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Role of genetic and reproductive factors in breast cancer.
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To study the effects of genetic and reproductive factors simultaneously on breast cancer (BC), family data were systematically collected in two French hospitals (Instituts Gustave Roussy and Curie) between 1987 and 1989. Information on BC status and detailed reproductive factors among 288 probands and their female relatives was recorded. Comparisons with respect to the reproductive factors were made between 160 probands with at least one unaffected sister and each of the two following control groups: 160 unaffected sisters and 573 unrelated hospital-controls. Whatever the control group considered, the estimates of BC risks associated with the reproductive factors are similar to those commonly reported, except for age at menarche and abortion experience. When the age at menarche increases, the risk of BC increases using the sister as controls, whereas the risk decreases using the hospital-controls. Having at least two abortions is associated with an increased BC risk which seems higher with the sister-controls (OR=2.1, [0.9-5.0]) than with the hospital-controls (OR=1.4, [0.9-2.2]). The different results in risk, observed according to the different types of controls used, suggest possible interactions between genetic susceptibility and some reproductive factors. To estimate the effects of genetic and reproductive factors and their possible interactions, segregation analysis was conducted on 288 nuclear families using the class D logistic regressive model accounting for a variable age of onset (Abel and Bonney, 1990, Genet Epidemiol, 7:391-407), as implemented in the REGRESS program (Demenais and Lathrop, 1994). Our results indicate the segregation of a rare autosomal dominant gene (q=0.001) with penetrances increasing with age. This age effect is found to be different in susceptible and non-susceptible individuals. Interactions of that gene with the reproductive factors, especially age at menarche and abortions, are investigated.

FEASIBILITY OF A FAMILY STUDY ON COLORECTAL CANCER FROM A FRENCH REGISTRY.
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In France, colorectal cancer (CCR) is the most frequent cancer for both females and males (26000 new cases each year). Although an increased risk has been associated with a family history of CCR in nearly all epidemiological studies, few family studies have been performed. A systematic family study is being carried out in Calvados, France. The main aim of this study is to define the role of genetic factors in the disease transmission from a sample of systematically recorded family data. Results of a feasibility study connected with the above study are presented in this report. This feasibility study was performed on 72 cases registered from the 1st May to 31st July 1992. A high proportion of contacted people agreed to participate: 89.5% of general practitioners, 78.4 % of CCR cases and 78% of relatives. However, only a relatively small number of cases were recruited (55.6%). This poor number was due mainly to the high proportion of early deceased cases (20.8%) which occured during the first six months after diagnosis (average time between diagnosis and interview). In the same way, the proportion of interviewed relatives was not high (57.1%). This was due mainly to recruited cases who refused to give consent for relatives to be interviewed (26.4%). The recruited cases were representative of the registered cases according to histological characteristics, though the most serious histological characteristics were slightly under-represented. These results show that the difficulty to conduct such a study is not due to a poor response rate of concerned people but due to the poor prognosis of this disease and to the recruited cases who refused to allow their relatives to be interviewed. In the definitive study, the response rate must be improved while still respecting people protection rules.

Frequencies of gluthatione-S transferase mu-null allele in Russia;its association with lung cancer & alcohol hepatic cirrhosis.
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Frequencies of GST gene deletion,extending through exon 5 of GST gene & resulting in null allele in homozygotes(NAH) was studied by PCR in native populations (NP)- 67 ,in lung cancer patients(LCP)- 32 & in patients with other types of cancer (OCP)-27 from North-West Russia.The relative frequencies of NAH in NP, OCP & LCP were 40%,62%&72% respectively.Direct biochemical analysis revealed NAH in 31% of native population in Moscow & assessed its clearcut preponderance (X=5,34) in alcoholic cirrhotic patients. Definite desrepancies in efficiency of NAT detection by direct biochemisal assay of liver samples & by PCR analysis were observed.Unusual amplification patterns of GST-mu gene gained with different sets of olygoprimers suggeststs the existence of new more extended deletion of GST-mu gene responsible for NAH in Russian slavs.

IS PARENTAL CONSANGUINITY EFFECTIVE ON HAVING HEARING-IMPAIRED CHILDREN ?

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In order to reveal if there is an effect of parental consanguinity on having hearing impaired child, data related to deaf children and their families studied in three different cities in Turkey have been reported. The mean hearing loss rates of both left and right ears of the cases were determined by the experienced audiometrist and the pertinent data and the degree of consanguinity were determined through direct interview with, at least, one parent of the child or by the evaluation of the files of the deaf children attending that school. The study population consisted of 1125 hearing impaired children gathered from the centers for deaf-mute children in Eskişehir (244), Ankara (309) and İstanbul (572). The parental consanguinity was found to be higher among parents having hearing-impaired children (21.2%) than those parents having normal offsprings (16.9%), and this increase was statistically significant. However, there was no significant difference in the mean hearing loss rate between the left and right ears of the cases having blood-related parents or not. Among the cases, there was parental concentration, that is, either the couples or two sibs or both of them have had hearing problems. These were also evaluated with respect to parental consanguinity, we were not able to see any significant difference. As a conclusion, both the consanguinity and the familial concentration have effects on having hearing-impaired offsprings.

Linkage analyses with polymorphic DNA markers of the 2, 3 and 17 chromosomes in 3 hereditary non - polyposis colorectal cancer families.

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Hereditary non - polyposis colorectal cancer (HNPCC) accounts for about 5 - 10 % of total colorectal cancer burden. We performed linkage analyses with the aim of searching the existence of a susceptibility locus on 17q, 2p and 3p. Three HNPCC families (60 collected members, 25 colorectal cancers, 9 other cancers and 2 with colorectal adenomas) were studied with 6 polymorphic DNA markers : Mfd15, Mfd 188, 42D6, 46E6 near the BRCA - 1 locus (17q11 - q23), D2S123 near COCA - 1 locus (2p15 - 2p16), D3S1029 near a second locus predisposing to HNPCC (3p21-p23).

After *in vitro* enzymatic amplification, the different alleles have been separated by vertical polyacrylamide gel electrophoreses and analysed with the automatic sequencing machine 373A (Applied Biosystems) with the Genescan software. Results pointed out that none of the studied markers of the chromosome 17q, 2p and 3p were linked to the HNPCC disease loci (lod - scores < -2 for $\theta = 0$), signifying a genetic heterogeneity in the predisposition to HNPCC.

Prevalence of HNPCC in Italy

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In 1985 we started a systematic recording of the family structure of all Istituto Nazionale Tumori colorectal cancer probands, in order to study the familial aggregation of cancer. The families of patients with positive family history were defined at high risk, and the complete pedigree structure was investigated. At the end of 1991 the total number of cases eligible for the study was 826. Ninety-nine of them (12%) had one first degree relative affected by colorectal cancer, and 23 (2,8%) two or more relatives. Among these, seven families, including eight probands, met the Amsterdam criteria for HNPCC. This finding leads us to an estimate of HNPCC prevalence in Italy, measured as total colorectal cancer burden, of 8/826, or about 1%.

We compared the mean age of cancer onset of the youngest affected relative between the HNPCC families

and those with ≥3 cases but missing one or more of the other definition criteria ("near-Hnpcc"). In HNPCC it was 48.8 (n=8) and in near-Hnpcc (n=15) it was 61.4 (P≈.03). The mean age at surgery among the near-Hnpcc probands (60.6 years) was very similar to that computed among the probands without affected relatives (62.2 years). The total number of individuals with colorectal cancer among the seven HNPCC families was 31, or 4.4 per family on the average, and the overall mean age at surgery was 46.2 years.

Haptoglobin Polymorphism: Association with Essential Hypertension and Cardiovascular Risk

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Haptoglobin phenotype Hp1.1 was described associated with salt sensitivity and phenotype Hp2.2 with cardiovascular risk in hypertension. Our purpose is to confirm these associations. Polyacrilamide gel electrophoresis for haptoglobins, R.I.A. for hormones and fluorometry for urinary dopamine were the methods used. 96 hipertensive individuals were studied, 65 of which were less than 65 years old; they were compared with 138 normotensive of which 116 were less than 65 years old.
When analyzed as a whole there was no difference in the frequencies of the three haptoglobin phenotypes (Hp1.1; Hp2.1; Hp2.2) between hypertensive and normotensive individuals. When age subgroups are analyzed, the risk of development of hypertension was 2.5 times higher in Hp1.1 when compared with Hp2.2, in the subgroup over 65 years old and the inverse situation was observed in the subgroup under 65 years of age. Hormonal profile of renine activity, urinary aldosterone and urinary dopamine agree with Hp1.1 higher sensitivity to salt and Hp2.2 higher cardiovascular risk in the elderly patients, confirmed by Triplex Scan of peripheral arteries.
In conclusion, although Hp1.1 predisposes older people to hypertension, the cardiovascular risk is higher in individuals with Hp2.2 phenotype.

Inferring a major gene for quantitative traits by using segregation analysis and tests on transmission parameters: How often do we miss?

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In an effort to safeguard against false inference of a major gene in segregation analysis, it has become common practice to require non-rejection of the Mendelian segregation and rejection of the no transmission hypotheses. However, it is unknown how often one would actually infer a major gene, when one exists, by using these criteria. Segregation of a Mendelian gene under a variety of models, under both recessive and dominant inheritance, and with/without a polygenic background, was simulated in families with both parents and 3 children. A minimum of 200 replications for each set of conditions was carried out, in which between 50 and 200 families comprised the "sample" for each replication. The data were analyzed by using POINTER; the assumptions under the generating and analysis models were identical. By design, the power to reject the no major effect hypothesis (q=0) was over 60% for all models considered; tests on the transmission parameters were carried out only when q=0 could be rejected, using $\alpha = 0.05$ for all tests. The rates of Mendelian inference were mostly in the range of 22-50% under recessive inheritance vs. 60-99% under dominant inheritance. Notably, it was not possible to resolve the transmission in roughly 20-70% of the cases under recessive models vs. 3-15% under dominant models. Thus, while tests on transmission parameters can serve to reduce rates of false inference of a major gene, close adherence to the recommended criteria can result in failure to infer a major gene when it does indeed exist in an appreciable number of instances, especially under recessive inheritance.

Epidemiology of haemoglobinopathies.

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Haemoglobinopathies which include the thalassaemias and sickle cell disorder (SCD) are the commonest recessive inherited diseases. At present about 200 million people (4% of the world population) carry a haemoglobinopathy gene. Each year about 240,000 infants are born with major haemoglobinopathies. Globally there are more carriers of thalassaemia than of SCD, but the high frequency of the SCD gene in certain areas leads to a high birth rate of homozygotes. As a result, SCD accounts for about 70% of haemoglobin disorders worldwide. Comprehensive haemoglobinopathy control programmes that combine optimal treatment with a community-based approach to prevention, which allows simultaneous monitoring of treatment and prevention, are promoted by the WHO and are now established in many countries.

Concordance for Alzheimer's disease in twins: relation to age and Apolipoprotein E genotype.

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We studied concordance for Alzheimers' disease (AD) in 62 twin pairs with known genotypes for Apolipoprotein E (ApoE). Thirty-three pairs were volunteers, while 29 were screened from the (US) NAS-NRC registry of aging veteran twins. There were 33 monozygous (MZ) and 29 dizygous (DZ) pairs; the DZ co-twins shared the proband's ApoE genotype in all but 7 instances (24%). The 15 ApoE $\epsilon 4/\epsilon 4$ probands developed AD between 56 and 70 (mean 62.7, s.d. 3.9) yrs and had been ill for 1-13 yrs. Seven of their co-twins (47%) were affected,

including one DZ ε3/ε4 co-twin. The 21 ε4-heterozygous probands had onsets at ages 55-83 (mean 66.2, s.d. 6.8) yrs and had been ill for 1-15 yrs. Six of their co-twins (29%) were affected, including one DZ ε4/ε4 co-twin. The onsets of 26 ε4-null probands appeared to be bimodal or heavily skewed, and 13 had onsets before age 65. Despite an average interval of 9.5 yrs since the latter probands' onsets, none of their co-twins was affected. Also, none of these pairs had a family history of AD. By contrast, there were 6 ε4-null probands with onset at 75 or later, 5 of whom had affected ε4-null co-twins. These data suggest: 1) that ε4-homozygous pairs show high concordance with increasing age, consistent with the idea that ε4/ε4 is sufficient to provoke AD by age 80 (as suggested by others); 2) that onsets of ε4-heterozygotes are more variable than those of ε4-homozygotes; 3) that there may be an early-onset, non-genetic (phenocopy) form of AD (21% of these relatively young probands); and 4) that there may be a late-onset ε4-null variant of AD that is strongly heritable.

The genetic consequences of the deportations in 1940-ies of the Caucasian ethnic minorities(Russia).
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Deportation and forced migrations from the historical environment of ethnic minorities of Russia in the 1940-ies had a tragic impact on the gene pool of these nations. During the period 1976-1992, were examined 17 populations of 11 aboriginal ethnics(Northern Caucasus, Russia). 48 characters were studied in each subject,representing demoghraphycal, medical, biochemical immunological, physical and psychoph siological properties. The genetic adaptation has been studied in two "separated" isolates, part of which was forsibly moved in 1940-ies from traditional highland regions into radically new lowland areas. Differences have been established between the parts in gene pool, in morphological and psychophysiological traits The differences are determined by a selective death of about 40% of the migrants in the first years. The survived part of the migrants showed sharp negative changes in all main criteria of genetic adaptability.

