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Joint segregation and linkage analysis compared to separate analyses when estimating the recombination fraction. C.L. Faucett, W.J. Gauderman, and D.C. Thomas. University of Southern California, Los Angeles, U.S.A.

Linkage analysis is usually performed by fixing penetrance parameters and allele frequencies to values obtained from prior segregation analyses. Using simulation, we investigated whether improved estimates of the recombination fraction (θ) are obtained by simultaneously estimating penetrance parameters, allele frequencies, and θ. A dichotomous disease, depending on a dominant, diallelic disease gene linked to a diallelic marker was assumed. For the separate analyses, SAGE REGD was used to estimate parameters, followed by a linkage analysis using LODLINK. The joint analysis was accomplished using Gibbs sampling. The simulation studies, each based on 50 replicate data sets, showed (see Table) that bias and efficiency of θ estimates, as well as the power to detect linkage, were improved by doing the joint analysis when θ was small.

True θ	Mean (SD) of estimates Separate (S)	Joint (J)	% POWER S	J
0.01	0.045 (0.06)	0.041 (0.05)	96	100
0.05	0.092 (0.08)	0.091 (0.07)	84	92
0.10	0.112 (0.09)	0.101 (0.08)	80	86
0.25	0.278 (0.18)	0.264 (0.18)	28	26
0.50	0.478 (0.17)	0.494 (0.16)	4	2

Detecting gene-environment interactions in segregation, linkage, and candidate gene analyses. W.J. Gauderman, C.L. Faucett, and D.C. Thomas. University of Southern California, Los Angeles, U.S.A.

We investigated estimation of GxE relative risk (RR) in the context of segregation (S), joint segregation and linkage (SL), and candidate gene (CG) analyses. We simulated dichotomous disease data depending on a diallelic gene, a continuous environmental covariate, and their interaction. Diallelic linked marker genes were also simulated at varying values of the recombination fraction (θ). Two series of 50 replicate data sets were generated, one series with true GxE RR=2.7 and the other with true GxE RR=7.4. Candidate gene analysis was accomplished using SAS PROC LOGIST, treating the simulated disease gene as an observed covariate. All other analyses were performed using Gibbs sampling. The results show that GxE RR estimates are nearly unbiased for all analyses, that efficiency increases as θ decreases, and that a candidate gene yields substantially higher efficiency than a tightly linked marker.

Analysis	Mean estimate RR=2.7	RR=7.4	Relative Eff. RR=2.7	RR=7.4
S	2.86	7.24	100%	100%
SL θ=.25	3.22	7.61	118%	102%
SL θ=.01	2.77	7.54	143%	130%
CG	2.69	8.17	426%	369%

Variation in HLA allelic risk of childhood insulin dependent diabetes in the Finnish population.
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Variation in the risk of IDDM across alleles at HLA A, B, and DR loci was investigated in 801 families of incident diabetic children diagnosed between 1986 and 1989. Parallel analyses assessed the relative frequencies of alleles in diabetics compared to age-matched sibling controls and to the four possible genotypes which could have been inherited. For the purposes of this descriptive analysis, we assumed allelic risks act multiplicatively in a conditional logistic regression. After controlling for the correlation between alleles, significantly elevated risks were found for B13, DR3, DR4, or DR13 alleles with carriers at more than twice the risk as non-carriers; alleles A24, B60, and B62 incurred relative risks between one and two. B51 and DR2 were significantly negatively associated with IDDM incurring less than half the risk. Unlike many populations, the relative risk for DR3/4 is well described by the product of the marginal effects DR3/x and DR4/x.

The effect of severity dependent ascertainment on risks to first degree relatives. J.N. Bailey and D.L. Pauls. Yale University School of Medicine, CT USA.

If severity is related to familial transmission, proband ascertainment through clinics could affect patterns of illness in the family. This simulation study was undertaken to examine the effect of severity dependent ascertainment on the risks to first degree relatives. A population of 100,000 nuclear families (with 1-7 children) was simulated. A mixed model was generated with prevalence of 10%. Parents were randomly assigned a liability score for the polygenic background and a major genotype (two allele system, q=0.05). Children were assigned liabilities based on their parents' mean liability score (and a heritability of 0.7), and a genotype based on Mendelian inheritance. Two ascertainment strategies were employed: 1)random ascertainment of affected cases (RAAC) independent of phenotypic severity; and 2) severity dependent ascertainment (SDA) in which the probability of being ascertained was a function of the severity of the individual's illness. Three different ascertainment probabilities (pi) were used: 0.01, 0.1, and 0.5. The results of the simulation showed that severity dependent ascertainment appears to increase the risks to relatives and affects the distribution of illness in the family. For example, when pi=0.01 the RAAC risks to parents and sibs were equal (0.37 vs 0.39), while the comparable risks calculated by SDA were 0.39 and 0.56. A similar pattern was seen for the other ascertainment schemes. Present work is being performed to examine the SDA bias in genetically heterogenous populations.

Beyond Baconian-Cartesian Mendelism: Genetics of common multifactorial diseases. C.F. Sing, S.L. Reilly and K.E. Zerba. University of Michigan Medical School, Ann Arbor, U.S.A.

An emerging challenge facing those who are concerned about the efficacy of public health programs is to understand how information from the DNA revolution might be used to improve our ability to predict the initiation, progression and severity of a common disease having a complex multifactorial etiology. We first discuss the features of a realistic biological model for studying such diseases. Then we will present evidence for complexity in the relationship between genome type variation and variation in risk of coronary artery disease (CAD). A review of our preliminary studies to determine whether information about genome type variation can improve our ability to predict the distribution of CAD among individuals in the population at large should convince all but the most ardent reductionists that new analytical methods are necessary to deal with the plethora of genome type information available for the evaluation of risk of a common disease like CAD. This shift in the research paradigm will build upon new strategies to understand the organization of natural systems that are coming from outside the mainstream of genetic research.

Noninsulin-dependent diabetes mellitus aggregates in families independently of body mass index. B.D. Mitchell[1], C.M. Kammerer[2], J.W. MacCluer[2], M.P. Stern[1]. Univ. of Texas Health Science Center[1] and Southwest Foundation for Biomedical Research[2], San Antonio, TX.

