactivation in her T cells suggesting X linked inheritance in this family. Another woman who had had two affected males was found to have a random X inactivation pattern suggesting autosomal recessive inheritance in this family. One mother of a sporadic case has been shown to have non-random X inactivation in her T cells and is therefore a carrier of the X linked form. This information is valuable in giving accurate genetic counselling to the proband and the extended family.

Linked genetic markers for multiple endocrine neoplasia 2a on chromosome 10
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We have detected linkage between the gene for the inherited cancer syndrome MEN 2a and the retinol binding protein gene (RBP) located on chromosome 10p11.2-q11.2. Six families were informative for at least one of three RFLPs at the RBP locus and all showed linkage with a combined lod score of 7.57 at a recombination fraction θ=0.04. The families were of Danish, Swedish, Dutch, British, and Irish origin, which suggests that more than one genetic locus is unlikely to be involved in this disorder. We have also detected linkage between MEN 2a and a random DNA marker MCK 2 isolated by Nakimura et al (HGM9) with Z=4.5 at θ=0.05, MCK 2 maps 12 cM from RBP (Nakimura et al), which suggests that these probes are flanking markers for the MEN 2a gene. Chromosome 10 specific genomic libraries are being screened in order to isolate probes which are more tightly linked to the MEN 2a locus and which could be used for accurate detection of gene carriers.

Deletions of muscle mitochondrial DNA in mitochondrial myopathy
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Biochemical studies of muscle mitochondria from adult patients with mitochondrial myopathy (MM) most commonly show defects of the respiratory chain affecting complex I or complex III. Of the 36 subunits in these two enzymes eight are encoded by mitochondrial (mt) DNA. The increased incidence of maternal, as opposed to paternal, transmission in familial MM suggests that these disorders may be caused by mutations of mt DNA. Multiple restriction endonuclease analysis of leucocyte mt DNA from patients with MM and their relatives showed no differences in cleavage patterns between affected and unaffected subjects in any single maternal line. When muscle mt DNA was studied, nine of 26 patients were found to have two populations of muscle mt DNA, one of
which was detectable by up to 7 kb. These observations show that mt DNA heteroplasmacy can occur in man and that human disease may be associated with defects of the mitochondrial genome.

Report on the results of 53 requests for the prenatal diagnosis of Duchenne and Becker muscular dystrophy using DNA restriction fragment length polymorphisms

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Chorionic villus sampling has been performed on 45 pregnancies at risk of Duchenne or Becker muscular dystrophy following an initial 53 requests from women at risk. The RFLPs that are currently available were informative in 51 of the 53 cases (96%) for the purposes of prenatal diagnosis. These included cases that were either sporadic or cases in which the affected boy had died and/or only limited family members were available for sampling. DNA linkage analysis offers clear advantages even for women with an uncertain carrier risk, since the risk to a ‘low risk’ male is always 5% or less. Seven babies have been born with phenotypes in accordance with our predictions, including one affected male diagnosed as being at ‘high risk’.

Deletions in the distal part of the gene for Duchenne muscular dystrophy

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The genomic probe p20 detected deletions in 17/124 unrelated boys with Duchenne muscular dystrophy (DMD) and 60% of males with Becker muscular dystrophy (BMD). It detects high frequency polymorphisms with EcoRV and MspI. The cDNA probes CF56, CF23a, and Cala detected deletions in 62/130, 23/124, and 8/115 DMD boys respectively. BMD males deleted for p20 are always deleted for one exon of CF23a and one or more exons of CF56. Polymorphisms and deletions can be distinguished using analyses with more than one enzyme. Analysis of deletion end points shows hot spots for deletions and suggests a strategy for carrier detection.

POSTERS

Molecular analysis of X chromosomal structural abnormalities

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Molecular analysis was undertaken in four families with X chromosomal structural abnormalities using a series of 25 arbitrary DNA probes from the X chromosome. In three families the proband has Turner syndrome with the karyotype 45.X/46.X(X). All families were informative with one or more probes and these showed the ring X to be maternal in origin in two families and paternal in origin in one. The region of the X chromosome contained in each ring varied in extent and when compared with existing evidence for linear order of the informative probes was consistent with simple terminal deletions of the long and short arms without duplication or other rearrangement. These families can thus be used as an aid to regional mapping of new X chromosomal DNA probes. In the fourth family the male proband was investigated for short stature and cryptorchidism. He was suspected to have a tandem duplication of Xq21→q24, a finding which was also present in his clinically normal mother and sister. GMGXY4 detects X and Y single copy sequences in TaqI digested DNA and with this probe a dosage effect was apparent for the X specific band in this proband which provides evidence that his chromosomal abnormality is indeed an X duplication. A similar dosage effect was also apparent with GMGXY8 and GMGXY10 and thus all of these probes appear to map to the duplicated region of this X chromosome.