Major Histocompatibility Complex (MHC) including TNF in Basques: relation with type I diabetes
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Basques (N=56) have been studied for their HLA genes and for microsatellites in the tumor necrosis factor (TNF) genes of the MHC. The most frequent haplotype is HLA-A30 or 24, B18, TNFb5,a1, DR3, DQ2 (10 %) which is associated in Southern Europe with insulin-dependent diabetes mellitus (IDDM). This association is mainly with HLA-DQ, but possible other genetic factors exist in the central part of the MHC where the candidate genes TNF are located. We thus studied 100 cases of IDDM from the French Basque region, with family members when available, half of them being of strictly Basque origin, the others mainly from the neighbouring county : Bearn. The results show that DR3, DQ2 is present in 87 % of the Basque patients vs 35 % in the controls ($p<0.0005$, odds ratio = 12.3 [4.8-31.2], either associated with B18 or B8, whereas DR4, DQ8 is less strikingly increased. However as in all caucasoid populations the highest odds ratio is for heterozygotes DR3, DQ2/DR4, DQ8 : 44 [2.5-67.7]. TNF a1, b5 and a2, b3 are also associated but show linkage disequilibrium with B18 and B8 respectively. However the odds ratio of DR3 with TNF a1, b5 is higher than that without TNF a1,b5 (16.4 [5.4-49.7] vs 6.5 [1.9-22.6]) suggesting that the susceptibility region could include TNF.

On the number of genotypic states for a genealogy.
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It is demonstrated that the 'peeling' method, previously used to compute probabilities on complex genealogies, will yield the number of possible states, i.e. distinct ways to assign genotypes to individuals consistently.

Theoretical results will be given for genealogies of particular regular, or random, form. The number of states will be of the form γ^n where γ depends on the form of the genealogy, and n is the number of individuals.

Census of the Irish cystic fibrosis patient population and screening for their most frequent mutations.

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Drawing from records of the Irish Cystic Fibrosis Association complemented with those of local clinics, we have compiled a census of Irish cystic fibrosis patients alive by December 1993. They number 861 cases, coming from 764 families. Prevalence is 1 case per 4,092 of the population, and incidence at birth is 1:1,545. 18% of patients are aged over 20 years, and 50% od deaths occurred before age 15 years. After screening 214 patients (1 in 3 of the patient population) seaching for known mutations, we have found that 86% of Irish CF chromosomes are accounted for by mutations ΔF508, G551D, R117H, 621 +1G ->T, R560T, 1717 -GA, G542X, N1303K and 3659delC. The geographic distribution of the mutations is discussed.

Genetic linkage analysis of a breast-ovarian cancer gene (BRCA1) in 19 families with breast and ovarian cancer

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The involvement of genetic factors in the etiology of breast cancer has long been recognized. Results from segregation analyses suggest that breast cancer is inherited through a rare autosomal dominant gene in some families. Close linkage of a breast-ovarian cancer susceptibility gene (BRCA1) on chromosome 17q in families with breast cancer and breast/ovarian cancer has recently been reported. The analysis of the Breast Cancer Linkage Consortium including 214 cancer families provided evidence that the BRCA1 gene lies in an interval whose genetic length is estimated to be 8.3 cM in males and 18.0 cM in females. Further mapping has confined BRCA1 to a region at 1-1.5 Mb in length.

Within the framework of a project on the genetic epidemiology of breast cancer our family study of breast and ovarian cancer aims to identify linked families in order to map the BRCA1 gene more precisely and to investigate the interaction between genetic and non-genetic factors in the etiology of breast cancer. Initial linkage analysis is performed in 19 families including 15 breast and 6 breast-ovarian cancer families. These families include 81 breast cancer cases (53 alive, 28 deceased) and 5 ovarian cancer cases. Linkage analysis using 3 polymorphic markers on chromosome 17q (D17S250, D17S579, D17S588) will be presented. The proportion and characteristics of families showing linkage and the extent of genetic heterogeneity in the families studied will be discussed.

A study of the genealogy and regional distribution of cystic fibrosis mutations in Brittany (France).

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A study on the origins and the distribution of cystic fibrosis (CF) is underway in Brittany. It is based on 901 CF patients distributed in 794 families. Most of the patients belonged to the Celtic population of Brittany. Only those CF patients in whom the mutations have been identified were included in the present analysis. The genealogical reconstruction was done in collaboration with the Cercle généalogique du Finistère. The regional distribution and genealogy of carriers of 5 mutations (DF508 on haplotype B or haplotype D, 1078delT, 1717-1 G->A, W846X and G551D) suggest a founder effect for all of them. Although these mutations have now spread in and outside Brittany from their "centers of origin", they are still clustering in some villages. With the exception of the DF508 mutation on haplotype B which has apparently 3 different centers of origin, each other mutation had only one center identified thus far, either in northern Brittany or in southern Brittany. No cluster has been identified yet in the center of the region. A high inbreeding, a low migration rate, a limited availability of mates and geographic barriers may have lead to genetic differentiation between several subregions of Brittany.

Genetics of obesity

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Obesity, characterized by increased adipose tissue, refers to a complex and heterogeneous disorder. One of the purposes in obesity research is to determine the mechanism of increased adiposity. Obesity is a multifactorial disorder determined by environmental and genetics factors. Epidemiological studies, particularly studies of twins, contribute to determining the genetic effect of various phenotypic traits. The effect reported for the various obesity phenotypes was assumed to be polygenic. Recent segregation analysis showed that in addition to a polygenic component, some obesity phenotypes are influenced by some or any major genes effects The study of molecular genetics in human obesity is just beginning. Several genes have the potential to cause obesity in human. Some mutations have been indentified in genetics models of animals obesity. The synthenic regions in human are certainly candidate regions for some subtypes of obesity. Studies on transgenic mice or backcross mice by quantitative traits loci mapping can give informations about the rôle of candidate genes on body mass or body fat content. Numbers of genes coding for protein implicated in energy balance, food intake, lipid and glucose metabolism are also "candidate genes" for human obesity. The candidate genes approach and the development of highly polymorphic markers throughout the genome seem to be strongly useful in identifying the susceptibility genes in multifactorial diseases. But the clinical heterogeneity of human obesity will certainly be a most challenging step in future genetics studies.

COMPLEX SEGREGATION ANALYSIS IN A SAMPLE OF CONSECUTIVE NEWBORNS WITH CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN ITALY.

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Cleft lip with or without cleft palate (CL/P) mode of inheritance has been extensively investigated, but the results are controversial. We have applied complex segregation analysis to the families of 636 consecutive newborns affected by CL/P registered in the North East Italy (NEI) and in the Emilia Romagna (IMER) congenital malformation registries to test hypotheses regarding CL/P inheritance.
The programs POINTER and COMDS have been used. POINTER could not distinguish between alternative genetic models, and only the hypothesis of no familial transmission could be rejected. COMDS results, after inclusion of the severity parameter (unilateral, bilateral), rejected the hypotheses of a single major locus and were consistent with the two locus model with a major dominant locus and at least one modifier locus.

Robust genetic linkage analysis: the weighted pairwise correlation statistic based on martingale residuals

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We have proposed a new robust test of genetic linkage based on a score test of homogeneity derived from a random effect model. This statistic can be simply written

$$S = \sum_{l=1}^{n-1} \sum_{l'=l+1}^{n} w_{ll'} U_l U_{l'},$$

where n is the number of subjects and $w_{ll'}$ is the number of alleles shared IBD or IBS and U_l is a residual of the model used for the trait. The statistic uses all the available pairs and does not depend on the marker alleles frequencies. The $WRPC$ statistic, uses rank residuals and is adapted to situations with age-dependent penetrance such as Alzheimer disease.

We consider using the so called martingale residuals: $U_l = Y_l - \Lambda(X_l)$ where Y_l is the status and $\Lambda(X_l)$ is the value of the Nelson-Aalen estimator of the cumulative hasard function at age X_l. When using a permutation distribution, this statistic performs as well as the $WRPC$ statistic for individual pedigrees and tends to perform better in terms of the global statistic for a set of pedigrees.

Application of logistic regression models for polychotomous data to the mapping of disease genes in nonobese diabetic mice.

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Using a new approach to the linkage analysis of polygenic traits, we have examined the linkage of 123 marker loci to insulin-dependent diabetes mellitus in nonobese diabetic (NOD) mice. A maximum of 106 diabetic and 190 non-diabetic progeny from the first backcross generation of NOD and the diabetes resistant strain C57BL/10NOD.$H28^7$(B10.$H28^7$) were typed. The extent of insulitis in the non-diabetic progeny was assessed by grading the pancreatic histology into seven categories of ascending severity. The log odds of developing the disease was regressed against genotype, allowing loci to be included in the equation only if they added significant improvement to the model. This removes effects caused solely by linkage between marker loci. The ordinal nature of the response was modelled using the polychotomous logistic model which models the log odds of falling into a category higher than j for j = 0, 1, 2...,7. Chromosomes 1 and 3 were analysed separately including interaction terms to account for the effect of chromosomal regions. Significant loci were found on five chromosomes, namely chromosomes 1, 3, 6, 11 and 14, with marginal effects on chromosome 9. Detailed analysis of chromosomes 1 and 3 suggested the presence of at least two and possibly three separate disease loci located in different regions of each of these chromosomes.

Correspondence of APOE and APOC2 genotypes with Alzheimer disease.

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Correspondence analysis was used to distinquish risk of Alzheimer disease (AD) for apolipoprotein E (APOE) and C2 (APOC2) genotypes. A contingency table was formed from APOE genotype (2/3, 3/3, 2/4, 3/4, 4/4) and age-AD status (A60=onset age 60-69, N60=unaffected age 60-69, etc.) for members of 42 AD families. APOE was associated with age-AD status ($p < 0.00001$) and 83% of the association involved a gradient from high (4/4, A60) to low (2/3, N80) risk, evident from a plot of the first two principal components. APOC2 polymorphisms did not follow this gradient nor did they establish a pattern of correspondence with age-AD status when separately evaluated. These results are consistent with the

reported gene-dose effect on risk for the APOE type-4 allele and protective effect of the APOE type-2 allele, and provide evidence that the APOE-AD association does not result from linkage disequilibrium of APOE with APOC2.

Methods for estimating population prevalence and incidence of Alzheimer's disease via a list sample linked to administrative data.

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More complete and generalizable application of tools developed by genetic epidemiology to study common disease awaits collection of genetic material as an adjunct to routine national surveys concerned with health and medical care. Recent advances in "cheek swab" technology make the collection of national samples of genetic material practical and feasible. We present an observational plan from an extant longitudinal national survey (The Long Term Care Survey) where substantial self, proxy, and administrative data (Medical Bill Records) is collected concerning common diseases as well as the correlates of the underlying etiology of disease in the population. We employ the available information to develop "best estimates" of Alzheimer's disease prevalence and incidence between point prevalences. The observational plan permanently and continuously links the individual survey record with the administrative medical bill file record, thus providing information on disease onset and progression in the intersurvey periods available. The surveys were conducted in 1982, 1984, 1989 and 1984 and included information on over 60,000 aged Americans. The Alzheimer's disease prevalence estimates serve as an example of the combination of information from multiple sources to identify a national population of interest to genetic epidemiology. We may thus identify population based estimates of risk in relation to susceptibility factors and identify probands for linkage studies. We conclude with a discussion of methods and observational plan modifications to add genetic material data collection to appropriate national in-person surveys.

Localization of a gene for dilated cardiomyopathy using sequential imputation for multipoint likelihood estimation (SIMPLE).

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Linkage screening on a 7 generation pedigree segregating for an autosomal dominant conduction system defect and dilated cardiomyopathy revealed linkage to markers on chromosome 1. A series of 3-point analyses (disease and 2 markers) was uninformative; multiple intervals had similar maximum lod scores, and discontinuities in the likelihoods from successive intervals prevented conclusions on localization. Multipoint analysis on more than 2 markers with disease was prohibative due to marker loci with many alleles and missing data in the upper generations. Sequential imputation, a Monte Carlo-based procedure, was used to estimate multipoint likelihoods of disease with a fixed map of 6 markers (150,528 haplotypes). The most likely interval had a maximum map-specific multipoint lod score more than 2 lod units larger than the next most likely interval.

REGRESS: a computer program including the regressive approach into the LINKAGE programs.

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The LINKAGE programs have been designed to map susceptibility gene(s) for diseases or continuous traits with respect to one or several marker loci in general pedigrees. Linkage is classically tested by assuming that a single gene accounts for the familial transmission of the trait. However, linkage detection may be seriously hampered when the trait results from multiple causes (genetic and/or environmental). The regressive models, introduced by Bonney (1984, Am J Med Genet, 18:731 - 749; 1986, Biometrics, 42:611-625), provide a general and computationally practical approach to describe family dependence in terms of a major gene effect, residual familial covariation of any origin (genetic and/or environmental), and measured covariates which can interact with the major gene. These models have been extended to linked marker loci (Bonney et al., 1988, Am J Hum Genet, 43:29-37). The REGRESS program has been developed to incorporate the penetrance function as specified by the general class D regressive model into the ILINK program of the LINKAGE package. The present version of REGRESS makes it possible to conduct the following analyses: (1) trait-marker associations; (2) segregation analysis; (3) linkage analysis; (4) combined segregation/linkage analyses. The trait can be either dichotomous, continuous or bivariate (dichotomous/continuous) with a variable number of observed covariates and several marker loci can be considered simultaneously.

Genetic epidemiology of breast cancer: interest of survival analysis methods.

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In an attempt to explain the controversy resulting from the analysis of the breast cancer data collected by Jacobsen (1946), a segregation analysis was performed on this sample using successively the unified mixed model (UM) and the logistic hazard function model (LHM) (Abel and Bonney 1990). In the UM, age of onset of the disease cannot be taken into account, each individual being assigned in a liability class according to his age at examination,

whereas in the LHM variable age of onset is modelled using a survival analysis functions.