Noninsulin-dependent diabetes mellitus (NIDDM) and obesity both aggregate in families. Because obesity is a risk factor for NIDDM, we asked the question, "Does NIDDM aggregate in families independently of obesity?" To address this question, we examined the prevalence of NIDDM in 2 sets of families: 1 set ascertained on a diabetic proband (n=42 families; 207 1st degree relatives) and 1 set ascertained on an individual without diabetes (n=32 families; 108 1st degree relatives). As expected, the prevalence of NIDDM was higher in the 1st degree relatives of the diabetic probands than in the 1st degree relatives of the nondiabetic probands (30.0% vs 19.4%; p = .04). To account for differences in body mass index between the groups, these comparisons were then repeated for lean, moderate, and obese subjects separately. At each level of obesity, relatives of diabetic probands had higher NIDDM prevalence than relatives of nondiabetic probands (lean: 15.8% vs 6.7%; moderate: 29.6% vs 9.1%; obese: 39.2% vs 36.4%). These results suggest that familial aggregation of NIDDM cannot be explained entirely by familial aggregation of body mass index. Supported by NIH grants RO1-DK42273 and PO1-HL4522.

A family study of Early-Onset Alzheimer disease in three-generations french pedigrees.

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A family study was undertaken in order to investigate the characteristics of familial aggregation of early-onset (≤60 years) Alzheimer disease (EOA) in a sample of 69 French families. Data were systematically collected on the sibships of probands, of their father and their mother. Genetic models that could account for the data were assessed using survival methods. Lifetime risks for first (n=360) and second (n=299) degree relatives and the distribution of the mean age-of-onset by family were first investigated. Then, the analysis of the disease segregation within the three sibships was undertaken using a maximum likelihood approach and under different age at onset distributions. The estimated lifetime risks by age 80 for relatives of probands are : father (≤8%), mother (20%-46%), uncles (≤4%) and aunts (4%-19%). These results show that either the penetrance is not complete by age 80 (H1) or that there are non genetic cases among our EOA probands (H2). The segregation analysis allowed us to discreminate between these two hypotheses. H1 is firmly rejected ($p<10^{-6}$). The proportion of genetic cases among our EOA probands is estimated to be 0.16 ± 0.065 and the cumulative risks predicted for carriers and non disease carriers by age 80 are equal to 0.89 and 0.03 for males and equal to 1 and 0.15 for females.

Methods for the analysis of associations between binary traits and markers from family data.

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It is often of interest to analyze associations between binary traits of unknown genetic etiology and genetic markers from pedigree data. The statistical methods assuming independence of pedigree members cannot be used because they disregard the statistical dependence arising from the biological relationships and shared environments of members in a pedigree. Two procedures are developed for studying the association between genetic markers and binary disease traits. Both are based on a likelihood ratio test and both treat the binary trait as though the trait was continuous. The first procedure assumes a constant variance whereas the second one uses a logistic function as the mean and allows the variance to be mean dependent. Both methods' validity are assessed and compared to the validity of a model for quantitative traits. The first method performs well when compared with the model for quantitative traits, but the second method does not perform as well as the first.

Genetic control of basal IgE level after accouting for specific atopy

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The genetic control of the total level of IgE, the immunoglobulins involved in atopic allergy remains still unclear. Although high IgE levels were found to be determined by a recessive major gene in several studies, other modes of inheritance have also been reported. To elucidate the different genetic factors controlling the basal IgE level and the general or specific allergic response, data including total IgE level, skin test reaction, specific IgE level and clinical symptoms were collected on a random sample of 234 Australian nuclear families. The focus of the present study is to clarify the genetic component regulating the basal IgE level independently of the IgE response to specific allergens (atopy). The class D regressive model was used to conduct segregation analysis of the age and sex adjusted total IgE level, with or without atopy as a covariate. When presence of atopy is ignored, the familial transmission total IgE level is

compatible with the segregation of a recessive major gene and residual familial correlations. When presence of atopy is accounted for in the analysis, whether defined by the positivity of skin tests for at least one allergen or by raised specific IgE level to at least one allergen, there is still evidence for a recessive major gene controling IgE levels but the residual familial correlations are no longer significant. The recessive major gene which accounts for 28% of the variance of the trait appears to control basal IgE level, independently of atopy.

Identification of that gene by linkage studies would facilitate the detection of other genes involved in the complex allergic process.

Linkage of LDL particle size and insulin levels to the apoA1C3A4 gene cluster: Evidence from relative pairs in pedigrees. RM Cantor[1], C Warden[2], B Lokensgard[2], Y-DI Chen[3], GM Reaven[3], X Bu[1], RM Krauss[4], AJ Lusis[2], JI Rotter[1]. [1]Cedars-Sinai Med Ctr, LA, CA, [2]UCLA, [3]Stanford Univ, [4]Lawrence Berkeley Lab.

We have previously reported that small LDL particle size and elevated insulin levels correlate within families enriched for coronary artery disease. Using quantitative sib-pair linkage analysis and a candidate gene approach, we found evidence for linkage of both phenotypes to the apoA1C3A4 gene cluster (n=43, p=.02) (Rotter et al, AJHG, 51:A26, 1992). The sib-pair approach, however, does not make use of the many other tested family members.

Using the statistical linkage method recently proposed by Olson and Wijsman (Genetic Epid 10:87, 1993) which analyzes data from all relative pairs in pedigrees, we tested these traits for linkage to the same gene cluster (with a C3 gene trinucleotide repeat) on data from 14 pedigrees including 41 sib, 29 avuncular, 20 first cousin, 12 grandparental, and 20 other more distant relative pairs. Results of these analyses strengthen the evidence for linkage of LDL particle size (p=.004) and insulin levels (p=.0001) to apoA1C3A4. Thus the use of additional relative pairs can significantly increase the information derived from a given set of pedigrees.

The unravelling of gene-environment interaction in disease etiology: opportunities and challenges. M. J. Khoury, Birth Defects and Genetic Diseases Branch, CDC, Atlanta, Georgia USA

With rapid advances in molecular genetics and progress in the human genome project, the coming decades will witness the continuous unravelling of the role of genetic factors and their interaction with environmental factors in the etiology of human disease. The increasing recognition and realization that all diseases are the result of interactions between genetic and environmental determinants will present both increasing opportunities and real challenges in the prevention of human diseases. By using illustrations on specific disease entities as well as theoretical considerations, I will briefly discuss the following issues: 1) the need for increasing resources in the search for gene-environment interactions, 2) the need for continued integration of genetic and epidemiologic study methods along with multidisciplinary approaches to the study of human diseases, 3) the need for improved biological markers of genetic susceptibility, 4) the need for improved biological markers of environmental exposures, 5) the need for better classification of disease endpoints, and 6) the need to translate scientific findings into disease prevention and health promotion in families and populations.

