SECTION 2  
Cancer genetics and cytogenetics

2.001  
A randomised trial of a genetic assessment service for familial breast cancer in Wales
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We present the structure of a 3-year study funded by the MRC, Welsh Office and NHS Wales R&D (and supported by Medical Genetics staff funded by ICRF). It is hoped that this trial will inform the future development and provision of genetic screening services for women at risk of familial breast cancer in Wales. A randomised-controlled trial will compare a new clinic with specialist genetic assessment, in addition to standard provision with a standard NHS clinic, in terms of their respective psychosocial and economic costs and benefits. Women identified by DGH surgeons as being at risk will be offered the opportunity to join the trial (an estimated 500 women per year). Women who agree to participate will be randomly allocated to receive either standard NHS breast care (Control group), or standard NHS breast care plus individualised pedigree analysis, genetic risk estimation, and the possibility of presymptomatic testing (Trial group). Psychosocial outcomes for women in these two groups will be compared at several time points, using standardised questionnaire measures of psychological functioning, health beliefs and risk perceptions, and risk management behaviours. The economic assessment will compare the extra costs of the genetic service with the extra benefits to women.

2.005  
Assessment of aniridia patients using the WT1 FISH probe to predict the development of Wilms' tumour
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Wilms' tumour (nephroblastoma) of the kidney accounts for 90% of renal tumours in childhood. A number of conditions are known to be associated with Wilms' tumour (WT) including aniridia, characterised by hypoplasia of the iris. The patient subgroup with WAGR syndrome (WT, aniridia, genital anomalies, mental retardation) are more likely to develop WT. Many of these patients have a visible cytogenetic deletion of chromosome 11p13. However, WT has occurred in patients with aniridia alone and no demonstrable 11p13 deletion using routine cytogenetic techniques. A WT predisposition gene has now been cloned at 11p13. The presence of this gene (WT1) can be shown using FISH probes and deletion of one homologue is associated with a risk of developing Wilms' tumour. We have now assessed patients with aniridia using the WT1 probe with the aim of identifying WT1 deletions and clarifying the risks of developing WT in this patient group. This would enable WT screening to be given to those at high risk and reassurance to those at low risk.

2.008  
Common exon 2 mutations in Ashkenazi Jews;
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20% of early onset breast cancer in the Ashkenazi Jewish population is due to a 185delAG mutation in exon 2 of BRCA1, which causes a stop codon 18 codons downstream. The population frequency of Jewish patients attending the Manchester breast cancer family history clinic is approximately 4%. We are screening affected relatives of these patients where possible, for the 185delAG mutation using blood and block material. This is primarily being performed using SSCP and automated sequencing, but we have developed an ARMS (Amplification Refractory Mutation System) using sequence specific primers for 185delAG. We have currently tested 15 affected individuals (or obligate carriers) from 13 families with Ashkenazi Jewish backgrounds, and have found the 185delAG mutation in 7 individuals from 7 families. One of these families has a history of early onset ovarian and bowel cancer only, without any documented evidence of breast cancer. These results suggest that specific screening for the 185delAG mutation in families with a family history of breast or ovarian cancer amongst the Jewish population would be of value. 1 Struwing, J.P. et al. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nature Genet. 11, 198 - 200 (1995).

2.009  
Detailed deletion mapping of chromosome 17 at 17q11.2 defines a commonly deleted region of < 2 Mb in Barrett's adenocarcinoma
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We recently demonstrated a high frequency of allelic loss (LOH) in Barrett's oesophageal tumours at the TCF-2 marker on chromosome 17 at 17q11.2 - 17q12 (Swinford et al., 1995). To determine the precise physical location of TCF-2, CEPH library YACs (Chumakov et al., 1995) forming a contig across this region were PCR screened, and TCF-2 was placed on the YAC map at 17q11.2. To define within narrow limits the extent of this frequently deleted region, 15 Barrett's oesophageal tumours were analysed for LOH with 14 polymorphic markers spanning an approximate 4.4 Mb region surrounding TCF-2. LOH was found in 75% of the examined tumours (10 out of 15). Moreover, 60% (9 out of 15) displayed LOH at multiple adjacent informative markers flanked by markers that retained heterozygosity; and in all but one of the remaining tumours no losses were found. Our LOH data further defines a common minimum region of loss of less than 2 Mb which spans 5 markers from D17S805 (at the proximal limit) to D17S959 (at the distal limit). Our results strongly suggest that the < 2 Mb region between D17S805 and D17S959 at 17q11.2 contains a novel tumour suppressor gene involved in the pathogenesis of Barrett's adenocarcinoma.
2.010
Mapping of the focal non-epidermolysis palmpalantar keratodermia (PPK) locus associated with oesophageal cancer (TOC)