Analysis of the origin of Turner syndrome using polymorphic DNA probes

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Nineteen nuclear families with a child or fetus with Turner syndrome were studied using DNA restriction fragment length polymorphisms (RFLPs). The karyotypes of the probands were as follows: nine had 45.X karyotype, five were mosaics with 45.X/46.Xr(X), two were 46.Xiso(Xa), one mosaic 45.X/46.XX, one mosaic 45.X/46.Xiso(Xa), one mosaic 45.X/46.XX, and one was 46.XXp-. Of the 45.X probands, five were children and four were terminations following prenatal diagnosis. Using the DNA probes St14 (DXS32) which maps to Xq28 and four short arm probes (L1-28, XJ1-1, 87-15, and p9B) parental origin of non-disjunction was determined in 16 cases. In the 45.X cases loss of the parental homologue was observed in all cases. By simultaneous use of DNA probes from the long arm and the short arm it was possible to determine the origin of mosaicism and isochromosomal formation.

Linkage of the tuberous sclerosis locus to a DNA polymorphism detected by v-abl

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In view of the initial suggestion of linkage between tuberous sclerosis and the ABO blood group locus (Cytogenet Cell Genet 1987;44:63–4) and its subsequent confirmation (Lancet 1987;i:659–61) linkage analysis was undertaken in six families with tuberous sclerosis using TaqI restriction fragment length polymorphism detected...
by v-abl. No recombinations were observed in 16 informative meioses (seven phase known) giving a maximum lod score of 4.05 at zero recombination (confidence limits 0 to 0.12). This provides further evidence for the assignment of tuberous sclerosis to 9q34 and should facilitate cloning of the structural gene, genetic counselling, and first trimester prenatal diagnosis.

Autosomal dominant inheritance of palmoplantar keratoderma, nail dystrophy, and hereditary motor and sensory neuropathy

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A syndrome comprising palmoplantar keratoderma, nail dystrophy, and hereditary motor and sensory neuropathy (HMSN) was observed in three generations of one family. Nail dystrophy affected the toe and fingernails and was present at birth or developed during early childhood. Palmoplantar keratoderma became apparent in later childhood. The skin of the hands and soles was diffusely dry and hyperkeratotic with longitudinal cracks and painful callosities over pressure points. The dermatological problems were of variable severity and tended to progress slowly with age. Each subject with nail dystrophy and keratoderma also had clinical and/or electrical evidence of HMSN with absent sensory action potentials and slightly reduced or normal motor nerve conduction velocity. Pes cavus deformity was a frequent consequence of the neuropathy but severe physical disability was not observed. Conventional Giemsa banded and flow karyotypes were normal in two affected subjects. Male to male transmission of the syndrome suggests that it is caused by an autosomal dominant gene.

Paramytony congenita excluded from the myotonic dys trophy region on chromosome 19

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As part of a study of non-dystrophic myotonic disorders we have examined the linkage of paramytony congenta (PC) to four chromosome 19 markers in nine German families and one British family. One of these markers, Apo C2 shows a close linkage to the myotonic dystrophy (DM) gene (θ max=0.05, Z max=3.00). The family members were typed for four chromosome 19 markers: Lewis and Lutheran blood group (Lu), the protein marker C3, and the gene probe Apo C2. The lod scores for these four markers versus PC using equal male and female recombination frequencies show negative values for C3 (lod score -9.38 at θ 0.01), Lu (lod score 0.08 at θ 0.01), Le (lod score 0.66 at θ 0.01), and Apo C2 (lod score -11.65 at θ 0.01). These results give clear evidence against linkage between PC-Apo C2, PC-C3, and PC-Le. Therefore PC is excluded from the region of chromosome 19 around the DM locus, confirming the clinical suggestion that the myotonic disorders PC and DM are non-allelic. These results exclude PC also from 19p13-2→19pter.