Coronary heart disease in a new multicenter genetic epidemiological family study: The Family Heart Study. D.C. Rao[1], G. Heiss[2], and M.A. Province[1] for the Family Heart Study Investigators. [1]Washington University Medical School, St. Louis, MO and [2]University of North Carolina, Chapel Hill, NC, U.S.A.

The primary goal of the Family Heart Study (FHS) is to evaluate genetic and non-genetic determinants of coronary heart disease (CHD) and cardiovascular risk factors in 600 randomly sampled families and 600 high CHD risk families. All 1,200 families will have comprehensive clinic evaluations and a variety of risk factors will be measured. Biological material will be stored for future studies. Previously collected (partial) family history data on 14,691 subjects at the 4 field centers have been used to calculate a family risk score for each family, one that quantifies the excess family risk [FRS = $(O-E)/\sqrt{E}$, where O is the observed number of CHD events in the family, and E is the expected number of events based on the gender and age distribution in the family]. Three categories of family risk are defined: Low (O=0 and FRS <-.5), High (O ≥ 2 and FRS ≥ .5), and Medium (all others). Some characteristics of the 3 categories are shown below using data from the two ARIC centers participating in FHS:

		Family Risk Category			
		Low	Medium	High	Total
Total N	:Whites	2,008	4,888	666	7,562
	:Blacks	114	340	31	485
Mean FRS		-.84	-.08	1.54	-.14
%hypertension	:Whites	22	25	33	25
	:Blacks	50	48	77	50
%obese	:Whites	33	35	39	35
	:Blacks	57	48	65	51
%high HDL	:Whites	30	29	21	29
	:Blacks	30	32	10	30

Distributions of risk factors and FRS are evaluated in each of the risk groups. The role of FRS is examined as an independent risk factor in predicting CHD risk at an individual level. In all, about 150 of the 600 random sample families are expected from the low risk category. This study offers great opportunities for studying special sub-groups of interesting families, including low risk families with high risk factors and high risk families with low risk factors.

Combining Two-Point Genetic Linkage Analyses using Mapping Functions.

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A likelihood ratio statistic is proposed for combining two-point genetic linkage analyses when the two-point analyses are between a trait and a well-defined map of markers. This method, similar to that proposed by Baron et. al [Nature 326:289-292, 1987], allows one to maximize the amount of linkage information obtained from several linked markers without the burdensome calculation of multipoint likelihoods. It is assumed that the inter-marker distances are known, which is reasonable for many markers currently available; a mapping function is specified; and the two-point analyses are independent, as in the case of choosing only the most informative marker per family. The asymptotic distribution of the likelihood ratio statistic is derived under the null hypothesis of no linkage of the trait with a map of 2 markers, with inter-marker genetic distance Δ. This distribution is shown to be a chi-square mixture distribution with mixing probabilities depending on Δ and the assumed mapping function. We use this asymptotic result to approximate the distribution of the likelihood ratio statistic for the more general case of more than 2 markers. Simulation results indicate that (1) the probability of claiming a false linkage between a trait and a known map of markers, i.e. Type I error, is adequately approximated by our method; and (2) our method, which constrains the inter-marker distances to their known values, tends to be more powerful than other methods proposed in the literature that do not constrain inter-marker distances.

Estimating sample size needed to detect gene-environment interaction in case-control studies.

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It is becoming increasingly important to systematically test for gene-environment interaction when considering the effects of an environmental exposure. Here we present a method for estimating minimum sample size and power in a case-control study of gene-environment interaction where certain marker genotypes in or near a candidate gene are hypothesized to increase susceptibility to an environmental exposure.

Two assumptions are made: 1) the prevalence of exposure is independent of the marker genotype among controls, 2) the control group is representative of the general population with respect to exposure and marker genotypes. Given these assumptions, six parameters (3 odds ratios, the prevalence of exposure, the proportion of susceptible, and the ratio of controls to cases) dictate expected cell sizes in a 2*2*2 table contrasting susceptibility, exposure and disease. The three odds ratios reflect the association between disease and (1) exposure in non-susceptibles (2) susceptible genotypes among non-exposed individuals and (3) the gene-environment interaction itself. Given these parameters, the number of cases and controls needed to assure any particular type I and type II error rates can be estimated.

For example, if the frequency of exposure is between 20 and 60% and proportion of susceptibles is 30%, studies with 119-147 cases and 2 controls per case will be able to detect gene-environment interaction with a $\geq$4-fold increase in risk among susceptibles with 80% statistical power and 5% type I error. This demonstrates that the case-control design can be used to detect gene-environment interactions when there are both a common exposure and a highly polymorphic marker of susceptibility.

Epidemiology of birthweight in a cohort of Norwegian sibs.

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Low birthweight is often associated with infant morbidity and mortality. Prior research has reported that maternal age, parity, smoking status of the mother, socioeconomic status of the mother, prenatal care, gestational age, and gender are factors associated with birthweight. This study uses data on 9,623 pairs of sibs from Norway to confirm these risk factors, while considering sibship correlations in birthweight.

First, the 9,623 sib-pairs were analyzed using multiple linear regression to estimate coefficients of predictors for both birthweight and ponderal index (weight/length^3), separately for first and second born children. Similarly, logistic regression was used to identify predictors related to intrauterine growth retardation (IUGR), low ponderal index (LPI), and small-for-gestational age infants (SGA). Second, an artificial dataset was created from a random sample of 4,500 first births and a random sample of 4,500 unrelated second births. Under this strategy, birth order was included as a new predictor. Maternal and infant covariates affecting birthweight and ponderal index, IUGR, LPI, and SGA infants were again studied. Finally, the third approach involved all of the subjects (n=19,246). Regression models including an intraclass correlation were fit to these data.

For all first births, a strong association was found between birthweight and both gestational age and gender (R^2=0.07). Ponderal index, however, was poorly predicted by all risk factors, although gender and maternal age were significant (R^2=0.007). For second births, birthweight was associated with gestational age, sex of the infant, maternal age, and birthweight of the first born (R^2=0.32). For ponderal index, significant predictors were gender, birthweight of the first infant, and gestational age (R^2=0.06).