Under the UM, we confirm the results of Demenais et al (1986), i.e. the transmission probabilities are significantly different from Mendelian expectations. The same results are obtained when taking into account the specific mortality for the computation of the morbid risk observed in a given liability class. Under the LHM, the analysis provides evidence for a monogenic autosomal model with a rare dominant allele responsible for the disease, with transmission probabilities compatible with Mendelian expectations.

We suggest that the rejection of the Mendelian transmission under the UM may be due to a violation of a constraint of this model (i.e. the probability of being and not being affected in a given liability class should sum to 1) when a specific mortality is induced by the disease as in breast cancer. Survival analysis methods avoid these problems by taking into account the onset of the disease as the failure time event and are more suitable when studying a complex trait such as breast cancer .

Association study between candidate genes for cardiovascular risk and aging.

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420 centenarians were recruited for a genetic study of longevity and pathologies of aging.
A set of candidate genes were chosen for their impact on cardiovascular risk, namely genes encoding : apolipoproteins : E (ApoE), CII (ApoCII), B (ApoB), AI (ApoAI) and angiotensin converting enzyme (ACE).
Polymorphic markers in these candidate genes have been genotyped for 410 centenarians and 200 adult controls. Three variants of Apo E on chromosome 19q have been previously described : ε2,ε3,ε4.We found that the ε4 allele Apo E, which is known to be associated with premature atherosclerosis, is significantly less frequent in centenarians (n=410) than in controls ($p<0.001$), while the frequency of the ε2 allele is significantly increased ($p<0.01$). We are presently investigating a polymorphic microsatellite in the ApoCII gene, which is closely linked to ApoE. No significant differences were observed in 2 RFLPs (EcoR1 and Xba1) of the apoB gene or in the Msp1 RFLP of the ApoA1 gene. We also genotyped a biallelic insertion/deletion (I/D) polymorphism in the ACE gene. Unexpectedly, the D variant of ACE, which is associated to coronary heart disease, is more frequent in centenarians (n=400), with a significant increase of the homozygous genotype ($p<0.01$). Another closely linked microsatellite located in the hGH gene (human growth hormone) on chromosome 17q23 is being genotyped.
We are currently testing possible interactions between different alleles at the ApoE and ACE genes. We find an indication of interaction between alleles ε2 and D in centenarians.

The genetics of Man's reaction to lepromin. **M.F. Feitosa[1,2], I. Borecki[2], D.C. Rao[2], B. Beiguelman[3], H. Krieger[4]. [1]Dept. Genetica-FIOCRUZ, Rio de Janeiro, RJ, Brazil; [2]Div. Biostatistics-Washington Univ. School Medicine, St. Louis, MO, USA; [3]Dept. Genetica Medica-UNICAMP, Campinas, SP, Brazil, [4]Dept. Parasitologia-USP, Sao Paulo, SP, Brazil.**

Lepromin is a sterile suspension of heat killed leprosy bacilli (*Mycobacterium leprae*), which may induce a delayed type response (Mitsuda reaction), about 28-30 days after the intradermal injection of 0.1 ml lepromin (*cf.* Beiguelman, *Rev. Brasil. Leprol.*, *30*:153-172, 1962). Some reports showed (*cf.* Beiguelman & Quagliato, *Int. J. Lepr.*, *33*:800-807, 1965; Beiguelman, *Acta Genetic. Med. Gemellol.*, *21*:21-52, 1972) that presence of this reaction exhibited familial aggregation, probably due to a genetic mechanism. Here, a sample of 544 nuclear families with 2,925 tested individuals was studied in order to test genetic hypotheses. Segregation analyses (Lalouel et al., *Am. J. Hum. Genet.*, *35*:816, 1983) applied to this sample showed evidence of a major effect ($\chi^2_3 = 14.66$, $P = 0.002$) with no multifactorial component ($\chi^2_1 = 0.05$, $P = 0.82$), and the estimated transmission parameters did not differ significantly from the Mendelian expectation ($\chi^2_3 = 1.39$, $P = 0.73$). Despite the fact that nontransmission of the major effect is not rejected, the dominant Mendelian model is most parsimonious ($q = 0.50$) for the positive reaction phenotype. These results are of importance for the understanding of genetic mechanisms involved not only in resistance to leprosy but also in several resistance/susceptibility phenomena in man.

Simultaneous application of association and linkage tests to sets of affected sib-pairs.

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The transmission/disequilibrium (TD-Test) proposed by Spielman as a test for linkage in Falk-Rubinstein samples is also applicable to sib-pair data (Spielman et al., Am J Hum Genet, 1993, 52: 506-516). In this situation the test seems to be complementary to usual tests for identity by descent. In fact one may regard the TD-test as a test for association, because it has power only if there is linkage disequilibrium. This is also a reasonable explanation for beeing complementary to a linkage test.

The statistical properties of the simultaneous application of an association test (TD-test) and a linkage test (mean test, Blackwelder and Elston, Genet Epidemiol, 1985, 2:85-97) to sib-pair data are investigated. The amount of necessary correction for the double testing is determined. With respect to a given set of bipolar sib-pairs we look wether different alternatives can be detected by both tests, only one test or none of the tests.

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Reliability assessment of normal and premutation status in the fragile X syndrome.

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Recent studies of the fragile X [fra(X)] mutation have shown that amplification of a CGG repeat is diagnostic of the syndrome. Between 6-54 copies of the repeat have been associated with alleles from a normal population, whereas 50-200 copies are associated with the premutation. Typically, differences in copy number between normal and premutated states are large, but there is a grey area in which individuals from both populations overlap. We sought to quantify the probability of misclassification from a normal or premutation population. DNA obtained from normal individuals and transmitting females was analyzed from 3 centers in North America. Distributions of normal alleles from 2 independent datasets were not significantly different from one another and therefore combined. The pooled distribution of normal alleles was compared with the pooled distribution of premutations. Using 50 repeats as the cutoff criterion, sensitivity is 100%, specificity is 99%, and probability that the subject is fra(X) given that the copy number $\geq$ 50 is 95%. Other nearby cutoff values produced like findings. Similar reliability estimates were obtained when an independent dataset was used to verify the original assessments. We recommend that family studies be done to establish stability/instability of alleles when $\geq$ 50 repeats are found in the proband.

Association of Taq I B RFLP of the CETP gene with myocardial infarction and HDL levels in the ECTIM study.

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Cholesteryl ester transfer protein (CETP) facilitates the exchanges between lipoproteins and is involved in the reverse cholesterol transport. ECTIM is a case-control study designed to identify genetic factors involved in the development of myocardial infarction (MI). Subjects were recruited from 4 male populations in France (Lille, Strasbourg, Toulouse) and Northern Ireland (Belfast). In this sample, we studied the RFLP Taq I B of the CETP gene by PCR amplification followed by digestion. In France, the genotype B2B2 was less frequent in cases than in controls: 11.8% vs 17.4% respectively (P=0.02). This effect was not observed in Belfast. Lipid variables were analyzed in controls to avoid the bias resulting from lifestyle changes after MI. HDL-cholesterol, apolipoprotein A-I and Lp A-I levels were associated with Taq I B RFLP (ANOVA, $P<10^{-4}$, no interaction with country).

	B1B1 n=238	B1B2 n=328	B2B2 n=116
HDLC (g/l)	0.49 ± 0.12	0.51 ± 0.15	0.57 ± 0.18
Apo AI(g/l)	1.39 ± 0.24	1.45 ± 0.27	1.56 ± 0.28
Lp A-I (g/l)	0.46 ± 0.12	0.48 ± 0.14	0.52 ± 0.15

The Taq I B RFLP modified the relation between alcohol consumption and HDL levels: the correlation coefficients were 0.107, 0.236 and 0.353 in B1B1,B1B2 and B2B2 genotypes respectively (P interaction = 0.001).
The Taq I B RFLP could be linked to a variant of the CETP gene which influences the MI risk through an effect on reverse cholesterol transport and HDL related variables. This variant could modify the effect of environmental parameters (alcohol) on the CETP metabolism.

Segregation analysis of blood infection levels in malaria.

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The profound influence of host genetic factors on resistance to malaria infection has been shown in numerous animal studies. In human malaria, a recent segregation analysis has detected a major gene (MG) controlling blood infection levels (Abel et al., Am. J. Hum. Genet, 1992). We present a segregation analysis of the same phenotype, i.e. blood parasite density (PD), in a different population living in an hyperendemic area of malaria (southern Cameroon).

The family study was carried out from April 92 to April 93 with complete selection of 44 pedigrees from the same village (315 subjects). Several individual measurements of PDs were performed (mean = 3.8 ; range 2-6), and PDs were adjusted on the period of measurement. The individual mean of adjusted PDs was the phenotype under study. Correction for the age effect was performed prior to segregation analysis. No effect of sex, prophylaxis intake and area of residence was found. The analysis was carried out using the class D regressive model of Bonney (Am. J. Med. Genet, 1984), as implemented in the software package SAGE.

The results were consistent with the presence of a codominant (nearly recessive) MG controlling the degree of infection in human malaria. Familial correlations residual from the MG were not significant and, in this case, the Mendelian transmission was compatible with the data and the hypothesis of no parent-offspring transmission was rejected. Parameter estimates showed a frequency of 0.24 for the deleterious allele, indicating that about 6% of the population is predisposed to high levels of infection. When residual familial correlations were included in the model, we noted that the nontransmission hypothesis could not be rejected. More complex mechanisms (e.g. genotype x age interaction) are now being investigated.

Posterior probability of linkage and maximal lod score.

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To detect linkage between a trait and a marker, Morton (1955, Am J Hum Genet 7) proposed to calculate the lod score $z(\theta_1)$ at a given value θ_1 of the recombination fraction. If $z(\theta_1)$ reaches +3, then linkage is concluded. This criterion of +3 was chosen by Morton to avoid a false conclusion of linkage. Using Bayes' theorem, Smith (1959, Am J Hum Genet 11) derived a posterior probability of no linkage (the probability that linkage does not exist when linkage was concluded) which is easier to interpret. Under the conditions defined by Morton, this probability is less than 5%. However, in practice, the test is performed on different conditions. Indeed, lod scores are calculated for

different values of the recombination fraction in the range between 0 and 0.5 and the test is based on the maximal lod score Zmax. The alternative hypothesis to the null hypothesis of independance is then no more a single one. For a Zmax of +3, we showed that the posterior probability of no linkage is 16.4%. Thus, considering a composite alternative hypothesis instead of a single one decreases the reliability of the test. The reliability decreases rapidly when Zmax is less than +3 and given a Zmax of +2.5, there's a 33% chance that linkage does not exist. Moreover, the posterior probability depends not only on the value of Zmax but also on the family stuctures and on the genetic model. For a given Zmax, the chance that linkage exists may then vary.
In this context, it is interesting to discuss the results obtained for an extended pedigree with numerous affecteds of Alzheimer's disease in which linkage with markers on chromosome 21 was claimed.

Apolipoprotein E genotypes and cardiovascular disease : a quantitative overview of 41 studies.

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Relative risks in ε2- and ε4-allele carriers (compared to ε3-homozygotes) were estimated from odds ratios in 41 studies in which the common apoE genotypes have been determined in patients with cardiovascular disease (CVD) and in controls, or in offspring of parents with and without ischaemic heart disease (IHD). Logistic regression models were used to test homogeneity assumptions, and to estimate pooled odds ratios in 8 groups of studies, differing by the kind of CVD considered or by design: *A.* Myocardial infarction (MI), true case-control studies (n=7). *B.* MI, other designs (n=8). *C.* Angiographically determined coronary artery disease (n=8). *D.* Various manifestations of IHD (n=5). *E.* Various manifestations of IHD in diabetic patients (n=2), or in patients with familial hypercholesterolemia (n=2). *F.* Peripheral vascular disease (n=3). *G.* Cerebrovascular disease (n=3). *H.* Offspring studies (n=3). The estimates (with 95% confidence limits) were:

Group	*RR in ε2-carriers*	*RR in ε4-carriers*
A	1.00 (0.76-1.33)	1.45 (1.19-1.77)
B	0.80 (0.67-0.96)	1.26 (1.09-1.47)
C	0.96 (0.77-1.21)	*NE*
D	*NE*	1.39 (1.08-1.79)
E	0.83 (0.29-2.35)	1.91 (1.28-2.86)
F	*NE*	1.58 (1.09-2.30)
G	1.89 (1.07-3.33)	2.11 (1.40-3.18)
H	0.79 (0.41-1.56)	1.53 (1.02-2.29)

NE = not estimated, due to heterogeneity

Conclusion : The results strongly support the notion that apoE genotype has an effect on risk of developing CVD.

Genetic Epidemiology of Manic-depressive Illness and Schizophrenia

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These separate disorders fit inheritance patterns of common diseases. Segregation analyses have not revealed a mode of inheritance or a single-locus subtype. Linkage studies in manic-depressive illness (Bipolar type) have focused on a large pedigree from the Amish, a genetic isolate. At least three large genotyping efforts, with several hundred markers each, have not revealed a linkage. Intra-pedigree heterogeneity is possible in a very large pedigree with a common disease. Recent data from U.S. pedigrees suggest a linkage to a pericentromeric region on chromosome 18.

Schizophrenia is less familial than Bipolar illness, and pedigrees tend not to be large. Linkage to markers on chromosome 22 was suggested in the past year, and there exists a syndrome, velo-cardio-facial syndrome, with interstitial deletions on 22 and psychosis as one of its (inconstant) features.

In any case, these are not Mendelian disorders, and even if true, these are genes of small effect or contributing to only a small proportion of cases.