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We have investigated three apparently unrelated families from Liverpool, Midwest US and Germany with focal non-epidermolysis palmpalantar keratodermia (PPK) that is associated with an increased risk of oesophageal cancer. The two phenotypes segregate together in all three pedigrees, two of which are extensive (6-7 generations with >100 members with the skin phenotype), thus implying that it is the same gene that causes the skin disorder and oesophageal cancer in these individuals. The disease locus (the tylosis oesophageal cancer gene [TOC]) has been mapped to 17q23-qter by linkage analysis. This region is located telomeric to both the BRCA1 gene and the keratin 16 gene, in which mutations have been identified in focal PPK families who show no increased cancer risk. Close range mapping of this locus using haplotype analysis of additional Genethon markers locates TOC to an interval of approximately 1cm between D17S1839 and D17S1603. In addition, although the American family is unlikely to be related to either of the other two, the UK and German pedigrees may share a common descent. This work has provided a basis for physical mapping leading candidate gene analysis in order to identify gene(s) that may be involved in familial oesophageal cancer.

2.012
Analysis of the p16 gene in oral squamous cell carcinomas

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Oral/oropharyngeal squamous cell carcinoma (SCC) accounts for ~350,000 new cases per annum world-wide and carries a high mortality (5yr survival <40%). We have analysed the p16 (MTS1/CDKN2) tumour suppressor gene in both primary oral SCCs and cell lines in order to elucidate its role in oral carcinogenesis. Allelotyping with 6 STRPs on chromosome 9p in 36 primary oral SCCs revealed loss of heterozygosity (LOH) in 28/36 (78%) samples. A majority of these were large deletions. The smallest common region of deletion centred on D9S171 between D9S259 (cenotricentric) and IFN (telomeric); 17/27 (~62%) tumours informative at D9S171 showed LOH. However, analysis of all exons revealed mutations in only 3/30 (10%) samples - all in exon 2. Methylation of 5' CpG island was observed in 7/28 (25%) of tumours suggesting that this may be a more common way of p16 gene inactivation in primary tumours. In contrast to primary tumours, both mutations and methylation were more frequent in cell lines: 2/7 showed mutations only, 3/7 showed methylation only and 1/7 showed both. Our data suggest that other mechanisms such as small homozygous deletions may be more important in inactivating the p16 gene in primary oral SCCs.

2.013
Mutations and alternative splicing of the BRCA1 gene in UK breast/ovarian cancer families

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We have used single strand conformation polymorphism analysis, direct sequencing, allele specific oligonucleotide hybridisation, and reverse transcription polymerase chain reaction (RT-PCR) to look for mutations in the BRCA1 gene in forty-nine breast or breast/ovarian cancer families. Five distinct mutations, three novel and 2 previously observed, were detected in 7 families. Each novel mutation was identified in one family: 3896delT in exon 11, a splicing mutation in the intron 9 - exon 10 junction, and an inferred regulatory mutation. Affected individuals in these families, BOV3, ICRF178 and ICRF546, have the 185delAG in exon 2, which has been predominantly identified in Ashkenazi Jewish families. The 185delAG allele is on the same haplotype in BOV3 and ICRF546, but this haplotype is different from that shared by the Ashkenazi Jewish families, suggesting that the 185delAG in our families may have arisen independently. Another previously reported mutation, the 3875del4 in exon 11, was identified in the BOV4 family. Of the 49 families examined, linkage analyses for both the BRCA1 and the BRCA2 regions were performed on 33 families, mutations in the BRCA1 gene were identified in all but one family that have a lod score above 0.8 for BRCA1. All of the mutations cause either a truncated BRCA1, or loss of a BRCA1 transcript, thus are likely to be functionally disruptive. In addition, we found that alternative splicing is a common phenomenon in the processing of the BRCA1 gene. Seven variant BRCA1 transcripts were identified by RT-PCR, all but one maintained the BRCA1 open reading frame. We believe that alternative splicing may play a significant role in modulating the physiological function of BRCA1.