Although the percentage of variance explained by each of these models was modest, in all cases the weight of the firstborn sib was a significant predictor and should be incorporated into predicting the weight of future births.

Segregation analysis of HDL3 levels in families of patients undergoing coronary arteriography at an early age. J. Coresh[1], T.H. Beaty[1], V.L. Prenger[2] and P.O. Kwiterovich Jr.[1]. [1]Johns Hopkins Medical Institutions & [2]University of Maryland, Baltimore, MD.

High density lipoprotein level (HDL) is a risk factor for coronary heart disease. HDL3, the subfraction of HDL with density >1.125 g/ml, includes newly secreted HDL particles. We studied the hypothesis that a major gene exists for HDL3 levels. The study population included 695 family members of 116 subjects who underwent coronary arteriography at an early age (men ≤ 50 and women ≤ 60). HDL3 level was measured after preparative ultracentrifugation on plasma of density >1.125 g/ml. Segregation analysis using REGC in S.A.G.E was conducted on unadjusted HDL3 levels since the influence of covariates on HDL3 level was small ($r^2=.01$, vs. $r^2=.15$ for total HDL). The familial correlations for HDL3 levels were: spouse $.03\pm.08$, parent-offspring $.14\pm.05$ and sibling $0.24\pm.05$. A mixed model with means at 30.0, 36.2 and 48.2 mg/dl and relative frequencies of 52%, 40%, and 8% fit the data better than a model with familial correlations but no major gene ($\chi^2=22.8$ d.f. 3, $p<0.001$). Compared to the most general model, this mixed model gave a marginally poorer fit ($\chi^2=7.9$ d.f. 3, $p=0.05$) but a non-transmitted model with residual familial correlations fit much worse ($\chi^2=14.6$ d.f. 3, $p=0.002$). These results suggest the presence of a major gene for high HDL3 levels similar to previous findings for apoAI in this study population.

Genetic and epidemiologic analysis of rheumatoid arthritis. A.H. Lynn[1], C.K. Kwoh[1,2], C. Venglish[2], C.E. Aston[1], T.A. Osial, Jr.[2], C. Vavassori[1], M. Trucco[1], A. Chakravarti[1]. [1]University of Pittsburgh and [2]Saint Margaret Memorial Hospital, Pittsburgh, PA, USA.

Patterns of risk were examined in the first degree relatives of 166 probands with rheumatoid arthritis (RA) identified from a consecutive series of patients who were ascertained without regard to family history. There were 135 simplex and 30 multiplex families (one family contained two probands). The sex ratio for probands in multiplex families (1:1) was significantly different from that for simplex families (1:2.6) ($p < .01$).

A statistical test of familial aggregation, using gender and age as predictors of risk, revealed 19 multiplex families with excess risk. The most parsimonious log-linear model for familial risk included gender of the proband, a dichotomy of multiplex or simplex family and the interaction between these factors. The risk of RA among first degree relatives varied by gender and age of the relative and the proband, with the greatest risk being observed in young female relatives of young male probands.

Complex segregation analysis on the total sample, using the computer program POINTER, showed that a recessive major gene model (displacement t = 7.2 units, mutant frequency q = .005) best explained the observed pattern of inheritance. Further analysis, in which families were subdivided by gender of the proband, revealed a recessive model (t = 3.8, q = .008) in families with male probands and sporadic occurrence of disease in families with female probands.

39 probands in 25 multiplex and 13 simplex families were genotyped for HLA-DR alleles at the DNA level. Alleles 0404, 0408,1601 and 1104 were found in significant excess when compared to a control population. Analysis of the cosegregation of HLA-DR haplotypes and RA, using the affected-pedigree-member method in 15 of the multiplex families, resulted in significant evidence of cosegregation.

The pattern of risk of RA in these families is thus heterogeneous, with gender of the proband, age of onset and HLA genotype being important factors. For future genetic analyses, families with male probands and probands with younger age of onset may be the most informative in further defining the proposed recessive gene and the formal genetics of RA.

Another quantitative measure of familial loading. A.F. Wilson[1], E.W. Pugh[1], B.E. McDermot[2], F.J. Sautter[2]. [1]Louisiana State University Medical Center and [2]Tulane University Medical Center, New Orleans, LA.

The presence of a positive family history is often taken to be an indication of a genetic and/or a familial environmental effect. Several measures have been previously proposed to quantify the level of familial loading (familiality) within a family - ranging from simply counting the number of affected individuals among first degree relatives to calculating the likelihood of family under a presumed genetic model. A simple measure that produces a continuous measure over the unit interval is proposed. The measure does not require assumptions concerning disease incidence or a specific genetic model.

Denoting the coefficient of relationship for a class of relatives to the proband as r_i, and the proportion of affected individuals in that class as f_i, the degree of familial loading (F) can be represented as:

$$F = \left(\sum_i^n r_i f_i\right) / \sum_i^n r_i$$

The method is illustrated using six traits related to measures of neuropsychological performance in families with schizophrenia. Approximately half the families are family history positive and half are family history negative.

Susceptibility markers and TCDD toxicity.
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Genetic susceptibility factors may modulate the toxic effects of exposures such as 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). Prior to the study of a large TCDD exposed population, we have investigated 20 healthy Caucasian volunteers with a set of putative susceptibility markers: a *CYP1A1* MspI restriction fragment length genetic polymorphism (RFLP), *CYP1A1* mRNA expression, and Ethoxyresorufin-O-deethylase activity (EROD), in peripheral blood lymphocytes. EROD activity was measured in cultured cells by the method of Pohl and Fouts (1980). For the *CYP1A1* genotype, a PCR was used to amplify a 298 bp fragment surrounding an MspI RFLP locus 3' to the last exon of *CYP1A1* (Hayashi et al, 1991). Slot-blot *CYP1A1* mRNA analysis with ^{32}P-labeled cDNA probes was performed (Cosma et al, 1992). EROD activity was significantly higher in persons with less frequent mutant *CYP1A1* genotypes in either basal ($p=0.008$) or induced ($p=0.0001$) conditions. Induction by TCDD significantly increased EROD activity in both mutant and wild type *CYP1A1* subjects, however the absolute increase was evidently larger in the former. An additive interaction between genotype and TCDD induction is suggested: the mean of the differences (but not of the ratios) between induced and basal EROD values was significantly ($p=0.0001$) larger among subjects with mutant genotypes than among wild type subjects. *CYP1A1* mRNA expression, both basal and induced, did not vary across the genotypes.