Candidate genes have been extensively examined, particularly including dopamine receptors D2 and D4, but no associated mutations have been discovered in these illnesses.

Load and diversity of hereditary disorders in Russian population.

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Medical and population genetic studies were carried out in some regions of Russia: in three provinces of north-east, one province in the south-west and one pro-vince in the west part of European Russia. The size of investigated population was more than 1mln.of peoples. Special investigation protocol permitted to identify more than 500 hereditary conditions. There was no difference in the load of autosomal dominant (AD) and X-linked (X-l) recessive disorders between the populations and the prevalence of these disorders is somewhat greater than 1 affected per 1000 for AD and 1 affected per 2500-2600 males for X-l recessives. The significant difference in the prevalence was found only for autosomal recessive (AR) disorders that exists between North and West rural and all other populations. The mean prevalence of AR diseases for all urban and South rural populations is approx. 0.7/1000 and the prevalence of these disorders in North rural population is approx. twice higher. The study of genetic structure has shown that there is clear isolation of the North rural population with the mean value of random inbreeding (Fst) equal to 0.00083 (0.000075). The level of isolation of West rural population is significantly smaller. Association between Fst and load of AR disorders was established by regression analysis (r>0.9). 143 AD, 94 AR and 26 X-l recessive disorders were found, some of them were common for the whole Russian population. It was shown that genetic structure of population influences not only the size of the load but diversity of AR disorders too.

17q11-q21 Linkage analysis of 15 French families with a breast and/or ovarian cancer history.

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A susceptibility gene for hereditary breast-ovarian cancer, BRCA1, has been assigned to the 17q12-21 region. The aims of our study was to search recombinants for a finer BRCA1 location (mapping between the polymorphic markers Thra1 and Mfd188) and to precise the BRCA1 involvment in breast/ovarian cancer families and in rare hereditary site-specific ovarian cancer families. Therefore a linkage analysis was performed in 10 site-specific breast cancer, 3 breast/ovarian cancer and 2 site-specific ovarian cancer families. DNAs from members of these pedigrees (125 people and 39 patients) were tested using at least 3 markers : Thra1-D17S800-Mfd188, completed with study of D17S846 and D17S855 in some of them. We found 2 potentially informative recombinants wich led us to favour a BRCA1 location centromeric to D17S855. Morever the 2 ovarian site-specific families seem to be linked (Lod-score Z=1,13 at θ=0 for the larger) and 2 of the 3 breast/ovarian families appear unlinked. Interestingly, several men with the"risk-haplotype" developped other types of cancers. Lod-scores of the whole study are under evaluation and would precise our results.
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Investigation into the risk constellation of PTCA patients in the Central German region

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Considering local characteristics of probands living in the Central German region we investigated coronary risk factors (familial-genetic anamnesis, the individual way of living and parameters of the ACE-polymorphism and of the lipid and coagulation-fibrinolysis balances) of 70 patients (57 male, 13 female) with percutaneous transluminal catheter angioplasty (PTCA). 26 families showed a provable coronary affliction. 50% of the patients had adiposity and 18% diabetes mellitus. Investigating the lipid balance we found significantly increased serum triglyceride, serum cholesterol and apolipoprotein B in the patient group. The plasminogen-activator-inhibitor (PAI) was very increased whereas other factors such as plasminogen, ATIII, protein C, protein S and factor VII had normal levels. Our case-control study of the distribution of the ACE types in the Central German population demonstrated a D/I quotient of 0.59/0.41 in the control group (n=240) and of 0.58/0.42 in the PTCA group.

Age at diagnosis and transmission of invasive melanoma in 23 familial melanoma/dysplastic nevi (CMM/DN) families.

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We evaluated the age at diagnosis, and transmission pattern of CMM in 23 US white CMM/DN families. The median diagnosis age (n=105) was 33 years, much less than that observed in sporadic cases in the US white population (54 years). Ten percent of the cases developed CMM before age 20 compared to 2 percent in the general population. There was little difference in the transmission pattern of melanoma between males and females in the 23 families. Family members had a high probability of developing melanoma. It rose rapidly from 3% at 15 years to 85% by age 75. For the combined trait CMM/DN, the probability of developing either CMM and/or DN rose from 9% at age 15 to 97% by age 75. There was a statistically significant 10-16 year reduction in age at diagnosis of CMM in successive generations. The mean age at CMM diagnosis decreased from 56 ± 10 years in the first generation to 14 ± 6 years in the fourth generation. 80% (4/5) of the cases in the fourth generation developed CMM before age 15 vs. 0% (0/100) in all other generations. Although this reduction may result partly from increased surveillance in these families, differences in melanoma risk in genetic (eg anticipation) and/or environmental factors, across generations, should be considered.

Association of apolipoprotein B gene polymorphism with cholesterol concentrations is affected by genetic and non-genetic factors.

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In a cross-sectional sample of 464 Danish men, all born in 1948, up to 7% of the interindividual variation in s-cholesterol and apo B was associated to the Ins/Del and the XbaI polymorphisms of the apo B gene, with the highest cholesterol levels associated with the Del and the X+ alleles. This association depended significantly on body mass index (BMI) being strongest for BMI < 25 kg/m². In 445 Danish men and women with ischemic heart disease and moderate hypercholesterolemia, this association was less strong and only significant in the younger 3 quartiles of age. Further, another apo B haplotype (Ins/X-) not associated with cholesterol variation, was more frequent

among female and older male patients than in the general population. In 99 unrelated patients with familial hypercholesterolemia (FH), no such association was detectable. Likewise, the common association of apo E gene polymorphism with cholesterol variation (E_4-subjects having higher cholesterol) could be confirmed in the cross-sectional sample of Danish men but not in FH patients. We conclude, that the effects of minor genotype variation to interindividual phenotype variation can differ by body composition, age, gender, level of the continously distributed phenotype of study, and presence of major mutations affecting the phenotype.

Familial risk of diabetes by obesity of index case.
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Non-insulin-dependent diabetes mellitus (NIDDM) is familial, but obesity is also a risk factor for this disease. If lean individuals with NIDDM have a greater "load" of diabetes susceptibility genes, one might expect a higher prevalence of diabetes in relatives of affected individuals with low body mass index (BMI).

Among 721 Pima Indian nuclear families with ≥ 2 siblings (≥ 1 with NIDDM), an "index case" was randomly selected from among the affected siblings. Among 1722 remaining siblings, prevalence of NIDDM was evaluated in relation to the BMI of the index case. Odds ratios (OR) and 95 % confidence intervals (CI) for a sibling to have NIDDM among categories of index case BMI were calculated, accounting for the lack of independence between siblings.

The age-standardized prevalence of NIDDM was lower in siblings of an index case with BMI above the upper tertile (36 %) than in siblings of those in the middle (46 %) or lower (40 %) groups ($p=0.002$). Controlled for age, sex and BMI, the OR for NIDDM was 1.7 (95 % CI, 1.2-2.4) for the lower and 1.8 (1.3-2.5) for the middle group, relative to the upper group ($p=0.002$). Similar results were obtained in relation to BMI of diabetic parents ($p<0.001$).

NIDDM in the presence of a low BMI is more strongly familial than that at a higher BMI. This may indicate that a greater "load" of diabetes susceptibility genes is present in leaner diabetic subjects and should be taken into account when designing and analyzing studies to detect these genes.

Linkage analysis of pre-eclampsia/eclampsia with chromosome 8 markers.
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Pre-eclampsia/eclampsia is a disease which occurs in 1-5% of first pregnancies in most human populations. Although the physiological basis of the condition is unknown, it has been shown to be highly heritable. The aim of this project is to search for linkage between maternally expressed genes for susceptibility to pre-eclampsia/eclampsia and various marker loci in ten multi-case pedigrees. To allow for uncertainty about the exact mode of inheritance of the condition, we have analysed the data for several genetic models. Positive (but non-significant) lod scores were obtained for several chromosome 8 markers. The highest lod scores came for the ankyrin (ANK1) locus which is on the short arm of this chromosome, raising the possibility of a pre-eclampsia/eclampsia susceptibility gene in this region. We are currently collecting more pedigrees affected with pre-eclampsia/eclampsia in an attempt to gain a more definitive answer to this question, and these data will also be presented.

Cancer risk in relatives to testicular cancer patients.
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Two previous studies have found an increased risk of testicular cancer in brothers of testicular cancer cases. There has been no reports on excess of other cancers in such relatives.

798 (92%) out of 867 patients with testicular germ cell tumours treated during a 10 1/2 year period in our hospital returned a questionnaire with information on cancers in first degree relatives and grandparents. All cancers included in the calculations of Standardised Incidence Ratios (SIRs) have been verified in the Norwegian Cancer Registry. Expected number of cancers in the relatives were derived from the Cancer Registry.

Standardised Incidence Ratios for all cancers were increased for brothers (1.54). This was entirely due to an excess of testicular cancers (16 cases observed vs. 1.86 cases expected, SIR for testicular cancer 8.6). The SIR for testicular cancer was 3.85 for fathers (5 cases observed) and 6.25 for sons (2 cases observed), respectively. The increase of the SIRs were statistically significant in brothers and fathers.

We did not find an increased risk of all other cancers in any group of relatives. The SIR for cancers other than testicular for first degree relatives was 0.89 (95% CI: 0.78-1.00), and the corresponding value for grandparents was 0.79 (95% CI: 0.70-0.89).

In conclusion, testicular cancer, like most cancers, shows familial aggregation. Testicular cancer seems to be associated with a decreased risk for other cancers. Work is in progress to determine SIRs for cancer at specific sites in the relatives.

A coding polymorphism for FcεRI-β_{Leu181} in a random population sample: associations with atopy.

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[1]Nuffield Dept. Clinical Medicine, University of Oxford, England, [2]Dept. Respiratory Medicine, Perth Medical Centre, Australia, and [3]University Dept. Paediatrics, Princess Margaret Hospital, Perth, Australia.

Following genetic linkage studies on chromosome 11q12-13, the beta chain of the high affinity receptor for IgE (FcεRI-β) has been identified as a candidate gene for symptomatic atopy (Allergic Immunoglobulin E responsiveness). Linkage has only been seen in maternally derived alleles (Cookson et al, Lancet 1992;340:381-4). A common coding variant of this gene, FcεRI-β_{Leu181}, is maternally inherited in 15% of asthmatic children (Shirakawa et al, in press). In order to confirm the significance of this result, 1020 individuals in 232 two-generation families from a random Australian population sample were genotyped for the FcεRI-β_{Leu181} variant. FcεRI-β_{Leu181} was identified in 28 subjects (2.8%). All 8 children who had inherited the variant maternally were atopic. 3 had physician-diagnosed asthma, and 6 had seasonal rhinitis. Differences between these and the other 548 children were assessed by the Wilcoxon Rank Sum Test. Despite the small number of FcεRI-β_{Leu181} individuals, they showed significant elevations of the prick skin test wheal response to House Dust Mite (HDM) (p=0.0027), eosinophil counts (p=0.053), RAST (specific IgE titres) to HDM (p=0.0013), and a "RAST index" (sum of RAST scores) (p=0.004). Skin tests to timothy grass (p=0.15), RAST to grass (p=0.18), the total serum IgE (p=0.18), and bronchial responsiveness to methacholine (p=0.10) did not show significant association. The results indicate that FcεRI-β_{Leu181}, when maternally inherited, is a genetic risk factor for symptomatic atopy. The low population prevalence of the variant compared to that in asthmatics, emphasises that general population samples may have limitations for the detection of disease-associated genes by segregation or linkage analysis.

Efficiency of typing unaffected relatives in an affected sib-pair study.

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It is known that typing unaffected relatives will increase the power of an affected sib-pair study when the marker is not completely polymorphic. This paper aims to investigate the magnitude of this increase, and the consequent efficiency of typing such relatives, for varying degrees of marker polymorphism. Particular interest is paid to unaffected siblings, since these are often available when the parents are not, especially for diseases of late onset. The method of analysis used is the likelihood-ratio test of Risch (1990), which has been improved by Holmans (1993). This has been extended to incorporate unaffected siblings, and the efficiency of so doing investigated by simulation and asymptotic theory.
It was found that the proportionate increase in power was always less than the corresponding increase in the number of individuals needing to be typed, so typing unaffected relatives could be regarded as inefficient. However, the actual increase in power was sometimes quite large, especially for markers with low PIC.

If there is no highly-polymorphic locus in the region under study, it may be possible to "build" haplotypes from neighbouring tightly-linked loci. This will increase the polymorphism of the system, but will introduce problems in determining the phase of the alleles at the loci. The effect of these on power, and the relative efficiency of typing unaffected relatives, were investigated and found to be small.

Association study of oral clefts: Examples of potential gene-environment interaction. S-J Hwang, T.H. Beaty, S. Panny, N. Street, J.M. Joseph, S. Gordon, T.W. Hefferon, I. McIntosh, C.A. Francomano (The Johns Hopkins University, Schools of Hygiene & Public Health and School of Medicine, Baltimore MD 21205, and MD Dept. of Health & Mental Hygiene, Baltimore MD 21202)

Infants with isolated birth defects [83 cleft palate only (CPO), 140 cleft lip with/without palate (CL/P) cases, and 383 other birth defect controls] in Maryland born during 1984-1992 were examined to test for associations between genetic markers and oral clefts. Two markers were examined: a TaqI polymorphism at the transforming growth factor α (TGFα) locus and Mfd188, a microsatellite marker close to the retinoic acid receptor alpha gene. Results of this study suggest an interaction between maternal smoking and infant's TGFα genotype may be important in the etiology of CPO. Analysis of the Mfd188 marker further suggests a significant effect of maternal vitamin intake on risk to CL/P for certain infant genotypes. Methods for simultaneous analysis of environmental risk factors and genetic markers will be presented.