Psychosocial aspects of presymptomatic predictive testing for Huntington’s chorea

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The use of DNA probes for predictive testing in adults at risk of Huntington’s chorea (HC) presents several new problems for genetic counselling. These include not only the risk of inducing psychiatric disorders such as depressive illness in those who receive unfavourable results, but also the danger of inadvertently divulging information about other family members in the process of giving a result. A further hazard arises from unspoken assumptions by patients that a counsellor would have divulged unsolicited information had this been favourable. We present guidelines developed for the Manchester HC predictive testing programme to overcome some of these difficulties. In view of the potential hazards of predictive testing, the demand for such tests may be limited. Previous surveys suggest that up to 80% of those at risk would opt for predictive testing, but experience in Manchester suggests that no more than 30% will actually do so.

Interstitial deletion of 4q in a mother and child

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A three year old male infant was referred for cytogenetic investigation because of delayed development, particularly of speech, and minor dysmorphic features. He was otherwise in good health. Analysis revealed a small interstitial deletion of the long arm of chromosome 4, del(4)(q33q35-1). Subsequently, the same deletion was shown to be present in his mother. Her physical and facial features were unremarkable, but she had attended a school for the educationally subnormal and could neither read nor write. There was no evidence in either case that the deleted material was present in any other chromosome. The maternal grandparents were unavailable for study. The inheritance of autosomal interstitial deletions from affected parents has only rarely been reported. To our knowledge this is the first report of an interstitial deletion of distal 4q in a mother and child. The detection of such small deletions is dependent upon careful cytogenetic examination of high resolution banding and to date these deletions may have eluded the cytogeneticist.

A de novo deletion of 11p13p14-2 without Wilms’ tumour

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A case report of a patient with aniridia, bilateral cataracts, ambiguous genitalia, and mental retardation, but without Wilm's tumour to date (at 13 years of age) is presented. Laparoscopy revealed absent internal genitalia but the biopsy of the gonads situated in the labia showed a histological picture of testis. Cytogenetic analysis of peripheral blood lymphocytes by GTG banding revealed a male karyotype, 46,XY. In addition, examination of GTG and RBG banded prometaphase cells has revealed a microdeletion in the short arm of one chromosome 11, with the karyotype 46,XY.del(11)(pter→p14-2::p13→qter) involving the loss of band p14-1 and the distal part of band p13 adjacent to it. Preliminary examination of the lymphoblastoid cell line by flow cytogenetics suggests that this deletion may be detectable by this method.

Further evidence localising the gene for Hunter syndrome to Xq28
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We have recently reported genetic linkage between the Hunter syndrome gene and DNA markers located distally on Xq, the most likely order of the loci being Xq26-52A-F9-Hunter-DX13-St14-F8C-Xqter. The linkage between the Hunter gene and distal Xq markers has been confirmed by other workers. However, this localisation appeared to be contradicted by the evidence of the X-autosome translocation in a young girl with Hunter disease reported by Mossman et al (1983) in which a breakpoint was considered to be within Xq26 to Xq27. We have therefore re-evaluated this case. Cytogenetic investigations were undertaken on a fibroblast culture established from the Hunter female. Both GTG and RBG banding patterns were consistent with the breakpoint being in Xq28 rather than being more proximal as previously suggested. Replication studies indicated that the normal X in this patient was preferentially inactivated. There thus remains no disagreement between the linkage and cytogenetic data. Furthermore, additional linkage data based on DNA markers defining loci DXS86, DXS144, DXS100, DXS102, DXS134, F8C, and DXS105 support our original conclusions.

Detailed mapping of breakpoints in three X-autosome translocations using a human X centromere specific probe, psV2X5, visualised with a non-isotopic in situ hybridisation technique
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A biotinylated human X centromeric alpheid repetitive sequence probe, psV2X5, was used for in situ hybridisation in three cases of X-autosome translocations in which conventional cytogenetic analyses had assigned the breakpoint proximal to the X centromere at Xpl-1. The unrelated females carrying these translocations all presented with some clinical features of severe incontinentia pigmenti (Hodgson et al, Hum Genet 1985;71:231–4). Gilgenkranz et al, Ann Genet (Paris) 1985;28:90–2. Avidin/peroxidase and diaminobenzidine/hydrogen peroxide visualisation of the psV2X5 hybridisation signals showed that in two cases (both X:9 translocations), only one of the two derivative X chromosomes (together with the normal X) gave an X centromeric specific signal whereas in the third case, t(X;17), both X derivatives (together with the normal X) showed centromeric signals. In this latter case, therefore, the X chromosome breakpoint had occurred within the alpheid repetitive sequence recognised by the probe psV2X5.