Correlations of age at diagnosis and other epidemiologic factors with loss of heterozygosity on chromosome 17q among cases with multiple primary cancers of the breast and ovary.
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To further study the genetic overlap of breast and ovarian cancer on chromosome 17q, we present analyses of LOH on chromosome 17q12-21 using paraffin-embedded tumor tissue from a unique population of patients with multiple primary cancers of the breast and ovary. All patients included in this study were identified at the tumor registries of the University of North Carolina Hospitals or Duke University Medical Center and had both primary and tumors diagnosed between 1970-1990. The prevalence of LOH on chromosome 17q in breast and ovarian tumors was found to be 46% and 78%, respectively. The mean age at diagnosis of patients with breast cancer was 10 years younger when the tumors displayed LOH on chromosome 17q was 10 years greater than those with no LOH on chromosome 17q. However, statistically significant younger ages of diagnosis of both breast and ovarian cancer were detected among tumor-pairs with LOH in the breast tumor or both tumors as compared to tumor-pairs with LOH in the ovarian tumor only. Our data support the concept that chromosomal region 17q12-21 is important in early onset multiple primary breast and ovarian cancers and the site of a tumor suppressor gene. Correlations between menopausal status, parity, race, histologic subtype, grade and LOH on 17q were also analyzed. Associations between grade and LOH on 17q for both breast and ovarian tumors were found. We propose that LOH on chromosome 17q among breast tumors from multiple primary breast-ovarian cancer patients is a marker for a small subgroup of early onset breast and ovarian cancers with a common genetic etiology.

Interactions of ApoE Genotype, Cholesterol Level, Age, and Sex in Prediction of Alzheimer Disease.
GP Jarvik, GD Schellenberg, EB Larson, WA Kukull, EM Wijsman. U. Washington, Seattle, USA.

Linkage and association studies of the apolipoprotein (apo) E/CI/CII gene cluster implicate this region in late onset Alzheimer disease (AD). The apo E, e4 allele has been reported to be in excess in AD. E4 is also associated with elevated total cholesterol levels (TC). Therefore, the relationship between AD, apoE genotype, TC, age, and sex was explored in an unmatched case-control cohort of elderly Caucasians, mean age 79 yrs. E4-containing genotypes were more frequent in cases, 67 of 153, than in controls, 75 of 228 ($p=.03$). E4 frequency declined significantly with age. TC was lower in AD cases than in controls ($p<.005$). Genotype-by-TC-by-age-by-sex ($p=.007$), genotype-by-sex ($p=.008$), and genotype-by-age ($p=.07$) interactions and age ($p<.003$) were predictive of affected status using logistic regression.

Current TC levels do not fully explain the e4-AD association; however, higher TC levels earlier in life may be involved. Nutritional differences after the onset of disease may explain the lower TC seen in AD cases. Evidence of apoE genotype effects on TC's response to diet has been described, and diets or TC responses may differ between sexes. Such differences are a possible explanation of the 4-way interaction in prediction of Alzheimer disease status.

Heritability of waist-to-hip ratio in adult women: The Iowa Women's Health Study. T.A. Sellers, C. Drinkard, S.S. Rich, A.R. Folsom. University of Minnesota, Minneapolis, MN.

There is increasing recognition that the distribution of body fat centrally rather than peripherally is associated with an increased risk for a variety of chronic diseases. Consequently, there is considerable interest as to the heritability of body fat distribution. Since few studies have been performed on adult relatives, we studied nuclear family members of 311 participants in the Iowa Women's Health Study - a prospective study of 41,837 women between the ages of 55 and 69 at baseline in 1985. A total of 611 living sisters (mean age 65.7 years) and 415 living daughters (mean age 41.2 years) were identified through a mailed 'family tree'. Family members were then mailed a questionnaire to obtain self-reported measures of current height and weight. A paper tape measure and written instructions were enclosed to obtain circumferences of the waist and hips, a technique we have validated. Sister-sister and mother-daughter correlations were computed using the FCOR program of S.A.G.E. The age-adjusted correlations of waist-to-hip ratio and body mass index (kg/m^2) were 0.19 and 0.23, respectively, between mothers and daughters ($p < 0.05$). The corresponding correlations between sisters were 0.23 and 0.19, respectively ($p < 0.05$). After adjustment for body mass index the correlation of waist-to-hip ratio increased to 0.20 for mother-daughters and 0.26 for sisters. These data suggest the heritability of waist-to-hip ratio is nearly 50% in adult women.

Familial risk of breast cancer among relatives of postmenopausal breast cancer patients. P-L. Chen, T.A. Sellers, S.S. Rich, J.D. Potter, A.R. Folsom. University of Minnesota, Minneapolis, Minnesota.

Studies consistently demonstrate that close relatives of breast cancer patients are at a two- to three-fold excess risk of breast cancer. However, none examined possible confounders in first-degree relatives, precluding the ability to discern between shared environment or genes as the cause of familial aggregation. A nested case-control study was conducted in 1988 -1989 of 485 Iowa families. Incident breast cancer case probands were selected from a prospective cohort study. Control probands were matched by age, in a 1:1 ratio. A 'Family Tree' form was mailed to identify first degree female relatives. A questionnaire and body measurement protocol were mailed to identified living relatives or surrogates. Most mothers of probands were deceased and most daughters of probands were unaffected. Sisters of case probands were 50% more likely than control probands to have developed breast cancer (p=0.18). Logistic regression models were fitted to predict odds of breast cancer adjusted for the effects of non-genetic risk factors (e. g. body mass index, waist-to-hip ratio, etc.). Sisters of breast cancer probands remained at an increased risk of both early-onset (age<50 years, odds ratio (OR)=1.59, p=0.48) and late-onset (age≥50 years, OR=1.81, p=0.14) breast cancer. These data suggest that risk to sisters of postmenopausal breast cancer probands is evident for early- and late-onset breast cancer and is not accounted for by other risk factors.

The French Wilms' tumor study: no clear evidence for cancer prone families.