Alternative specifications of the age of onset distribution in logistic GxE models: application to early-onset bilateral breast cancer data. S.A. Ingles[1]
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A logistic model was fit to data from 63 multiplex early-onset bilateral breast cancer families in which BRCA1 genotypes were inferred from 17q haplotypes. The linear predictor included BRCA1 genotype, oral contraceptive (OC) use (ever/never), BRCA1-OC interaction,

family-specific random effects, and the age at disease onset (for affected) or age at censoring (for unaffected individuals).

Alternative age of onset distributions were explored by alteration of either the linear predictor or the link function. A goodness of link test was performed for each model, and models were compared for goodness of fit using Akaike's information criterion (AIC). A log-logistic accelerated failure time model, which allows skewness in the age of onset distribution, was found to fit the data better than either a logistic age of onset model or a proportional hazards model.

ApoE and non-apoE genetic effects in Alzheimer disease (AD).

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We investigated whether apoE genotype influences inheritance of AD in a community-based case-control AD sample in which the $\epsilon 4$ allele is associated with AD. Complex segregation analyses for prediction of AD risk (using history of memory disorders as a surrogate in nonprobands) included 266 AD probands, plus sibs and parents. For all models tested, Mendelian taus and equal τ's are rejected in the entire sample and in subsets defined by 67 e4+ and 78 e4- probands. Logistic regression detects an interaction of apoE genotype, family history and age (ExFxA), ExF, ExA, E and F effects in prediction of AD in cases and controls (all $p<0.04$). Odds ratios for AD in $\epsilon 4\epsilon 4$ and $\epsilon 2\epsilon 3$ vs. $\epsilon 3\epsilon 3$ genotype are 4.4 (0.8-22) and 4.9 (1-25) with and 1.4 (0.4-4) and 0.24 (0.1-0.8) without a positive family history. The results of both analyses are consistent with non-apoE familial effects which modify the risk of AD for any given apoE genotype, to which the $\epsilon 2\epsilon 3$ genotype individuals may be particularly susceptible.

POLYMORPHISMS PVU II AND HIND III OF THE LPL GENE : ASSOCIATIONS WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS IN THE ECTIM STUDY.

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1 INSERM U286 and 2 INSERM SC7, Paris France; 3 Belfast MONICA, Northern Ireland; 4 MONICA Bas-Rhin, Strasbourg France; 5 SERLIA Institut Pasteur, Lille France; 6 MONICA Haute-Garonne, Toulouse France.

Lipoprotein lipase (LPL) is a major determinant of the hydrolysis of triglyceride rich lipoproteins.Two DNA polymorphisms of the LPL gene were examined (Pvu II and Hind III) to detect associations with lipid and lipoprotein levels and with the occurrence of myocardial infarction in ECTIM, a large multicentric case-control study. The population studied included 629 patients with myocardial infarction and 790 controls, aged between 25 and 64 years and recruited from 4 populations in France (Lille, Strasbourg, Toulouse) and Northern Ireland (Belfast). Lipid variables (TG, TG-VLDL, LDL-C, VLDL-C, HDL-C, ApoA1, ApoCIII, Apo-B) were investigated in all patients.

Hind III polymorphism was associated with apolipoprotein (apo) C-III levels ($p=0.03$). Pvu II polymorphism was weakly associated with Triglyceride, and apo B levels ($0.05<p<0.10$).

Hind III and Pvu II polymorphisms were significantly associated with the occurence of myocardial infarction ($p=0.01$ and $p=0.005$ respectively, after adjustement for country by multiple logistic regression). The relative risk of myocardial infarction (estimated by the odds ratio) was 1.23 for H1H2 and 1.50 for H2H2 when compared to H1H1. The relative risk was 1.18 for P1P2 and 1.40 for P2P2 when compared to P1P1

These results indicate an effect of genetic variations of LPL on myocardial infarction. This could be due to the central role of LPL in lipoprotein metabolism, including the post- prandial phase, and not only to an effect on fasting lipoprotein.

Age of menarche and relative weight: a bivariate twin analysis from the FinnTwin16 study.

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Finnish twins, their siblings and parents from five consecutive birth cohorts (1975-1979) form the FinnTwin16 study sample. The twins are ascertained from the national population registry, which identifies nearly 100% of all living twins. Baseline questionnaires are mailed to the twins within 60 days of their 16th birthday. Ascertainment is unbiased and compliance is high: pairwise response rates ~ 85% across gender and zygosity, and 30 months of data-collection yielded results from 1,285 twin pairs. Questionnaire assessment included a survey of health behavior and attitudes, a symptom checklist, MMPI personality scales and relationships with parents, peers, and cotwin. Age of menarche (AOM) was reported by 468 monozygotic (MZ) girls, 378 girls from like-sexed dizygotic (FDZ) pairs, 434 girls from opposite sex (OS) pairs, and 141 older female sibs of the twins. The one month test-retest reliability of AOM in an independent sample (N=136) of 16 year olds from a national survey was 0.96. Girls from OS pairs had a significantly higher mean AOM (13.33 years) than FDZ girls (13.13 years; difference 0.20 years 95%CI 0.05-0.35)), suggesting possible prenatal or postnatal masculinization influences. The MZ correlation for AOM was 0.75, the DZ correlation 0.31 and the sib-twin correlation 0.32. The best model from a bivariate twin analysis of AOM and body mass index (BMI, wt/ht^2) indicated that 37% of the variance of AOM can be attributed to additive genetic effects, 37% to dominance effects and 26% to unique environmental effects. The correlation between additive genetic effects on AOM and BMI was 0.57, indicating a substantial proportion of genetic effects in common. Environmental effects were weakly correlated (r=-0.21).

ASSOCIATIONS OF BLOOD GROUP-RELATED ANTIGENS TO FEV$_1$, WHEEZING, ASTHMA AND GASTRIC ULCER.

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Associations of FEV1 (forced expiratory volume in one second), wheezing and asthma with secretor, Lewis and AB0 phenotypes were studied in a cohort of 215 coal miners. Interactions of genetic systems with environmental factors (smoking, alcohol, occupational exposure) and gastric ulcer on respiratory outcomes were looked for. Asthma was related to non secretor. Lower FEV1 and higher prevalences of wheezing and asthma were observed in Lewis negative or nonsecretor subjects of blood group 0. Very low FEV1 values were observed in the small group of subjects lacking both the Se and the H fucoses (Lewis negative and nonsecretor, 1% of the general population). In the large group of subjects with the two fucoses (Lewis positive and secretor, 70 % of the general population), lower FEV1 values were observed in subjects with terminal αGalNAc or/and αGal, i.e. A, B or AB subjects than in 0 subjects. Low FEV1 among subjects with peptic ulcer was restricted to non secretors. Neither AB0 blood group, Lewis negative or nonsecretor appear to explain the greater risk of some smokers to low FEV1, as associations were stronger in non smokers. On the contrary, alcohol consumption appeared to exert a protective effect on lung function in Lewis negative subjects (10 % of the general population). Further studies of the combined effects of various glycosyltransferase genetic systems seem worthwhile, particularly for airflow limitation, wheezing and asthma, as well as other respiratory and non respiratory outcomes, considering in particular infections and their interaction with alcohol consumption.

Congenital anomalies in the offspring of survivors of childhood leukemia (ALL). LB Kenney[1], C Brasseux[1], HS Nicholson[1,2], GH Reaman[1,5], JL Mills[3], LL Robison[4,5], J Byrne[1,5]. [1]Childrens National Medical Center, Washington DC, [2]National Cancer Institute, Bethesda, MD, [3]National Institute of Child Health and Human Development, Bethesda, MD, [4]University of Minnesota, Minneapolis, MN, [5]Childrens Cancer Study Group, Arcadia, CA, USA.

To determine if offspring of survivors of childhood ALL have an increased incidence of congenital anomalies, due to pre-conceptional exposure to radiation and chemotherapy, CCG/NIH conducted a large retrospective cohort study of adults treated for childhood ALL. 593 ALL survivors, average age 22.6 years, and 409 sibling controls, average age 25.2 years, were interviewed by telephone. Ninety-three survivors (15.7%) gave birth to or fathered 140 live born offspring, average age 3.4 years at interview, and 122 (29.8%) sibling controls had 228 live births, average age 5.9 years. There was no statistically significant difference between survivors and controls in the frequency of offspring with congenital anomalies 3.6% vs 3.5%, (RR=1.02, p=0.97). Evaluation of preconceptional cancer therapy suggested no effect of radiation therapy on rates of anomalies (p=0.6), but offspring of survivors treated with alkylating agents were three times more likely (RR=2.9, p=0.07) to be born with congenital anomalies compared to children of survivors not so treated. The results of our study, the largest cohort of leukemia survivors studied to date, suggest that adult survivors of childhood ALL do not have an overall increased risk of having children with congenital anomalies, but a possible association exists between preconceptional alkylating agent exposure and congenital anomalies in offspring. This study is limited by its power to detect a significant difference in a rare event such as the occurrence of congenital anomalies. Future collaborative studies of larger cohorts of survivors will be necessary to adequately quantify the risks.

Power of two-marker-locus affected sib-pair tests.
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Recently, Schork et al. (Am J Hum Genet, 1993, 53:1127–1136) found that two-trait-locus, two-marker-locus (parametric) linkage analysis can provide substantially more linkage information than standard one-trait-locus, one-marker-locus methods. But due to the increased burden of computation, Schork et al. do not expect that their approach will be applied in an initial genome scan. Further, the specification of a suitable two-locus segregation model can be crucial.

Affected sib-pair tests are both computationally simple and do not require an explicit specification of the disease model. In the past, however, these tests mainly have been applied to data with a single marker locus. Here, we consider sib-pair tests which make it possible to analyse simultanously two (unlinked) marker loci. The power of these tests is investigated for different (epistatic and heterogeneous) two-trait-locus models, each trait locus being linked to one of the marker loci. We compared these tests both to the test being optimal for a certain model and to the strategy which analyses each marker locus separately. The results indicate that a straightforward extension of the well known mean test (Blackwelder and Elston, Genet Epidemiol, 1985, 2:85–97) for two marker loci can be much more powerful than single-marker-locus analysis and that its power is only slightly inferior to the power of the optimal test.

Apo(a) Polymorphisms - a tool to study the evolution of human populations?
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The unique characteristic of the apolipoprotein(a) [apo(a)] gene is the presence of multiple tandemly repeated 5.6 kb units which code for socalled kringel 4 (K4) motifs. The number of K4 repeats in individual alleles varies from 11 to > 50 resulting in a size polymorphism which is present at the DNA, RNA, and protein level. In addition there is sequence polymorphism in apo(a). A ATG → ACG substitution in codon 12605 of the only sequenced apo(a) results in a Met → Thr exchange.

We have determined the frequencies of apo(a) size alleles (Kpn fragments) by PFGE-Southern blotting

and of the Met/Thr alleles by a PCR based restriction assay in Bushmen from South Africa (n = 172), Black Africans (n = 256) and Caucasians from Austria (n = 224). In double heterozygotes the phase of the two polymorphisms was determined on PFGE - separated alleles. The frequencies of Met alleles were 0.00 in Bushmen, 0.114 in African Blacks and 0.34 in Caucasians. In Caucasians there exists a significant linkage disequilibrium (χ^2 = 10.09, P< 0.05) of Kpn allele #18 with Met alleles. In both, African Blacks and in Caucasians the Thr homozygotes had smaller apo(a) size alleles than Met / Thr hetero-zygotes. The combination of size and sequence polymorphism in the transcribed apo(a) gene may provide valuable evolutionary information.

Reproductive and lifestyle risk factors for breast cancer in African-American women.

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As part of a survey to determine risk factors for breast cancer (BC) in African-American women and their interactions with genetic susceptibility, data on lifestyle and reproductive variables were collected from incident cases of BC at Howard University Hospital and Washington Hospital Center (Washington, D.C). Between September 1989 and December 1993, 90% of women diagnosed with BC agreed to be interviewed, making a total of 202 African-American incident cases from the D.C. area. Seventy percent of these cases had at least one unaffected sister to serve as a control. Conditional logistic regression analysis was conducted on 138 pairs of cases/sister-controls. Significant increases in risk for BC are found to be conferred by experiencing induced abortions (OR=2.44, p=0.05), having ever breastfed (OR=2.07, p=0.03) and ever smoked (OR=1.86, p=0.05). Menopausal status, increasing age at first pregnancy and having at least one miscarriage lead also to an increased risk which approaches significance. Parity, age at menarche, alcohol consumption an oral contraceptive use have no significant effect on risk. Some of the estimated risks differ from those commonly reported in studies mainly done in Caucasians. The risk associated with abortions agrees with our retrospective study using hospital-controls (Laing et al., 1993, JNMA) and a recent observation in French data using sister-controls (Andrieu and Demenais, 1994). Comparisons will be made by using a set of hospital-controls, collected as part of the present study, to assess which risk factors may be specific to African-American women and/or which may result from interactions with genetic susceptibility.

Parametric and non-parametric tests for major genes in atopy and asthma.

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We have applied clustering, commingling, path, segregation, linkage and association analysis to 8 indices of atopy and asthma in 131 random families with at least 3 children. Nonparametric tests with unbiased type I error were developed for association and linkage. Evidence for major loci is suggestive, but there is no evidence for imprinting or linkage to 11q.

Experience and estimates from this analysis are being used to search for linkage and allelic association to candidate loci in these and multiplex asthma families from Wessex and in a collaborative meta-analysis. Results of this ongoing study will be presented.