Section continued over
2.014
Incidence of the BRCA1 5382insC mutation in sporadic breast and ovarian cancer patients.
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The BRCA1 5382insC mutation was identified in a large West Lothian kindred with 54 adults at a 50% prior risk. An RG PCR assay was developed to offer this family presymptomatic testing. A local population of patients presenting with breast or ovarian tumours but with no prior family history were tested for this mutation. Tumour DNA was extracted from two hundred and fifty randomly selected breast cancer patients between the ages of 19 and 86 years and from eighty ovarian cancer patients aged between 25 and 90. Only one DNA from the breast tumour DNA set (BC185; 26 yrs) was found to have the 5382insC mutation. The West Lothian kindred haplotype for the markers D17S585, D17S1322, D17S1323 and D17S1327 differs from all other reported 5382insC haplotypes, including BC185, at the marker D17S1327. Although this result shows a low incidence of the BRCA1 5382insC mutation in the population studied, it reveals that the common 5382insC haplotype is probably the ancestral haplotype with the West Lothian haplotype having arisen by mutation or recombination. Our results indicate that all Scottish women from suspected breast cancer families should be screened for the mutation 5382insC.

2.015
Exclusion of xeroderma pigmentosum group A (XPA) as a candidate gene for multiple self-healing squamous epithelioma (ESS1).
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We have investigated xeroderma pigmentosum group A (XPA) as a candidate gene for multiple self-healing squamous epithelioma (ESS1), an autosomal dominant trait characterised by development of well-differentiated squamous carcinomas which invade locally but then resolve spontaneously. The majority of affected individuals are of known Scottish origin, and a shared haplotype on 9q22-q31 has been demonstrated, suggesting a common founder mutation (Goudie, et al., 1993, Nature Genetics 3, 165-169). The XPA gene is involved in DNA excision repair and maps between D9S287 and D9S180 on 9q22, in the ESS1 interval, we investigated the possibility that a novel, dominant, mutation in XPA may be responsible for ESS1. SSCP analysis and sequencing of the six PCR-amplified exons of XPA revealed no mutations in the entire coding region, 5UTR or 3UTR of XPA in ESS1 families. However, an A to G polymorphism was identified in the 5UTR. Of eight informative families which share 9q22 haplotypes, ESS1 segregated with XPA allele A in six and with allele G in two. Combined with the haplotype data, this places ESS1 proximal to XPA and excludes XPA as the ESS1 gene. We are currently investigating other candidate genes in the region.

2.016
Clinical and molecular study of a sibship with a very mild variant of Ataxic Telangiectasia
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Ataxic telangiectasia (AT) is a recessively inherited multi-system disorder characterised by progressive cerebellar ataxia, ocuicutaneous telangiectasia and increased risk of malignancy. Onset is usually in early childhood; death usually occurs by early adulthood. The gene was cloned in 1995. Milder, atypical variants have been reported. We describe three sibs, aged 48, 50 and 61 years, with progressive cerebellar ataxia from mid-childhood. Their parents were first cousins, native to the Orkneys. The proband developed breast cancer aged 44, and had a very severe reaction to standard doses of radiotherapy in skin and breast tissue. She has minimal ocuicutaneous telangiectasia and no increased tendency to infections. She has recently developed a ducal carcinoma in-situ in the contra-lateral breast. All three sibs have greatly increased chromosomal radio-sensitivity. Homozygosity for marker alleles in the region of the AT gene was found in them, and a homozygous point mutation in the AT gene was identified. This mutation has previously been detected in a compound heterozygote in an unrelated family with an intermediate phenotype between this family and patients with classical AT. We will present the clinical, biochemical, immunological, cytogenetic and molecular details of the sibs. We believe they may have the mildest AT phenotype ever reported.

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2.017  
**BRCAl mutations in a systematic screen of a consecutive series of women with early onset breast or bilateral breast cancer**

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A consecutive series of 200 women with breast cancer diagnosed before the age of 40 years (n=154) or with bilateral breast cancer where the initial cancer was diagnosed after the age of 39 years (n = 46), were ascertained through the Southampton Breast Clinic over a period of 2 years. DNA was extracted from peripheral blood leukocytes and subjected to SSCP (single strand conformational polymorphism) analysis under standard conditions using PCR primers covering the 22 coding exons of the BRCAl gene. 4 protein terminating mutations were detected in 154 patients (2.6%) with early onset breast cancer (one had bilateral disease) and none were detected in patients with later onset but bilateral disease. (all previously described - exon 11 nt3875 del 4bp, exon 20 nt 5382 insC and exon 2 nt 185 delAG), two occurred in sisters (exon 11 mutation) sampled separately through the same clinic, there were therefore three familial mutations. All three families had other affected relatives. In addition to the clearly disease causing mutations we detected one missense mutation previously listed as a causative mutation but whose functional significance is unclear (exon 15 nt 4654 G to T), and three unrelated individuals were found to have the 12bp intron 20 insertion previously described as a mutation. We were able to demonstrate with loss of heterozygosity studies that in all three cases the insertion rather than the wild type was lost in tumour tissue making this very likely to be a rare polymorphism. Four further polymorphisms were detected.

