SECTION 10
Linkage mapping/marker polymorphisms

10.001
Linkage analysis and clinical studies in British families with dominant optic atrophy

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The gene for dominant optic atrophy (Kjer type) has been mapped to 3q27-qter, and linkage studies have been reported in Cuban, Danish and French families. We aimed to perform linkage analysis in 9 British families with this disease, including an extensive five-generation pedigree, and to validate the efficiency of domiciliary screening for affected individuals. Ten microsatellite markers in the region of 3q27-q28 were used. Positive LOD scores were obtained with several markers and haplotypes segregating with the disease were identified in affected individuals. Informative meioses defined a disease interval of 2cM. Domiciliary screening was successful in identifying affected individuals. The location of the OPA1 gene in the British families appears to be in the region of 3q27-q28 and the same as that reported in families elsewhere in the world, suggesting there is no genetic heterogeneity in this disease.

10.002
Molecular Studies in Rett Syndrome: A 1996 Update.

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One accepted model for Rett syndrome [RS] is that of an X-linked dominant disorder observed in females, but lethal to males in utero. All cases should result from the presence of a new mutation. The very infrequent occurrences of affected sister, or other familial cases, has been explained by germinal mosaicism; by differences in X-inactivation patterns between individuals or their tissues; or by the presence of a premutation - a type of anticipation. Analysis of the segregation of X chromosomal markers within RS families containing more than one affected individual should, in principle, permit the exclusion of regions of the X chromosome, thus refining the regions to be searched for potential RS candidate genes. We have gathered a panel of familial cases of RS, including 7 families with affected sister-sister, or half-sister, pairs, as well as 2 RS families with affected aunt-niece pairs. These RS families have now been screened with an extensive panel of microsatellite markers from across the X chromosome, searching for evidence of discordancy or concordancy at each of the marker loci. To date, discordant segregation of markers in these families has been observed for many of the loci and no consistent region of concordancy, and hence a potential RS candidate gene region, can yet be defined.

10.003
Informativity of Wiskott-Aldrich syndrome (WAS) gene linked marker at locus DXS6940 in different ethnic groups

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Since cloning the gene over 80 mutations associated with WAS and its allelic disorder X-linked thrombocytopenia (XLT) have been identified. A short tandem repeat (STR) polymorphism (CA)n has recently been identified at locus DXS6940 within 30kb of the WAS gene. Genotyping errors are less likely than with more distant markers. STR allele frequency was studied in 90 individuals (168 X-chromosomes) from four ethnic groups by polymerase chain reaction and CA repeat number determined by dideoxy DNA sequencing. Two novel alleles, (CA)11 in Asian Indian and Afro-Caribbean populations and (CA)15 in Middle Eastern subjects were seen. Caucasian and Oriental populations exhibited five and two alleles respectively, of which the (CA)13 allele was most frequent (61% and 93%, respectively). In contrast, (CA)12 is most common in Africans (60%) and Afro-Caribbeans (57%). The observed heterozygosity (>50%) for all groups except Orientals (14%) was in accord with that expected. Inheritance of the DXS6940 marker was studied in six WAS families in which 57% of females were informative. In one kindred a G291A mutation was shown to have arisen de novo during grandpaternal gametogenesis. The DXS6940 STR offers a rapid approach to the molecular diagnosis of WAS and XLT.

10.004
Progressive familial intrahepatic cholestasis (Byler disease): Evidence that the disease haplotype in the Old Order Amish is also found in the Irish "Traveller" population.