ARCAD : a method for estimating disease risk in mutation carriers from family data.

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ARCAD is a method to estimate disease risk for carriers of a mutation associated with this disease from families ascertained through many affected relatives. Because the event of interest is the age of onset which is censored for unaffected individuals, the method uses the survival analysis approach to formulate the likelihood. A correction term is introduced to remove the ascertainment biases. We present an application to families selected through individuals affected by cancer and screened for germline mutation of the tumor suppressor gene p53. The families are selected through a proband affected by cancer before age 17 and a first or second degree relative affected by cancer before age 46. We have to take into account three possible sources of bias : an excess of tumors before age 17 and 46 because of the presence of the proband and affected relatives, but a deficit of individuals affected at young age because the parents and grandparents of the proband reached reproductive age without affection. We show through the analysis of simulated data that these biases are important, and that ARCAD provides reliable estimates even when there are numerous untested individuals who provide non negligible information. We identified 5 families selected through the predefined criteria where the germline p53 mutation segregates. The cancer risk for mutation carriers is estimated to be 42% between 0 and 16 years, 38% between 17 and 45 years, and 63% after 45 years, with a lifetime risk of 85%.

Apolipoprotein(a) phenotypes as predictor of coronary heart disease in a Danish population.
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We have compared lipoprotein(a) concentrations and apolipoprotein(a) phenotypes in 101 Danish men (age 35 to 55 years, mean age 49.8 years) with ischemic heart disease with those in 466 Danish reference men (age 40 years). The median Lp(a) concentration was significantly higher in IHD patients (19.0 mg/dl; 95% CI 14.4-26.4) than in reference men (6.33 mg/dl; 95% CI 5.5-7.3). The phenotype distribution in IHD patients and reference men was also significantly different (P=0.00811): frequencies of the apo(a) low molecular weight isoforms, comprising any of the isoforms F,B S1 or S2, were higher in IHD patients. Median Lp(a) concentrations were statistically significant higher in IHD patients for each of the most common phenotypes. In conclusion, Lp(a) is a risk factor for IHD in a Danish population and alleles at the apo(a) gene locus predict the risk of IHD.

Apolipoprotein E Σ4 allele doses in late-onset Alzheimer's disease (AD).
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The cumulative probability of remaining unaffected over time for Alzheimer's patients decreases for each dose of apolipoprotein E allele Σ4. Our retrospective study includes 132 unrelated french patients, most of them having a clinical diagnosis of probable AD. All of the patients retained are classified as late-onset (>60) and ages of onset were estimated from age at the first examination. Genomic DNA were amplified by PCR and restricted with *Hha*I, and four genotypes (E4/4, E4/3, E3/3, E3/2) were observed. Gene dosage was as follows: 2 doses (E4/E4), 1 dose (E4/3), 0 dose (E3/3 + E3/2). Onset curves were estimated by Kaplan-Meir product limit distributions. The study shows that risk of AD is increased for each dose of apoE-Σ4 in our serie: for example at age 75 an estimated of only 1% of subjects without apoE-Σ4 were diagnosed with AD, compared to 60% of subjects with one Σ4 dose, and almost 87% of subjects with two doses of apoE-Σ4 allele.

Familial aggregation of Amyotrophic Lateral Sclerosis, Dementia and Parkinson's Disease: a case control study.
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We compared 149 newly diagnosed ALS patients with 136 controls, in terms of a family history for ALS, Parkinson's disease (PD) and/or dementia in parents, siblings and grandparents. A family history of dementia and PD aggregated within the families of ALS patients (OR= 9.7, 95% CI 3.0-30.9) as well as in the families of controls (OR=5.6, 95% CI 1.4-22.9). A family history of dementia (N=33), PD (N=15), or either (N=38) was found more often in families of ALS patients compared to controls (resp. in 20, 9 and 25). This association was strongest in those with familial ALS (N=7): a family history of dementia or PD (OR=5.92, 95% CI 1.3-28.1), dementia (OR=5.55, 95% CI 1.1-29.6), or of PD (OR=8.22, 95% CI 1.2-55-7). These findings indicate familial aggregation of dementia and PD in (at least) some families of ALS patients and controls. This association suggests there may be a shared genetic susceptibility to these disorders. Familial co-occurrence of ALS, dementia and PD may represent another distinct genetic subtype. It would be interesting to study if in families with dementia and PD, both of ALS patients and controls, the disorders are linked to the same genetic defect, and if so to determine the factors responsible for variability in expression of clinical symptoms, whether genetic, environmental, or combination.

Towards a resolution of Early-Onset Alzheimer etiologies.
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Early-onset Alzheimer disease (EOAD) is clearly an heterogeneous disorder. A French family study of EOAD has been set up in order to delineate its different etiologies. For such a goal, (n=133) patients with an age at onset before 60 years were ascertained. We carried out a segregation analysis of AD in 92 families. It was assumed that among our probands only a proportion of them are determined by a rare dominant disease allele and the remaining are due to random effects. Age-at-onset for probable or possible AD secondary cases and age at exam/death for unaffected members in first and second degree relatives were taken into account. Two age-at-onset distributions were considered: a normal and a hazard logistic one. The hypothesis that all our early-onset AD probands are due to a dominant disease allele is strongly rejected. Our results suggest that rare dominant disease allele(s), completely penetrant by age 60, can fully explain the transmission of AD in less than 1 out of 5 early-onset probands. This analysis allows the classification of probands in three groups: Type I (n=17) with EOAD secondary case(s), type 2 (n=29) with late AD secondary case(s) and type 3 (n=46) without secondary case. The type I patients have a posterior probability (PP) of being carrier of a rare dominant disease allele greater than 52%, whereas the remaining cases have a PP value <4%.

Besides, different markers are currently under investigation (APP, APOE and chromosome 14). The information on these markers will be used through classical association studies. It will also be incorporated in further segregation analyses. Indeed, such combined analyses appear to be necessary to better delineate the different etiologies of EOAD.

Clinical and molecular study of four breast-ovarian and breast cancer families.

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1. Centre René Gaudducheau, C.R.L.C. Nantes-Atlantique, France and 2. LOM, Centre Jean Perrin, C.R.L.C. Clermont-Ferrand, France.

Previous studies have demonstrated linkage between early-onset breast cancers and ovarian cancer and genetic markers on chromosome 17q. The locus was designed BRCA-1 (BReast CAncer-1). We analysed 4 families with multiple affected individuals for evidence of linkage to the BRCA 1 region. Three breast cancer and one breast/ovarian cancer families were selected according to Breast Cancer Linkage Consortium diagnosis criteria. Three markers on 17q were tested : - THRA 1, Mfd 188, D17S800, using DNA of relevant individuals within these families. Two of the four families appear to be linked to this region.
All of them will be included in a largest study with the French cooperative network in order to allow a multipoint linkage analysis study to define more precisely the characteristics of linked families and the penetrance of gene. Lod-scores are under calculation and will be presented.
Our preliminary results confirmed the genetic heterogeneity of breast cancer families.

Interpedigree phenotypic comparisons and linkage results on 11q21-22 in Eastern Quebec pedigrees densely affected by schizophrenia.

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The 11q21-22 region was surveyed by linkage analysis in 4 large multi-generational pedigrees that are densely affected by DSM-III-R SZ and 6 others by DSM-III-R bipolar disorder (N = 234). These pedigrees were selected through systematic ascertainment in a large area of Eastern Quebec and Northern New Brunswick. These pedigrees are still being extended. The phenotypic features of one large SZ pedigree (pedigree 255) with a positive linkage trend were compared to that of the SZ pedigrees showing no linkage.

Family members were administered the same "consensus best-estimate diagnosis procedure" (DSM-III-R criteria) blind to probands and relatives' diagnosis and to pedigree assignment (SZ or BP). Extended clinical quantitative measures about the lifetime presence of symptoms, severity, and clinical course were also taken. For linkage analysis, 10 microsatellite polymorphism (CA repeat) markers, located at 11q21-22, and comprising DRD2, were genotyped.

Results show a linkage trend (lod score 2.86 to 3.44) at the D11S35 locus in one large family, pedigree 255. When compared to the 3 other SZ pedigrees and to a sample of SZ familial cases, our measures suggest that the DSM-III-R SZ cases of pedigree 255 have a distinctive phenotypic trends corresponding to a more severe, unremitting, nonresponsive form of schizophrenia corresponding to the original concept described by Kraepelin. Implications for replication of linkage are discussed.

Genetic modelling of dizygotic twinning in families of spontaneous and induced dizygotic twins.

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We investigated the inheritance of dizygotic twinning through segregation analysis.
Spontaneous dizygotic proband twins were obtained through two population-based twin registers: the East Flanders Prospective Twin Study and the Dutch Twin Register. Three generational pedigrees of the mothers of the dizygotic proband twins were analyzed. Results showed that the trait of "bearing dizygotic twins" in families of spontaneous dizygotic twins, is inherited by an autosomal dominant model with a gene frequency of 3%. One in fifteen individuals were carrier of the gene, but due to the female-specific expression of the trait, only female carriers had a 10% probability of giving birth to dizygotic twins. Recessive, polygenic and sporadic models were rejected.
Segregation analysis detected a dominant major gene for spontaneous dizygotic twinning in the 300 maternal families of induced dizygotic twins. Comparison with the above described dominant model in families of spontaneous dizygotic twins revealed that we were dealing with the same model in the maternal families of both induced and spontaneous dizygotic twins.

Conditional probability calculations in atypical hyperplasia in genetic breast cancer.

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Prevalence of atypical epithelial hyperplasia (AH) is is reportedly 0.0005 in controls. AH is considered a precancerous lesion, and the group with this finding has increased risk for cancer (Dupont et al. 1993). AH is not treated as cancer.

We have defined a cohort of healthy women in breast cancer (BC) families. Each woman is considered to have 25% or higher risk for BC. This cohort is being followed by repeated examinations. By now, prevalence of AH is 0.02. We may then calculate:

	BC	no BC
Prior probability	0.25	0.75
Conditional probability	0.02	0.0005
Posterior probability	0.93	0.07

The interpretation that 93% of women with AH will contract BC, is based upon the assumption that that excess AH in the cohort will progress to BC. The validity of this assumption will be discussed. If it is correct, treatment of these women should be considered.

Updated figures from our activity will be given.

Segregation analysis in families of soft tissue sarcoma patients

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Clinical and family data were obtained for 239 children treated for a soft tissue sarcoma at the "Institut Gustave Roussy" in Villejuif (France). Pedigree structure included first and second degree relatives and first cousins. Among the 4448 probands' relatives, 169 had developed a malignant neoplasm, 49 of them being diagnosed ≤ 45 years of age. Germline p53 mutations were searched in families with at least one cancer diagnosed before age 45. In order to determine which model best explains cancer distribution in pedigrees, we performed segregation analysis using the mixed model. This method effectively allows to compute conditional likelihood to the parents' phenotype. We show evidence for a major gene with autosomal dominant transmission. Penetrance was estimated by using a new method based on survival analysis and exactly adapted to our ascertainment scheme. It was estimated to be 38% at age 16, 69% at age 45 and 100% at age 84 in germline p53 mutation carriers. This mutation almost entirely explains the genetic componant which means that most non carriers are at the same risk for cancer than the general population.

A note on the power of jointly using information on association and linkage rather than using information on only one of the two phenomena.

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In many studies the involvement of a candidate region or candidate gene using information on polymorphic markers is tested using either association studies or marker-trait cosegregation (linkage). Other methods (such as the MASC method) use information of both phenomena jointly. We aimed to estimate the power of a joint approach vs a single phenomenon approach by calculating the expected sample size of a) the AGFAP method, b) the segregation distortion in a sibpair with unaffected parents and c) appropriately combining the significance levels contributed by a and b. We systematically scanned the space of single gene models that give rise to a recurrence risk of 5% in the sibs of an affected. The locus involved in the disease as well as the marker used were assumed diallelic, with the penetrance constrained to be zero in the persons homozygote for the second allele of the disease locus. In over 50% of the models thus considered, the expected sample size was minimum for the joint approach. In addition the joint approach was never very far from the best approach for a given model (maximum difference in expected sample size <= 69). This latter figure was considerably higher for the other approaches. We conclude that using a joint approach (as in MASC) carries a lot of benefit over the single approaches.

The ecogenetics of pancreatic cancer: A registry of families. J. Mulvihill,[1] M. Shaffer-Gordon,[1] C. Rodriguez,[1] S. Finkelstein,[2] M. Virji.[2] Departments of [1]Human Genetics and [2]Pathology, University of Pittsburgh, Pennsylvania, USA.

To help clarify the genetic and environmental origins of pancreatic cancer, a registry of pancreatic cancer families was begun in 1988 at the US National Cancer Institute and transferred to the University of Pittsburgh in 1990. By January 1994, 69 families met the definition of medically documented adenocarcinoma of the exocrine pancreas in 2 first-degree relatives or in 2 second-degree relatives connected by a person with any cancer. Apart from the defining pancreatic cancers, 197 additional cancers reportedly occurred in the families, including 39 pancreas, 51 breast, 18 skin, and 16 colorectum. There are 3 three-generation kindreds, 36 two-generation families (including male-to-male transmission), and 29 affected sibships without an affected parent. A panel of serum tumor markers was devised (CA125, CA19-9, CEA, SPan1, and DUPan2) and, in 30 tested persons, showed the expected elevations in cancer patients and no elevations in first-degree relatives, including 7 with serial specimens. By inspection, there was no striking environmental agent beside smoking and no apparent excess of diabetes mellitus. Like two case-control studies, the registry suggests familial pancreatic cancer is not rare and may serve as a route to understanding the etiology of this lethal cancer.