X inactivation in conjoined twins
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In 1986 Burn et al (J Med Genet 1986;23:494–500) reported a monozygotic twin girls discordant for Duchenne muscular dystrophy and proposed the hypothesis that clonal grouping of maternally and paternaly derived cells may have precipitated the twinning process. As a mechanism unique to female zygotes, this observation raised the possibility that similar 'unequal X inactivation' may account for the general female excess in the later forms of monozygotic twinning. Independent mouse human hybrids from female conjoined twin pair were established. Using the probe L1:28 on DNA extracts to identify the active X, it was found that the six independent hybrids from the 'right half' of the twin pair all used the same parental X chromosome. There is a 3% probability that this is due to chance. In the left twin four independent hybrids with a single retained X were equally divided with two using each parental X chromosome. These observations lend some weight to the concept of clonal separation as a cause of MZ twinning.

Identification of a Y:15 translocation by means of in situ hybridisation
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Following two raised serum AFP values a patient was referred for amniocentesis. The amniotic fluid AFP results were normal; however, chromosome analysis of cultured amniotic cells revealed that the fetus had a 46,X,Y karyotype, with additional material on the short arm of one homologue of the chromosome 15 (15p+). Analysis of the father's chromosomes revealed a 46,XY karyotype, with a similar polymorphism to that found in the amniotic fluid. The use of different banding techniques revealed...
that the enlarged short arm of chromosome 15 is Q bright, C positive, and has not retained its active nucleolus
organiser region. The acrocentric chromosomes in man are
known to be highly heteromorphic. On the other hand
chromosome 15 is more often the recipient of Y translocation
than other chromosomes (review: Fryns et al, The Y
chromosome. New York: Alan R Liss, 213-47). In order to
determine whether Y material was present, in situ
hybridisation experiments were carried out using the Y specific
The clustering of silver grains over the short arm of the
15p+ chromosome demonstrated that Yq material has been
translocated onto 15p in the fetus and her father.
Recently the techniques of recombinant DNA technology
and in situ hybridisation have become especially useful as
further diagnostic tools in cases of Y:A translocation
(Cook et al, Hum Genet 1979;37:39-44; Lau et al, Hum

Prenatal diagnosis of mosaic trisomy 20 associated with an
embryonic tumour

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A 36 year old woman was referred for an amniocentesis
because of advanced maternal age. Ultrasound scan at the
time of amniocentesis showed a ‘cyst’ on the right side of
the neck. Two of the four cultures set up showed mosaicism
for trisomy 20. Severe abnormalities have not been a feature of mosaic trisomy 20; however, detailed
ultrasound scan suggested an embryonic tumour. Follow-
ing termination 14 of the 16 tissues cultured showed a
normal karyotype. An extraembryonic origin of the
trisomic cells could not be discounted, as skin and placenta
failed to grow. Post mortem examination identified the
 tumour as a teratoma and this was the only abnormality
noted. Thirty cases of mosaic trisomy 20 detected by
prenatal diagnosis are reviewed. This is the first report
of mosaic trisomy 20 associated with an embryonic tumour.

Linkage disequilibrium around the cystic fibrosis locus

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M Farrall‡, and R Harris*

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Children’s Hospital; and ‡St Mary’s Hospital, London.

Seventy-five families, mainly from the North-West Re-
gion, with a living child with cystic fibrosis (CF) were typed
with the probes met D (TaqI), met H (TaqI), pJ3-11
(MspI), XV2C (TaqI), and KM19 (PstI). Haplotypes up to
five loci were established for the CF and non-CF chromo-
somes for each parent. Previously we have shown some
evidence of weak linkage disequilibrium between the
met H 1 allele and CF. Here we show much stronger linkage
disequilibrium between CF and the two closest markers
XV2C and KM19 (=0-487 and =0-723 respectively). This
strong linkage disequilibrium has enabled high and low risk
haplotypes to be defined for the population studied. This
definition can be of practical help when faced with
counselling a couple with no surviving affected children,
one or both of whom has an increased risk of being a carrier.