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Progressive familial intrahepatic cholestasis (PFIC, Byler Disease) is a recessive disorder characterised by impairment of bile flow leading to attacks of jaundice, hepatosplenomegaly and early death. PFIC was originally described in an Old Order Amish kindred, but has since been reported in different ethnic groups, often associated with consanguinity. A locus for PFIC was mapped to 18q21-q22 by searching for shared segments in two distantly-related Amish patients (Carlton et al. Hum. Mol. Genet. 4:1049-1053, 1996). We have studied a Irish PFIC kindred from the "Traveller" population, a community of closely-related families with a nomadic lifestyle. These patients were investigated for homozygosity for four microsatellite markers in the 18q21-q22 region. Four affected siblings and an affected first cousin were homozygous for all four markers. To our surprise, the alleles observed in our Irish Traveller family appeared similar to those reported in the Amish kindred. Inclusion of an Amish patient on the same gel as the Traveller samples demonstrated that the Travellers have an identical haplotype at the PFIC locus to that seen in the Old Order Amish. These results strongly suggest that the Old Order Amish and Irish Travellers share the same PFIC mutation, most likely inherited from a common ancestor.

10.006
Paget's disease of bone: evidence for linkage to chromosome 18q and for genetic heterogeneity

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Paget's disease is characterised by foci of abnormal bone remodelling. We have studied 37 pedigrees each containing 2 or more affected individuals. In pedigrees where sufficient details were available, the pattern of inheritance was consistent with that of an autosomal dominant trait. A series of affected sibling pairs from this cohort have been identified and genotyping performed using microsatellite markers from 18q21-22. Using the SPLINK program, preliminary evidence of linkage was found to D18S42 (LOD=1.0) and D18S465 (LOD=1.4) in the 38 sib pairs analysed so far. In 2 large sibships it has been possible to construct multimarker haplotypes, infer parental haplotypes and thereby make the genotype data fully informative. In these 2 pedigrees, the haplotypes are fully consistent with the inheritance of an autosomal dominant gene on 18q (7 & 5 informative meioses). Haplotype analysis in 2 other pedigrees appear to rule out the possibility of a Paget's disease locus in this area thereby raising the possibility of genetic heterogeneity. Familial Expansile Osteolysis (FEO) is inherited as an autosomal dominant trait, presents with a severe Pagetic phenotype, has been mapped to 18q21-22 and raises the possibility that Paget's disease and FEO are allelic disorders..

10.007
Mapping susceptibility genes for inflammatory bowel disease

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Epidemiological studies have shown that first degree relatives of patients with ulcerative colitis (UC) or Crohn's disease (CD) have a 10-fold increased risk of inflammatory bowel disease (IBD). We have collected blood samples from 110 families with multiple members affected with IBD and have been searching for susceptibility genes by linkage analysis with microsatellite markers, using both parametric and non-parametric methods of statistical analysis. There was no evidence for linkage to the HLA region (Naom et al, Am J Hum Genet, in press). We have therefore analysed markers within or flanking 10 additional candidate genes for linkage, including several T-cell receptor and mucin genes. We have also investigated the loci on chromosome 16 and on chromosome 1, which showed evidence of linkage to CD (Hugot et al, Nature 379:821,1996) for linkage to IBD. Families affected with only UC (N=32) or with both CD and UC (N=38) were typed with 8 markers from chromosome 16 and 8 from chromosome 1 in a total of 489 individuals. An excess of haplotype sharing in affected sib pairs was observed at D16S419 and D1S239. A detailed statistical analysis of the linkage data will be presented.

10.008
Corneal stem cell graft

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Corneal donor stem cell grafting was used to treat symptomatic primary stem cell deficiency in a case of aniridia caused by a PAX6 mutation. With ethical committee approval and informed consent, corneal epithelial samples were taken from the 48 year old aniridic lady 2½ years after limbal stem cell grafts to her right eye. The donor was her non-aniridic but histocompatibly well matched 21 year old son, thus it was possible to look for male (donor) cells against a background of female (recipient) cells. We evaluated 3 methods for the detection of Y-specific material in corneal tissue based on the PCR amplification of Amelogenin, DYZ1 and SRY respectively. PCR was carried out using fluorescently labelled primers and the products run on a 373 genescanner (ABI). The data was analysed using 672 software. All 5 test samples were found to contain less than 10% male (donor) cells. However lower levels of Y material were detected using the SRY probe; the significance of this is currently being evaluated.