Disease risk in hereditary hemochromotosis heterozygotes. Nelson RL, Davis FG, Persky V, Becker G., Depts. of Surgery & Epidemiology/Biometry, University of Illinois at Chicago, USA.

Disease risk in hereditary hemochromatosis (HH) heterozygotes was investigated. Individuals homozygous for HH were identified through the membership files of two hemochromatosis societies. These individuals were mailed questionnaires concerning the health histories of their parents, who would be HH heterozygotes. Spouse controls received similar questionnaires. Death from cancer, heart disease and stroke and the incidence of heart attack, diabetes, stroke, hypertension, colonic adenoma and cancers

of the lung, colon, breast, cervix,pancreas, stomach, and blood were determined. Data are available from 1950 HH heterozygotes and 1656 controls. Controlling for age, statistically significant differences were observed for diabetes in the males (RR=1.4; 95% CI = 1.0 - 2.1), colonic adenoma in females (1.3; 1.1 - 1.5) and males (1.2; 1.1-1.5), colon cancer (1.3; 1.1 - 1.5) and blood cancer (1.3; 1.0 - 1.6) in males, for fatal stroke (1.4; 1.0 - 1.8) in and total gastrointestinal cancer (1.4; 1.1 and 1.9) in the combined genders. Heterozygosity for HH may be associated with increased risk for colonic neoplasia and fatal stroke in both genders and diabetes and hematologic malignancy in males. No increase risk of heart disease as a cause of death or event could be demonstrated in this population.

The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) as a resource for genetic epidemiology.

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ALSPAC (an initiative of the Division of Epidemiology, Institute of Child Health, Bristol) is a prospective study of the health and well-being of children within Avon from fetal stage until the age of 7 in 1999. The criteria for inclusion were that the expected date of delivery lay between April 1st 1991 and December 31st 1992 and that the baby was born whilst the mother was resident in Avon. Some 15,000 births (about 85% of the total) have been enrolled with cord and maternal blood stored for DNA PCR-based analysis. 98% have granted permission for genetic studies within the confidentiality system approved by the ALSPAC Ethics and Law Committee. ALSPAC will determine the pattern of environmental, social, psychological, biological and genetic factors independently associated with common disorders affecting children's health, growth and development. Information is largely by self-completion questionnaires (supplemented where appropriate by clinical records), and a medical examination planned towards the end of the 7 years. A 10% sample are being studied and examined in more detail, and will be the initial focus of genetic studies, e.g. the impact of mannose binding protein deficiency (3 mutations) on infant infection especially otitis media.

Geographical variation in the allelic distribution of ACE-gene in high and low risk areas for coronary heart disease (CHD) in Finland.

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Peculiar enrichment of specific alleles in the isolated population of Finland is best exemplified by rare inherited diseases found in Finland at higher frequency than anywhere else in the world. In the mortality from CHD, two geographical regions of Finland, North Karelia (NK) and Turku-Loimaa (T-L) area still demonstrate clear difference despite of almost 20 years documented decrease of the disease prevalence in both areas. Since the DD-genotype of the ACE-gene polymorphism has been shown to predispose to CHD, a hypothesis was raised whether this geographical variation could be observed in the frequency of the ACE-genotypes in these two regions. Two random samples of males 30-59 years of age of both areas were drawn. The allelic frequencies and corresponding genotypes were in the Hardy-Weinberg equilibrium (total n=363). The DD genotype was significantly more frequent in the population from NK: 38.7% of the NK population had the genotype DD whereas only 28.6% of the T-L population carried this genotype (p=0.042). However, when the distribution of the three genotypes (DD, ID, II) was compared, they did not significantly differ between these two areas (p=0.085), nor did the allelic distribution (p=0.197). We suggest, that the DD-genotype of the ACE-gene could represent one of the influencing factors behind the regional difference in mortality from CHD in Finland.

Cancer risk among the relatives of probands with large bowel cancer

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In order to study the familial aggregation of colorectal cancer, we collected the pedigrees (including the four grandparents and all their second generation descendants) of patients with adenocarcinoma of the large bowel. The final sample included 99 probands and 1455 relatives, and a control group (proband spouses) of 72 families, including 1163 individuals. The frequency of both colorectal and extracolonic cancers was higher in the relatives of cases than in the control group, for all the relationships. Among the first degree relatives, the empirical risk of colorectal cancer was 1/30 among the case families and 1/139 among the control families, for a 4.6 fold increase. For cancers at all sites (colorectal excluded), the corresponding risks were 1/8 and 1/12. For an individual with one first degree relative affected by colorectal cancer the posterior (Bayesian) risk of the same tumor was 1/15, compared with a value of 1/70 for the control population. Considering all cancers, colorectal excluded, we obtained the result that for a person with at least three affected relatives, one of first, one of second and one of third degree, the posterior probability of dying from colorectal cancer was 1/17. For both the cases of colorectal cancer and for all-site cancer, a few families were responsible of a large part of the observed familial aggregation. However, no family fulfilled the current criterion of hereditary non-polyposis colorectal cancer (Lynch syndromes I or II).

A new model for the analysis of family study clinical trials: Searching for genes regulating the response to exercise training in the HERITAGE Study

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In the multicenter HERITAGE study (funded by NHLBI.), all 5+ members of 130 nuclear families are measured at baseline in a sedentary state, undergo 20 weeks of progressive exercise training, and are re-measured. A variety of measurements are made, including many cardiovascular risk factors. Our primary goal here is to identify the genetic determinants of the differential degree of response to exercise, using a new model which combines the treatment effect aspects of a clinical trial with the transmission components typically found in family studies. Viewing the problem as a repeated measures family design in which the same genotype is phenotypically expressed under two different environments (pre-and post- treatment), we decompose each phenotypic realization into a latent single major gene, polygenic and familial environmental components, as well as an arbitrary number of measured covariates (either genetic or environmental), with correlated residuals. Of interest are the different degrees of genotypic expression (penetrance) of the same genotype with treatment. The model is developed using SEGPATH, a software tool for creating general, combined segregation and path analysis models for family data. Preliminary screening of the pre-treatment data on the first 37 families shows considerable familial clustering: e.g., fat mass through underwater weighing shows an intra-class estimate of transmissibility of 0.61.

Epidemiology of Colon Cancer. JD Potter. Division of Epidemiology, University of Minnesota, Minneapolis, MN.

Models of the etiology of cancer have been defined at the epidemiologic, physiologic and molecular biologic level. It is of some benefit, both for colon cancer itself and for the more general understanding of disease etiology, to consider the coherence of these models. The consistent epidemiologic risk factors are low physical activity and diets low in vegetables and fiber and high in meat, fat, and alcohol. There is some evidence of variation in the pattern of these risk factors by sex and age. The epidemiologic risk factors appear to relate, in straightforward fashion, to physiologic and biochemical processes that may provide mechanistic explanations - higher bile acid excretion, intra-colonic fiber fermentation, and the specific effects of known plant-food anticarcinogens. The likelihood that the meat/fat associations are in part related to carcinogens and promoters that are produced when food is cooked add further complexity to the model. Linking the dietary exposures, genetic predisposition, and the molecular processes of colon carcinogenesis is acetylator status - the genetically variable capacity to metabolize arylamines. It appears plausible that a diet both high in arylamines formed in cooked meat and low in vegetables, and therefore folate, could be related directly to the early somatic molecular changes described for colon cancer. Whether other connections exist between dietary exposures and physiologic processes on the one hand, and molecular mechanisms on the other will be considered.

Validity of Psychiatric Diagnoses Based on the Family History Methdod
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We sought to validate psychiatric diagnoses obtained by family history (FH) against those obtained by a best-estimate (BE) procedure and to explore the factors influencing the accuracy of the FH report.
Subjects were 1,459 first-degree relatives of probands with schizophrenia, affective illness and community controls. FH diagnoses were obtained using the FH Research Diagnostic Criteria, while Best-Estimate diagnoses were obtained from personal interview, medical records and FH information.
The overall agreement between the FH and BE diagnoses was relatively poor (kappa=0.42). Predictors of a false negative FH included younger age of the subject, absence of previous psychiatric hospitalizations, belonging to a control family and poor quality of FH. Predictors of a false positive FH included female gender, older age of the subject, a history of previous psychiatric hospitalization, female gender of the informant and an informant's diagnosis of major affective disorder. Diagnostic inaccuracies (i.e., both methods assigned some diagnosis but disagreed on the category) are predicted by a BE diagnosis of schizoaffective disorder, other nonaffective psychosis or bipolar illness and by poor quality of FH information. Finally, the effect of subject's diagnosis showed significant variations depending on proband's diagnosis. When validated against a BE diagnosis, the overall accuracy of the FH method is relatively poor and is furthermore subject to several biases. In most situations, the FH method is not a satisfactory substitute for personal interviews in psychiatric genetic investigations.

Familial occurrence of Cluster Headache.
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Objective. To investigate the familial occurrence of Cluster Headache (CH).
Methods. Probands with CH according to the operational diagnostic criteria of the International Headache Society were included. They were from Århus, east central Jytland, and Copenhagen County. Probands received a mailed questionnaire regarding the number of their first- and second-degree relatives and familial occurrence of CH. Possible affected relatives were telephone interviewed.

Results. The questionnaire response rate was 86.7% (365/421). A positive family history of CH was seen in 6.6% (24/365) of the families. As compared with the general population, the first- and second-degree relatives of the 365 probands had a 15- and 2-fold increase in the risk of having CH, after standardization for sex.
Conclusion. The increase in familial risk of CH strongly suggests that CH have a genetic cause.

Molecular study of cystic fibrosis in Kuwait.
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Contrary to a common view cystic fibrosis (CF) seems to be not rare in Arabs. For example, in Jordan the CF incidence of 1:2560 live births was shown by newborn screening with meconium albumin test (Nazer, 1992). However, the molecular characterization of CF chromosomes in this ethnic group is very scarce and mainly attributed to Arab patients from Israel. In the latter group ΔF508 mutation was found to be the most common one, but its frequency (26%) was significantly lower than in Europe (Abeliovich et al., 1992).

We studied six CF chromosomes from three unrelated Kuwaiti families. PCR and PAGE were used for identification of ΔF508 and ΔI507 mutations. All CF chromosomes examined were negative for both deletions. Testing of these chromosomes for other common CF mutations (W1282X, G542X, N1303K, 1717-1, R553X) is in progress and the results will be presented at the meeting. However, it is possible that Kuwaiti patients have other CF mutations (in Arabs the percentage of CF chromosomes with unidentified mutation is 45%).

Expected figures of an alive birth from childless families due to fetal wastage.
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In order to estimate the chances for a live birth, we studied families with no an alive birth but only losses. From 1984 to 1991, 1171 families referred to Genetics Clinic were included into this work. They were divided into 3 groups: those with abortions only; with stillbirths only, and with both. Respective figures are 618, 256 and 267 families as further divided into those with and without consanguinity.

All families were sent questionnaires after about 2 years asking to report the fate of a recent pregnancy, if any. Some 60 percent were replied. Only those with 1 to 3, 1 to 2 and 2 to 4 losses were evaluated in the respective groups because of the scarcety of families with more losses.

In abortion group 54.28, 39.53 and 38.81 percent; in stillbirth group 50.0 and 45.16 percent, and in combined fetal-wastage group 44.73, 37.5 and 36.0 percent are expected to give birth a live infant, not necessarily normal. No differences between families with and without consanguinity were found.

HLA-DRB associations with seropositive rheumatoid arthritis in Mexican Mayan Indians.
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HLA-DR4 has been found to be increased in rheumatoid arthritis (RA) patients in most ethnic groups studied, but not consistently in Amerindians. Furthermore, it has been reported that various Dw subtypes of DR4 confer greater susceptibility to RA -- DRB1*0401 (Dw4), 0404/0408 (Dw14), and 0405 (Dw15), while others do not -- 0402 (Dw10) and 0403/0407 (Dw13). We DRB typed 36 RA patients and 130 controls of predominantly Mayan Indian ancestry (Gm typing revealed some European and African admixture). The frequency of DR4 positive genotypes was 92% in patients and 77% in controls (P<.001). The DR4 allele frequency was 78% in patients and 52% in controls (P<.0001). Among patients, 46% of DR4 alleles were Dw13 and 32% Dw14, while among controls 57% were Dw13 and 22% Dw14 (differences not significant). There was no evidence of Gm association with disease, nor for DR4-Gm interactions. In conclusion, although there was a slight (non-significant) increase in the frequency of Dw14 DR4 subtypes in patients, the most dramatic difference between those with and without RA was in the frequency of serological DR4 *per se*.

Mendelian Inheritance of combined Trait: Gilles de la Tourette Syndrome and Tics?
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Segregation Analysis was performed to model the occurence of the combined trait Tourette Syndrome and Tics in 73 families ascertained through one affected individual. A transmission probability model with different susceptibility parameters and a common age of onset (SAGE REGTL) was used to test weather a genetic (dominant, recessive, codominant), no major gene effect or purley environmental model best fitted the data. These hypotheses were tested against the unrestricted model. According to DMS III-R, two different diagnostic schemes were used: 1.) TS (307.23) or chronic Tics (307.22), and 2.) additionally not otherwise specified Tics (307.20).

Preliminary results suggest that we can not confirm the major gene hypothesis with our families as published by other authors. Also, the no major gene hypothesis and the environmental hypothesis are identical. However, the following problems need to be addressed: we identified 1/3 sporadic families (only proband being affected), and we suspect that the affection status in the founder generation being classified as healthy may be uncertain. Further analyses will be carried out.

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An european collaborative study on the epidemiology of limb reduction defects.