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Wilms' tumor of the kidney is known to occur in the context of the Beckwith-Wiedemann syndrome. It has also been described in three cancer-prone families displaying a Li-Fraumeni syndrome but it is not usually considered to be part of this syndrome. In order to detect particular cancer familial aggregations associated with this tumor, we studied cancer incidence and mortality among relatives of the 501 Wilms' tumor patients of the French Wilms' tumor Study. We found no familial association with breast cancers and soft tissue sarcomas which are the most common cancers of the Li-Fraumeni syndrome. However, we found two significant familial associations of Wilms' tumor with bone cancers on the one hand, and with brain tumors on the other hand. These associations could reflect a small proportion of families segregating for some susceptibility gene. This should then be confirmed at a molecular level.

Familial Risk of Rheumatoid Arthritis. C.K. Kwoh[1,2], C.M. Venglish[1], D.M. Whitley[1], E. Young[2], A.H. Lynn[2], A. Chakravarti[2], T.A. Medsger, Jr.[2], [1]Saint Margaret Memorial Hospital, and [2]University of Pittsburgh, Pittsburgh, PA, USA.

The familial risk of rheumatoid arthritis (RA) was examined in the first degree relatives of 166 probands from a consecutive series of patients ascertained without regard to family history. Based on clinical evaluation (including structured history, physical examination and medical record review), there were 135 simplex and 30 multiplex families (one family contained two probands). All affected members met 1987 ACR criteria for RA.

Clinical evaluation of first degree relatives revealed 39 cases which had been falsely reported as RA, 40 verified cases of RA and no false negative cases. The crude rates of risk were 3.2% overall (40/1257), 4.2% for parents (14/330), 4.6% for siblings (25/546) and 0.7% for children (1/381). The risk of RA was 2.2% for male relatives and was 4.2% for female relatives. The relative risks for male and female relatives as compared to the general population were 12.1 and 10.6, respectively. There were no differences in average family size or number of years at risk between simplex and multiplex families. A statistical test of familial aggregation revealed 19 multiplex families with greater numbers of affected family members than would be expected. The sex ratio for probands in multiplex families (16 men: 15 women) was significantly different from that for simplex families (37 men: 98 women) ($p < .05$). The number of multiplex families decreased with increasing age of the onset in the proband and the age of onset was lower for probands in multiplex families as compared to those in simplex families (41 vs. 48, $p < .01$). The risk of RA among relatives varied by age of onset and gender of the proband, with greater risk associated with male gender and younger age of onset ($p < .005$).

We have defined the risk of RA among first degree relatives. The risk of RA varies, with gender and age of onset of the proband being the most important determinants.

The genetic epidemiology of hyperphenylalaninemias in Quebec. D.M. Lambert, K. Morgan and C.R. Scriver. McGill University, Quebec, Canada.

Newborn infants in the province of Quebec have been screened for both benign hyperphenylalaninemia (HPA) and phenylketonuria (PKU) since 1970 in order to identify individuals who require dietary management. Young adults with HPA or PKU are also offered genetic counselling. We reviewed the population database, case registry and annual reports of the newborn screening program to describe HPA, PKU and the screening program itself. HPA (1 in 25,000 births) and PKU (1 in 29,000 births) had similarly low average incidences. More males than females were affected with HPA: HPA, 50 ♂:28 ♀ (χ^2_1=5.2, $p<0.025$); PKU, 40 ♂:33 ♀ (χ^2_1=0.4, NS). The distributions of the births of PKU and HPA infants among the 10 administrative health regions were significantly different (χ^2_{10}=30.0, $p<0.001$) and were non-randomly distributed in the province compared to the general population of births (HPA: χ^2_{10}=23.6, $p<0.01$; PKU: χ^2_{10}=22.1, $p<0.025$). The ethnicity of HPA and PKU infants did not differ significantly (χ^2_{11}=12.8, NS).

Phenylalanine in the blood of newborn infants is measured by fluorometry of blood spotted onto filter paper. The mean phenylalanine values of the initial screening tests, over the past 20 years were 129.0 μmol/L in the normal newborn population, 403.0 μmol/L for HPA cases and 1100.6 μmol/L for PKU cases. There was seasonal variation of the monthly population phenylalanine values over 14 years of births (Friedman's χ^2_{11}=28.9, $p<0.005$): May through August ranked the lowest overall, while November and December ranked the highest.

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Comparison of Methods for Survival Analysis of Dependent Data using Simulated Data. TM King[1], TH Beaty[1], KY Liang[2]. [1]Department of Epidemiology, [2]Department of Biostatistics The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, U.S.A.

Survival analysis models for dependent data have many applications in genetic epidemiology. Analysis of dependent data with general Cox proportional hazard models results in unbiased estimates for regressions coefficients, but underestimates of the variance about these coefficients. This could result in erroneous conclusions about covariates. Two methods are proposed for analysis of dependent survival data. The first involves a direct correction of the variance for the clustered data structure. The second method is a multivariate marginal hazard model which conditions on the amount of correlation within a cluster. We analyzed simulated survival data using three models under a variety of conditions. To measure the performance of the three models, bias in the coefficient and the level of Type I errors were examined. All three methods provide an unbiased estimate of the regression coefficient. The conventional Cox proportional hazard model shows increasing Type I error with increasing levels of dependence within clusters. Both the variance correction method and the marginal hazard method have appropriate levels of Type I errors. These alternative methods are better suited for the analysis of clustered survival data.

The role of the angiotensinogen gene in human hypertension: Absence of an association among African Americans. C.N. Rotimi[1], R.S. Cooper[1], R.H. Ward[2] L. Morrison[2]. [1] Loyola University Stritch School of Medicine, Maywood, Illinois, U.S.A. [2] The University of Utah, Salt Lake City, Utah, U.S.A.

Data from a recent collaborative investigation of the angiotensinogen gene (AGT) in siblings from Utah and Paris, France found linkage between hypertension (Htn) and AGT, and demonstrated association of AGT molecular variant with Htn. In the present study the M235T molecular variant which demonstrated linkage and association among whites was examined in African Americans (AA).

Ninety-six AA subjects were selected from the participants of a population survey of Htn in Maywood, a suburb of Chicago. Cases (N=37) and controls (N=57) were selected from the extremes of the age-blood pressure (BP) distribution. Cases were younger individuals with high BP and controls were older individuals with low BP. BP, height, weight, hip and waist circumference were measured using a standardized protocol. Genotyping was conducted using standard PCR-based techniques.