Linkage analysis of the naevoid basal cell carcinoma
syndrome (NBBCS) and chromosome 1 markers

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The NBCCS (Gorlin syndrome) is an autosomal dominant
syndrome of high penetrance but variable expressivity
characterised by multiple basal cell carcinomata, jaw
keratocysts, skeletal anomalies, and other developmental
malformations including palmar pits and calcification of
the falx cerebri. As part of an ongoing clinical study of over
70 patients from 20 families, linkage analysis with 12
chromosome 1 markers was performed. All family
members underwent detailed clinical examination and
those at 50% risk had radiographs of skull, chest, and OPG
of the jaw. Suggestions that the NBCCS may be on
chromosome 1 have come from work by Anderson (Ann
Hum Genet 1986:22:113) who reported Z=0.784 at 0=0.2
with Rh, and Bale et al (Am J Hum Genet 1985:37: suppl
A44) who reported Z=1.2 at 0=0.0 in two kindreds with
AMY2. Our results (on 13 families) give small positive lod
scores using LIPED with Rh and MYCL. FUCAl was
uninformative. All other markers gave negative results,
and linkage was excluded to the map units shown with
PND (15), PGM (23), NGFB (1), AMY (4), and AT3 (10).

Patients’ attitudes to prenatal diagnosis for APKD

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Manchester M13 0JH.

The polymorphic marker for adult onset polycystic kidney
disease (APKD) identified by Reed et al is available for
clinical use. As the possibility for prenatal diagnosis now
exists, we considered it important to assess the attitudes
of families to this and other aspects of the condition.
Families affected by APKD were taken from the North
Western Regional Health Authority genetic register.
Those persons and their spouses, between the ages of 18
and 45, who were either affected, at 50% risk, or who had
an a priori 50% risk were interviewed at home, using a
questionnaire. Their attitudes towards prenatal diagnosis
and their understanding of the mode of inheritance were
assessed, along with other aspects. Initial findings on a first
cohort of 142 persons suggests that although the concept of
a prenatal test is acceptable to over 70% of the sample,
only 33% (n=47) said that they would want it. Of this 47,
70% considered the disease to be very serious. Termination
for APKD and the risk of miscarriage associated with
CVS were those aspects most difficult for people to accept.
Twenty-two percent of affected or high risk subjects in a
reproductive situation would opt for prenatal diagnosis
(n=9). There was imperfect general recall of the mode of
inheritance, although 68% of the sample knew the risks for
their offspring. We present these first initial trends from an
extensive questionnaire.
Changes in the maternal age distribution and their possible impact on the demand for prenatal diagnostic services

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Between 1977 and 1985 there was a 65% increase in births to women aged 35 or more in England and Wales, but only a 15% increase in total births. Two factors of approximately equal importance were responsible for this differential increase: the proportion of older women (ages 35 to 44) among all women of reproductive age (15 to 44) increased from 28.3% in 1977 to 31.3% in 1985; and in the same period the fertility rate for women aged 35 to 39 increased from 18.2 to 24.1 per 1000 and for women aged 40 to 44 from 4.1 to 4.6 per 1000. The increased fertility rate among older women is not the consequence of an extension of the reproductive period, but rather of a delay in child bearing. This delay is seen in women married only once and also in women who have remarried. Since prepregnancy diagnosis for the exclusion of chromosome abnormalities is customarily offered to older mothers, the increased number of women aged 35 or more and their increased fertility rate has implications for the provision of obstetrical and laboratory services. There were 51 859 live births to women aged 35 and over in 1985; the projected figure for 2001 is 85 000. If the utilisation of prenatal diagnosis continues to increase, facilities for about 70 000 prenatal cytogenetic analyses will be necessary at that time.

Epidermolysis bullosa atrophicans generalisata gravis

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*Institut für Humangenetik, Universitätssklinikum Essen; and †Institut für Ultrastrukurforschung der Haut, Ruprecht-Karls-Universität Heidelberg.

We report an 11 month old female patient with epidermolysis bullosa atrophicans generalisata gravis (Herlitz type), one of the 16 currently defined disorders of this group. This type of epidermolysis is characterised by junctional blister formation, that is, blisters within the junction of epidermis and dermis, between the basal lamina, and the basal cell plasma membrane. Hypoplasia of hemidesmosomes precedes blister formation and is constant finding in intact areas. Prenatal and early diagnosis is possible by electron microscopy of skin biopsies. Soon after birth, our proband developed the first blisters on her hands, especially on her fingers. Later, blisters erupted on areas exposed to minimal mechanical pressure as well as on oral mucous membranes. The blisters tended to occur in a generalised distribution. Since most patients with this disorder die within the first weeks or months of life, the survival of this patient seems remarkable. Among newborns with EB this disorder accounts for almost 50% of cases. It has the McKusick Number * 22670.