2.018  
**Mutation analysis of the BRCAl gene in familial and early onset sporadic breast cancer patients.**

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We are attempting to establish the incidence and spectrum of mutations in the BRCAl gene in a panel of 165 breast cancer patients who have either (i) a diagnosis at or before 35 years, (ii) a family history of breast and ovarian cancer, or (iii) at least one first degree relative diagnosed before age 45 years. In an initial study of 41 patients, all coding exons except exon 11 were screened by SSCP, whilst exon 11 was screened in three overlapping segments by fluorescent chemical cleavage of mismatch. Each fragment was labelled internally with a different colour, so that cleavage generates two labelled fragments. Multiplexing of the three fragments after PCR, currently allows analysis of the whole of exon 11 in one gel lane. We propose that the remainder of the coding sequence can be amplified in a further three fragments by RT-PCR, thus allowing the complete gene to be screened in six overlapping fragments on two lanes of a gel. Mutations were found in 1/9 sporadic cases diagnosed <35 years, 3/8 patients from breast and ovarian cancer families, and 1/26 site-specific breast cancer families. Three frame shift mutations, two of which were novel, and two missense mutations were identified.

2.019  
**Fluorescence in-situ hybridisation detection of abnormalities in chromosome 8p in squamous cell carcinomas of the head and neck**

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We have investigated chromosome 8p deletions in squamous cell carcinomas of the head and neck by microsatellite analysis. We have found a high incidence of loss of heterozygosity (LOH) in our panel of tumours (24/45 informative tumours showed LOH in at least one site) one pattern of interstitial deletions similar to that found in prostatic and colorectal tumours. In order to further correlate changes in chromosome 8p in individual interphase cells, we are developing a fluorescence in-situ hybridisation (FISH) technique from imprints of freshly excised tumours. Probes for 8 centromere, 8p telomere and cosmids from 8p11.1-21.1 are being used. The FISH technique is reliable and highly reproducible. Five tumours have been examined so far. Three tumours have been shown to be aneuploid for chromosome 8 and an 8p telomere is absent in one of these cases. Our approach is to correlate molecular and cytogenetic findings to give a more accurate and specific determination of genetic alterations in chromosome 8p in these tumours.

2.021  
**A novel human WNT gene, WNT10B, maps to 12q13 and is expressed in human breast carcinomas**

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Wnt genes are a family of highly conserved developmental control genes which have an essential role in patterning during embryonic development of species as diverse as Drosophila and mouse. A variety of vertebrate Wnt sequences have been identified, and to date, there is evidence for 9 human Wnt genes of which only four have been characterised in any detail. In addition, Wnt genes have been shown to cause mouse mammary tumours, and in human breast tumours, WNT5A and WNT7B are upregulated in the absence of gene rearrangement or amplification. Using PCR-based techniques, we have isolated the entire coding sequence of a gene, not previously described in human, encoding a peptide which is 96% identical to the mouse Wnt10b peptide (also published as Wnt12). Northern Blot analysis demonstrated expression of a 4.4 kb transcript of this gene in human adult heart, skeletal muscle, kidney, pancreas, and lung, and in human fetal liver, kidney, brain, and lung. Using YAC FISH, we have mapped this gene to 12q13, a chromosomal region frequently rearranged in various tumours. In mouse, Wnt10b is insertionally activated by MMTV in mammary tumours. In human, RNA protection assays detected no expression in normal human breast tissue but there was significant expression in 3 out of 50 primary breast carcinomas. Southern analysis of these 3 tumours showed no amplification or rearrangement of the gene.
2.022
BRCA1 and BRCA2 germline mutations in male breast cancer patients
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A population-based study of 54 male breast cancer patients collected in California were analyzed to determine the frequency of BRCA1 and BRCA2 germline mutations. In this population, 17% of patients have a family history of breast or ovarian cancer in at least one first-degree relative, and an additional 13% of patients report breast or ovarian cancer in at least one second-degree relative. Mutation analysis was performed using SSCP/heteroduplex analysis and protein truncation test. No mutations were found in the BRCA1 gene in this population. Truncating mutations in two patients (4% of the population) were identified in the BRCA2 gene. These mutations are in exon 11 and exon 14, indicating there is not a specific region in the BRCA2 gene conferring male breast cancer predisposition. One patient with a BRCA2 mutation has a family history of ovarian cancer, and the other patient with a BRCA2 mutation has no family history of breast/ovarian cancer. Eight of nine male breast cancer cases with a positive family history of breast/ovarian cancer in first-degree relatives remain unaccounted for by either the BRCA1 or BRCA2 genes, indicating there may be further breast cancer susceptibility genes to be discovered.