The magnitude of the effect of the sampling procedure is evident in the following mean values for cases and controls respectively: age 41 vs 57 years; systolic BP 138.8 vs 119.1; diastolic BP 86.2 vs 65.4; and BMI (kg/m²) 32.4 vs 29.0. The frequency of the variant M235T was 82% for cases and 81% for controls, twice that observed among whites (Utah: cases=49%, controls=36%; Paris: cases=52%, controls=38% - Jeunemaitre et al. Cell 1992; 71:169-180). Although the molecular variant is higher in blacks, there is no indication that the variant has any influence on the population distribution of blood pressure. The frequency of this molecular variant may be higher among black populations without European admixture. To test this hypothesis we collected blood samples from adults in Ibadan, Nigeria and are performing the genotype assays.

Familial Resemblance of Cardiovascular Disease (CVD) Risk Factors among African Americans (AA) in the Chicago area. C.N. Rotimi, R.S. Cooper, C.B. Sundarum and G. Cao. Loyola University Stritch School of Medicine, Maywood, Illinois, U.S.A.

It is well established that AA experience disproportionately higher rates of CVD than do whites. Despite widespread speculation that persons of African descent are genetically susceptible to CVD and associated risk factors including high blood pressure (BP), few direct studies have been carried out. Understanding how measured phenotypic levels of established CVD risk factors, including BP, lipids/lipoproteins, blood sugar and insulin, are influenced by environmental and genetic factors is key to understanding the underlying biological mechanisms which lead to the observed racial differential and in understanding how CVD - including hypertension and coronary heart disease - aggregates in families.

Within the framework of an ongoing population study of persons of African descent living in the Chicago area, a sample of 23 families, including 106 individuals, has been recruited. Detailed family health information was collected on each family member and BP, height and weight were measured. Fasting blood specimens were collected for lipids/lipoproteins, glucose, and insulin. Buffy coat was separated and stored at -70°C for future genetic studies.

The mean age of the participants was 40.4 (range 15 to 85). The mean years of schooling was 11.7±2.1, mean body mass index (BMI) was high (29.9±7.5), mean blood sugar was 116.2±59.8, and mean total cholesterol was borderline desirable (men=181.7±38.4; women=196.1 ± 56.9). The intraclass correlation, based on the maximum likelihood variance component procedure, was used to measure the tendency for siblings or spouses to be similar to one another. The between-sister correlations were consistently larger than those between brothers and between spouses. Except for triglycerides, correlations between brothers were larger than for spouses. These findings demonstrate the feasibility of carrying out pedigree studies in this population and suggest that the pattern and magnitude of familial correlations are similar to those in previous studies of whites.

Susceptibility to insulin-dependent diabetes conferred by the HLA and the insulin gene

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We have analyzed a total of 159 normal controls and 199 unrelated patients with insulin-dependent diabetes (IDD) and 126 patients from multiplex families for the HLA and the insulin gene (*INS*). The 1127/*Pst*1 polymorphism at *INS* was analyzed using restriction digestion of PCR-amplified product and the HLA-DQB1 gene was typed using PCR and denaturing gradient gel electrophoresis. The strongest susceptible DQ allele is 0302 with a relative risk of 6.5 in our population. The DQ6 alleles confer stronger protection than DQB1*0301 allele. We have been able to confirm association between IDD and *INS* in both DQB1*0302-positive and negative individuals. The relative risk conferred by INS is much weaker in our population (RR = 2) than in the other populations. We used the observed versus expected genotypic frequencies at both DQ and INS to assess the interaction between these two regions and found that the relative risks conferred by all DQ alleles are approximately two times higher in the IDD susceptible *INS* subset than in the IDD protective *INS* subset, suggesting that there are no interactions between these two systems in IDD. We have also been able to define the hierarchies of susceptibility to IDD among various genotypic combinations at these two loci.

Transmission analyses of parental *INS* alleles to diabetic offsprings in 50 IDD families suggest that there is a significant increase of the IDD-associated allele in the male meiosis but not in the female meiosis. Julier et al. observed a similar phenomenon and suggested that maternal imprinting may be the best explanation. However, other mechanisms may account for the male transmission bias (e.g. gamete or zygote selection). To distinguish these hypotheses, we propose to examine the parental origin of the IDD-associated allele in diabetic offspring. Maternal imprinting would result in a significant increase of the IDD-associated allele inherited from the fathers. Our preliminary results do not support a maternal imprinting effect.

Apolipoprotein E4 gene dose and Alzheimer disease: Epidemiologic Implications. E.H. Corder,[1] A.M. Saunders,[1] W.J. Strittmatter,[1] D. Schmechel,[1] P. Gaskell,[1] G.W. Small,[2] A.D. Roses,[1] J.L. Haines,[3] and M.A. Pericak-Vance[1]. [1]Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University Medical Center, Durham, NC; [2]University of California, Los Angeles, CA; and, [3]Massachusettes General Hospital, Boston, MA.

In our cohort of 42 late onset (age > 60) Alzheimer disease (L-AD) families, the proportion affected increased from 20% to 91% and mean age at onset decreased from 84 to 68 years as apolipoprotein E4 (APOE4) gene dose increased from 0 to 2 [Saunders et al, in press; Strittmatter et al, 1993; Corder et al, submitted]. Here we show that most incident and prevalent cases of L-AD have 1 or 2 APOE4 despite the relative infrequency of the allele. Incidence was evaluated in 234 members of the pedigree cohort with age at onset or age at examination > 60 years. The difference between mean age at onset and mean survival (Kaplan-Meier distributions) increased with APOE4 gene dose (dose, years): 0, 0.6; 1, 3.1; and 2, 9.7. In all, 80% of affected subjects had 1 or 2 APOE4 compared to 30% of 116 control subjects over age 60. Prevalence was evaluated by comparison of onset and survival distributions in 95 familial and 103 autopsy-confirmed sporadic cases: 80% of familial and 85% of sporadic prevalent cases had 1 or 2 APOE4 compared to 30% of the control series. We conclude that the earlier onset conferred by APOE4 profoundly influences the incidence and prevalence of L-AD.

Segregation analysis of fat mass and fat free mass. A.G. Comuzzie[1], J. Blangero[1], B.D. Mitchell[2], M.P. Stern[2], J.W. MacCluer[1]. [1]Southwest Foundation for Biomedical Research, and [2]University of Texas Health Science Center, San Antonio, Texas, U.S.A.