DNA markers linked to Von Recklinghausen neurofibromatosis (VRNF)

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The finding of linkage of VRNF to three DNA polymorphisms on chromosome 17 was an important step towards eventual isolation of the gene. As a first step towards this, we have studied the segregation of minor chromosome 17 DNA polymorphisms in our family panel to exclude the possibility of heterogeneity and to establish whether any are close enough for clinical application.

A pedigree database consists of 16 VRNF families which contain 119 potentially informative meioses. The polymorphisms studied are identified by DNA markers p17H8, p10-41, CRI L-946, CRI L-581, he-A1, pe, BS3, FG2, and GH. This two point linkage analysis between VRNF and 9 chromosome 17 markers is summarised in the table. Close linkage has been shown with the markers CRI L-946, CRI L-581, p17H8, p10-41, he-A1, and FG2. Non-allelic heterogeneity of VRNF was not suggested in our families.

Diagnostic difficulties in counselling families at risk for tuberous sclerosis (TS)

L I AL-GAZALI*, R J ARTHUR†, J T LAMB†, H M HAMMER, P HIRSCHMANN§, J GIBB||, AND R F MUELLER*
Departments of *Genetic Counselling, †Radiology, and

### TABLE Two point linkage analysis between VRNF and 9 chromosome 17 markers

<table>
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<tr>
<th>Probe</th>
<th>Recombinations/total</th>
<th>Recombination fractions (0)</th>
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<th>Z max</th>
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<td>Phase unknown</td>
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<td>p17H8</td>
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<td>0-23</td>
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</table>
Prenatal diagnosis of 21-hydroxylase deficiency using DNA probes

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We have investigated the informativeness of a battery of five polymorphic DNA probes in families with 21-hydroxylase deficiency. Of these, three are particularly informative and include a HLA-DRβ cDNA probe which is informative in about 60% of families, a complement C4 cDNA probe which is informative in about 45% of families, and a HLA-B specific gene probe. We expect that more than 95% of families will be informative for at least one of the five probes. We show examples of the use of these probes in prenatal diagnosis of 21-hydroxylase deficiency.

Informativeness of probes

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<th>Probe</th>
<th>Locus</th>
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<tr>
<td>C4B550</td>
<td>C4B</td>
<td>7/16 families=44%</td>
</tr>
<tr>
<td>pRVT1</td>
<td>HLA-DRβ</td>
<td>9/15 families=60%</td>
</tr>
<tr>
<td>C4B550†</td>
<td></td>
<td>13/15 families=87%</td>
</tr>
<tr>
<td>pRVT1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All five probes</td>
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<td>&gt;95%→100%</td>
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</tbody>
</table>

Classic Alport's syndrome: an X linked disease

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Forty-one families have been studied clinically and genetically. Strict diagnostic criteria were used for anyone presenting with haematuria/chronic renal failure, and each family has evidence of at least three out of four of the following: (1) Positive family history of haematuria/chronic renal failure. (2) Electron microscope evidence on renal biopsy of Alport's syndrome. (3) Progressive high tone sensorineural deafness. (4) Characteristic eye signs (lenticonus and macular flecks). The males are all severely affected and none has retained normal renal function beyond the age of 30 years. There is much greater heterogeneity of clinical expression of the gene in females, which is typical of X linked inheritance. There is confirmation of linkage between the gene for Alport's syndrome and probes 19-2 (DXS3) and S21 (DXS17). S21 maximum lod=3.03 at θ=0.09 and 19-2 maximum lod=2.94 at θ=0.09. This suggests that the disease may be much less heterogeneous than was thought previously.

Autosomal dominant hypogonadotrophic hypogonadism

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Aberdeen University.

A family in which members affected by hypogonadotrophic hypogonadism occur in two consecutive generations has been ascertained. The females present with primary amenorrhoea or with oligomenorrhoea and infertility and the males with failure to undergo puberty. Endocrine investigations of a brother and sister revealed isolated gonadotrophin deficiency with consequent low gonadal steroid levels. There was no anosmia, to suggest Kallman's syndrome, and no evidence of midline developmental defect either clinically or on CT scan. Previous reports of isolated hypogonadotrophic hypogonadism have suggested autosomal recessive inheritance, in contrast to this family, where inheritance appears to be autosomal dominant with wide variation in expressivity.