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Limb reduction defects (LRD) are common and present as obvious congenital anomalies at birth. However they are not well documented and classification of LRD is disputed. A new classification was used for the study of various aspects of the epidemiology of LRD in Europe. It is based on more than 600,000 consecutive births over 7 years in well defined populations and includes livebirths, stillbirths and terminations of pregnancy. The prevalence rate of LRD was 7.06 per 10,000 births including prevalence rates of 3.97, 1.75, 0.10, 0.54 and 0.70 for terminal transverse, longitudinal, proximal intercalary, split hand/foot and multiple types, respectively. The prevalence was significantly higher in Strasbourg and in the Basque Country ; 49.5% were isolated cases, without other major non LRD associated malformations after exclusion of the cases with a chromosomal anomaly (6%). The total prevalence rate did not vary over the time period considered. Sex ratio, maternal age, mean birth weight and gestational age did not vary significantly between regions. The percentage of prenatal detection of LRD was low, 11.9. The regional variability showed in this study, may either be the result of exogeneous factors such as climate factors for example or of differences in the gene pools of the population in the different regions covered.

ApolipoproteinAIV polymorphism:impact on serum total cholesterol level in Finnish men during a 30 year follow-up in the Finnish cohorts of the Seven Countries Study.

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We assessed whether apolipoprotein (apo) AIV polymorphism is associated with interindividual variation in six repeated measures of total serum cholesterol level (1959,1964,1969,1974,1984, 1989) in two cohorts of Finnish men, one in East (n=178) and the other in South-West (n=219) Finland. The Eastern cohort comprised 162 AIV-1/1 homozygotes and 16 AIV-1/2 heterozygotes. In the South-Western cohort respective frequencies were 195 and 23. No AIV-2/2 homozygotes were recorded. Heterogeneity of the relative allele frequencies between the cohorts was not statistically significant. Highest mean cholesterol level in both cohorts was in 1969 and lowest in 1989. Mean levels were approximately 0.2-0.3 mmol/l higher in the Eastern cohort at the three first measures ($p<0.09$, 0.02 and 0.06, respectively), but this difference disappeared in 1974 ($p>0.2$). ApoAIV genotypic variation was not associated with cholesterol level variation in any of the cross-sectional analyses. However, in a multivariate repeated measures analysis of variance there was a time by apoAIV polymorphism by cohort interaction effect ($F_{5,388}=1.96$; $p=0.08$). We conclude that the apoAIV polymorphism contributes to interindividual variation in the vector of yearly cholesterol means such that average differences between cohorts are dependent on the genotype and the year considered. This study documents that apoAIV effects on lipid metabolism are context dependent.

THE THYROID MEDULLARY CARCINOMA: 28 YEARS OF CASES RECORDING IN THE NUCLEAR MEDICINE DEPARTMENT OF THE INSTITUT JEAN GODINOT, REIMS, FRANCE.

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Since 1966 all of the new cases of thyroid cancer were registered in an hospital-based registry (HBR). Since 1979, the completeness of the registration has been obtained of the French administrative areas Ardennes and Marne allowing the creation of a population-based registry (PBR). The aim of this study was to present firstly the cases of medullary carcinoma (MC) registered in the PBR and secondly all of the cases of MC emphasising on family MC. The diagnosis was usually made before surgery when basal or stimulated calcitonin levels are raised and by fine needle cytology of the nodule. For each case a family pedigree was mapped. All of the first degree family members were tested by pentagastrin test. If an hereditary form was suspected genetic screening was carried out. We systematically looked for MEN2 before surgery. Between 1979 and 1992, 444 new cases in females (F) and 117 in men (M) have been registered in the PBR. The diagnosis of MC was done in 17 cases (4%) in F and 15 cases (13%) in M. The age standardised incidence ratios (world population standardisation) were equal to 0.23 / 100000 and 0.22 / 100000 in F and M respectively. Since 1966, 79 new cases of MC were notified to the HBR (43 F and 36 M): 7 family index cases allowed us to diagnose 9 other cases which all and two others represented 10 families. The median ages were equal to 53 (20-93) and 35 (17-67) in sporadic (SC) and familial cases (FC) respectively. The five year survival rates were equal to 77% and 86% in

SC and FC respectively. There were more stage I and II (according to the UICC) in FC than in SC and the distribution of the clinical staging was statistically different ($p<10^{-2}$). However, when adjusting for stages no difference was observed between FC and SC for overall survival. The early diagnosis of family MC with the help of genetic screening tests in detecting the gene carriers will allow us to reduce mortality and morbidity of MC.

Effect of lipoprotein lipase gene polymorphisms on triglyceride levels in NIDDM families with dyslipidemia.

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Lipid abnormalities are frequent in Non Insulin Dependent Diabetes Mellitus (NIDDM). This might be secondary to other metabolic disturbances but it is also possible that the effect of genes implicated in lipids variation might be different in diabetic patients.

To test this hypothesis, we analyzed 26 NIDDM pedigrees selected on the following criteria: the presence of at least 2 first-degree relatives with HDL-Cholesterol < 0.9 mmol/l or triglycerides > 3 mmol/l or LDL-cholesterol > 6 mmol/l or a hypolipidaemic treatment. The effect of two polymorphisms of the lipoprotein lipase gene (LPL), PvuII and Ser^{447}-Ter on triglyceride level variation was investigated. Familial analyses of cotransmission of LPL gene and triglycerides was performed using the mixed model and class D regressive model which can consider diabetic status as a covariate.

The sample included 210 subjects (55% of males , 48% of diabetic patients). The rare allele of Ser^{447}-Ter (Freq=0.88) was associated with a higher level of triglycerides ($P<0.05$) and explained 4% of the variance. The P+ allele (presence of the restriction site) of PvuII (Freq=0,55) was associated with a high level on triglycerides but this effect was restricted to diabetic patients (mean level was 1.5 fold higher in P+P+ genotype than in P- P- genotype). The interaction between PvuII polymorphism and diabetic status on triglyceride level was significant ($p<0,05$).

In conclusion, LPL gene is implicated in triglycerides variation in NIDDM families and this effect appears to be increased in diabetic patients. The LPL gene might be one of the genes contributing for the high risk of hypertriglyceridemia in NIDDM.

Apolipoprotein E polymorphism and predisposition to coronary heart disease - The EARS study.

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The European Atherosclerosis Research Study (EARS) was designed to assess the influence of genetic and environmental factors on predisposition to coronary heart disease (CHD). It was based on the comparison of offspring having a paternal history of premature myocardial infarction (MI) with age and sex matched controls, both being recruited from 14 European universities. 635 cases and 1,259 controls were phenotyped for the apolipoprotein (apo) E polymorphism.

The allele distributions differed between populations with a clearcut gradient for allele e_4 frequency decreasing from 0.18 in Finland to 0.11 in the South of Europe, following the gradient of CHD mortality rates. The association of apoE polymorphism with plasma total cholesterol, LDL-cholesterol, apoB and apoE levels were consistent with the now well identified effects of e_2 and e_4 alleles on these traits. Both e_2 and e_4 alleles equally increased the level of triglycerides, and e_2 had a lowering effect on Lp(a) concentration. There were also weak effects of e_2 and e_4 on HDL-cholesterol, apoAI and LpAI levels, parallel to those on apoE level. The main finding of this study was the significant association of the apoE polymorphism with a paternal history of MI. The association ($p<0.01$) was consistent across regions, except in South. When excluding this region, the population-adjusted odds ratios by reference to phenotype E3/3 were estimated as 0.23, 0.61, 0.78, 1.16 and 1.33 for E2/2, E3/2, E4/2, E4/3 and E4/4, respectively. The apoE locus largely explained the case/control difference of apoB level.

These results provide a body of evidence that apoE polymorphism strongly contributes to the development of CHD and is one major factor responsible for the familial predisposition to this disease.

Multilocus IBD distributions in sibships with applications.

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We present an algorithm to calculate the likelihood (L) of $P=(p_{lij}: l=1,...K, i<j=1,...S)$ where p_{lij} is the number of genes that sibs i and j share ibd at locus l. The K loci are assumed linked, with known locations; cross-over interference is incorporated via mapping functions.

Three related applications are discussed: (1) estimation of the amount of genetic material shared ibd at points between marker loci, (2) testing for linkage when the disease is determined by a single autosomal locus with two alleles, (3) testing for linkage for a quantitative trait using the Haseman-Elston approach.

Neural tube defects according to the Lithuanian registry of inherited diseases and congenital defects.

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Neural tube defects (NTD) include anencephaly, *spina bifida* and encephalocele. The total prevalence of NTD according to the Lithuanian registry of inherited diseases and congenital defects in 1992 was 11.9 per 10,000 livebirths and in 1993 - 18.5 per 10,000 livebirths, stillbirths and induced abortions following prenatal diagnosis. There are large local

variations in the frequency of these malformations, ranging from 0 to 61.2 in 1992 and from 0 to 67.6 in 1993.

An ultrasound scan is now a routine part of antenatal care in Lithuania. Prenatal screening with ultrasound was carried out in 50.5% of cases with NTD in 1993. In 79.5% of cases a prenatal diagnosis was performed. However, in 31.4% of cases the diagnosis was done late in pregnancy. In 22.9% of cases the pregnancy was not terminated for various reasons.

GENETIC EPIDEMIOLOGY OF HUNTINGTON'S DISEASE IN GREECE

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This study presents data from 88 unrelated patients suffering from Huntington's disease (HD). The patients were all of Greek origin and were diagnosed in our Department in the last 25 years. The mean age of onset of symptoms was 44.8 years. Sporadic cases comprised 14.8% of the total sample. In the cases with a positive family history, adifferentiation in the sex influence on the clinical presentation of the disease was observed : a) greater fertility in cases with maternal descent and b) an earlier onset in cases of paternal tranmittance of HD. Regarding geographic distribution,the incidence of HD, as expressed in the relative patient population sample seems to be higher in the Prefectures of Messinia and Lasithi. The results are discussed inview of the current possibilities of molecular diagnosis of HD presymptomatically and prenatally resulting in better genetic counselling.

Sources of variability of human plasma apolipoprotein A-IV levels and relationships with lipid metabolism

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Plasma apolipoprotein (apo) A-IV concentration was determined by immunoelectrophoretic-assay (EIA) in 119 nuclear families. No significant effect of concomitants such as age, weight, height, body mass index, tobacco, and alcohol consumption was observed on apo A-IV levels in men and in boys. In women, contraceptive use and hormonal status affected apo A-IV levels. In girls, only age influenced the quantitative phenotype. After adjusting by specific concomitants significant correlations were observed between apo A-IV levels and triglycerides, apolipoprotein A-I and apo B levels, suggesting a role of apolipoprotein A-IV in the hepatic lipid metabolism. Intrafamilial correlations were estimated to investigate the plausibility of a common family factor. The results obtained in this study showed a significant correlation between family members with the exception of mother/daughter pairs. Using a variance components model, the contribution of genetic and environmental factors was then investigated. Different statistical models were used and two major hypothesis were statistically acceptable: the first hypothesis supports that shared and specific environmental factors explain 35 % and 65 % respectively, of the total adjusted plasma apo A-IV variation. The fraction of apo A-IV variability attributable to genetic factors was null. The second hypothesis supports that the fraction of variability attributable to apo A-IV genetic variation is 67% and the common spouse environmental factors are responsible for 33% of the total variability and no specific environmental effect was found. Among the two hypothesis, taking account of the metabolism function, we support the first one without excluding gene/environment interactions which could mask the genetic influence.

IGHG1 and IGHG4 deletions in two Northwestern Siberian populations

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Multigene deletions in the IGH locus have been described in healthy individuals, either homozygous for these deletions or heterozygous for two different deletions. A few single gene deletions have been reported [1]. We collected blood samples from apparently healthy individuals from **Forest Nentzi** and adjacent **Sel'kup** populations in Northwestern Siberia. Five persons were found to be deficient in IgG1 either by serological typing of the Gm1 allotypes or by restriction fragment length polymorphism of the IGHG genes, using a Cγ (pSH3Cγ3) probe [2]. In addition, two persons from the Sel'kup population were found to be homozygous for IGHG4 gene deletion. Molecular analysis showed that only the IGHG1 and IGHG4 genes were deleted. Southern blot analysis of familial samples allowed to establish a qualitative method for the screening of the IGHG1 deleted heterozygotes. Population genetics studies are underway to estimate the frequencies of IGHG1 and IGHG4 deletions in the populations.

[1] Lefranc et al., Immunodeficiency revievs, 1: 265-281 (1991)

[2] Huck et al., FEBS Lett., 208: 221-230 (1986)

Affected parent and younger age of proband with adenoma as predictors for increased risk of colorectal cancer in siblings.

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The National Polyp Study was designed to assess whether familial risk for colorectal cancer varied by characteristics of the adenoma proband. Newly diagnosed adenoma probands from seven clinical centers were interviewed for cancer and vital status of first degree relatives. Based on the Cox proportional hazards model earlier age of adenoma diagnosis and a parent affected with colorectal cancer were independent predictors for colorectal cancer in 2508 siblings of adenoma probands. The hazard ratio was 5.2 ($P<0.0001$) for adenoma proband diagnosis at age < 55 and 2.7 ($P<0.0001$) for adenoma proband diagnosis at ages 55-64 relative to diagnosis at ages 65+. The hazard ratio was 3.7 ($P<0.0001$) for having a parent with colorectal cancer relative to both parents unaffected. The increased risk of colorectal cancer in siblings of adenoma probands diagnosed at age < 55 years and with an affected parent suggests there is a subgroup of families with an increased susceptibility for developing adenomas and subsequently colorectal cancer. These families could benefit from screening and surveillance.

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