2.023
Analysis of BRCA1 and BRCA2 mutations in individuals from 43 Hungarian families with a history of breast and/or ovarian cancer
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Individuals from forty-three Hungarian families with a history of breast and/or ovarian cancer were screened for mutations in both the BRCA1 and BRCA2 genes. One individual from each family was analysed. Thirty-four affected and 9 unaffected individuals were studied. Mutation screening was performed using either combined single strand conformational polymorphism (SSCP) and heteroduplex analysis (HA) or the protein truncation test (PTT). Fourteen percent of the families had mutations in BRCA1 and nine percent had mutations in BRCA2. This may be an underestimate of the frequency of BRCA1 and 2 mutations in these families as affected individuals were not available for all families. Several novel mutations in the BRCA2 gene were identified. Six sporadic male breast cancer patients were also screened for mutations in BRCA1 and 2. One of the patients was found to have a frameshift mutation in the BRCA2 gene.

2.024
Germline mutations of BRCA1 and BRCA2 in familial ovarian cancer
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One hundred and twenty five ovarian cancer families ascertained in the UK have been analysed for germline mutations of the BRCA1 and BRCA2 genes. Families were selected using a minimum criteria of two or more epithelial ovarian cancer cases amongst first degree relatives. Forty five families contained three or more cases of ovarian cancer while 24 families contained two or more cases of breast cancer under the age of 50 years. A combination of protein truncation test and SSCP/heteroduplex analysis were used to screen the entire coding sequence of both genes. Mutations were detected in 58 families of which 47 (37%) were BRCA1 and 11 BRCA2 (9%). Almost all mutations are predicted to result in premature truncation as a result of frameshift, nonsense or splice site alterations. Although a proportion of families selected for this analysis are likely to result from chance clustering of ovarian cancer, the absence of either a BRCA1 or BRCA2 mutation in approximately half of all families suggests that other ovarian cancer susceptibility genes exist and await discovery.

2.025
The application of FISH to buccal smear tissue in the detection of transient trisomy 21 related neonatal myeloproliferation.
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A female infant presented with leucocytosis at 11 days of age and a diagnosis of Acute Myeloid Leukaemia was suspected. Cytogenetic analysis of bone marrow cells showed 100% trisomy 21 as the only detectable abnormality, although there was no clinical indication of Down Syndrome. As transient myeloproliferative disease occurs predominantly in infants with Down Syndrome, it was important to establish the somatic karyotype. A 21-specific cosmide contig probe was used with the FISH technique applied to buccal smear tissue. This indicated normal disomy of chromosome 21, which was subsequently confirmed by cytogenetic analysis of skin fibroblasts. The child was monitored without treatment and there was a gradual reduction of the trisomy 21 clone until it was not detected cytogenetically at 14 weeks of age. She remains well with no clinical problems. The application of FISH to buccal smear tissue is a rapid and non-invasive technique which can be invaluable in assessing situations such as this.
The expanding AF10 gene family
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AF10 is one of the partner genes involved in rearrangements of MLL at
11q23. In contrast to the other partner genes of MLL however, AF10 is in
the opposite orientation to MLL which necessitates complex
rearrangement to generate the 5'MLL-3'AF10 fusion product. AF10 has
also been shown to be fused with the CALM gene in a t(10;11)(p12;q14)
observed in the U937 cell line derived from a patient with a histiocytic
lymphoma. Furthermore, recent evidence suggests a second fusion gene.
AF10-HEAB, exists in the complex translocations involving AF10 and
MLL. Through the cloning and sequencing of AF10, the structure of the
AF10 gene has been identified. AF10 belongs to a new class of putative
transcription factors characterised by a novel zinc finger motif (LAP
domain) and has significant homology to AF17 involved in the t(11;17) and
BR140 which we have mapped to 3p25-26. A new AF10 related gene,
BRL, has now been isolated with significant homology to BR140. BRL
has been mapped to 22q13 and its role in leukaemia is currently being
assessed by FISH analysis. Results of our studies on the AF10 gene
family will be presented.