Many studies have found an increased risk for several chronic diseases with increasing levels of obesity. The question that remains, however, is whether the accumulation of excess fat is itself a genetically mediated phenomenon. To address this question, a segregation analysis of fat mass and fat free mass, derived from bioelectrical impedance measures, was undertaken.

Data for this study were obtained from a large pedigree sample of Mexican-American individuals

residing in San Antonio, Texas (533 individuals in 44 families). Maximum likelihood techniques, as implemented in the program PAP, were used to compare a series of models with restricted parameterizations against a general model in which all parameters were estimated. Those models with a likelihood significantly worse than the general model were rejected.

The only model not rejected was a mendelian mixed model for fat mass, incorporating genotype-specific age and sex effects. Homozygous recessive individuals have a fat mass more than double that of individuals of the other two genotypes. No evidence of a major gene was detected for fat free mass. These findings support recent work by Rice et al. (1993) for these same measures of body composition derived from hydrostatic weighing.

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Genetic and dietary effects on complex traits. J.W. MacCluer[1], J. Blangero[1], and M.P. Stern[2]. [1]Southwest Foundation for Biomedical Research and [2]University of Texas Health Science Center, San Antonio, Texas, U.S.A.

Diet is suspected to be a major contributor to development of many complex diseases, including coronary heart disease, diabetes, and some cancers. However, genetic analyses of these diseases and their risk factors and precursors have tended to ignore dietary variables. Epidemiological studies have often included nutritional information, but the design of these studies generally precludes the possibility of detecting genetic effects. We review some of the known or suspected effects of nutrition on complex diseases and quantitative intervening variables, and describe methods for incorporating genetic and dietary effects and their interactions in analyses. Finally, we present evidence for interaction between genotype and diet in the determination of quantitative risk factors for coronary heart disease, diabetes, and obesity.

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Lp(a) and atherosclerosis. J.E. Eichner[1], W.E. Moore[1], N.Simpson[1], W.J.McConathy[2], E.Schechter[1] and D.W. Reynolds[1]. [1]University of Oklahoma Health Sciences Center and [2]Texas College of Osteopathic Medicine, [1]Oklahoma City, OK and [2]Fort Worth, TX, U.S.A.

A consecutive series of patients undergoing coronary angiographies in two Oklahoma hospitals are being studied for biological/genetic markers in relation to their degree of coronary artery disease (CAD). One of these markers is Lp(a). Lp(a) has been proposed as an independent, largely genetically determined, risk factor for CAD that increases risk partly because it is an atherogenic agent. In the first 84 white patients (72 males, 12 females), the odds ratio for cases ($\geq$ 50% average stenosis) to have exposure of 64 mg/dl or more of Lp(a) [75th percentile] compared to controls with < 64 mg/dl of Lp(a) and < 50% average stenosis is 2.9 (95% C.I. 0.9 to 9.5) [p=.09]. While these early data are not statistically significant at the p=.05 level, they show a trend for higher values of Lp(a) to be associated with increased severity of disease. As more patients and variables are collected, it will be possible to examine Lp(a) in subgroups of patients and in relation to other risk factors and markers of disease.

Segregation analysis of a relative fat pattern index (RFPI) in four Caucasian pedigrees. J.F. Korczak[1], A.F. Wilson[1], R.C. Elston[1] and R.M. Siervogel[2]. [1]Louisiana State Univ. Medical Center, New Orleans, LA, U.S.A. and [2]Wright State Univ. Medical School, Yellow Springs, OH, U.S.A.

Segregation analysis in pedigrees ascertained through cases of cardiovascular disease has previously suggested recessive inheritance of an allele for high RFPI, defined as subscapular skinfold thickness divided by the sum of subscapular and suprailiac skinfold thicknesses (Hasstedt et al., Am J Hum Genet, 1989). We sought to determine if RFPI follows a similar mode of inheritance in four Caucasian pedigrees previously described by Siervogel et al. (Hypertension 2 (Suppl 1), 1980). RFPI's were calculated for 463 individuals and then adjusted for age, sex, and family effects prior to segregation analysis using the transmission probability model. We found that the data fitted a mixture of two distributions significantly better than one distribution, and tested Mendelian and random major environmental effect models against a general two-distribution model with arbitrary transmission probabilities. A Mendelian model with high RFPI recessive had the lowest Akaike Information Criterion of all models examined and did not give a significantly worse fit to the data than the general model (χ^2=4.15, df=3). In the Mendelian model the proportions of low and high RFPI were 0.85 and 0.15 with means of 0.417 and 0.513, respectively. Both the Mendelian model with high RFPI dominant and the random major environmental effect model could be rejected at the α=0.1 level (χ^2=6.75 and χ^2=6.76, respectively, df=3). Our findings are consistent with those of Hasstedt et al. who, on the basis of a larger sample, were able to reject both the Mendelian model with high RFPI dominant and the environmental model at the α=0.05 and 0.005 levels, respectively.

Family history and concomitant clinical features in early-onset Alzheimer's disease. C.M. van Duijn, W.N. Samson, W.C.J. Hop, A. Hofman. Erasmus University Medical School, Rotterdam, The Netherlands.

The genetic etiology of early-onset Alzheimer's disease (AD) is heterogeneous. There is evidence for autosomal dominant inheritance and sporadic occurrence. The high percentage (40%-60%) of sporadic cases complicates molecular genetic and genetic epidemiologic studies. Early-onset AD is often associated with the development of extrapyramidal signs such as tremors and rigidity, myoclonus, psychosis and seizures. We have studied the occurrence of these concomitant clinical features and their relationship with family history of dementia in 198 patients with early-onset AD (onset before 65 years). The study comprised all patients living in two areas of The Netherlands. All cases met the NINCDS-ADRDA criteria for probable AD. Detailed information on the course of AD was collected by reviewing medical records of hospital clinics and nursing homes. Survival analysis was used to adjust for the duration of disease at intake and at last follow-up. The development of tremors and rigidity was not associated with family history of AD. Occurrence of myoclonus, seizures and psychosis early in the course of AD was significantly associated with the sporadic form. Myoclonus and seizures occurred significantly less frequent among patients with a pedigree structure compatible with autosomal dominant inheritance. These findings suggest differences between sporadic and familial AD at a phenotypic level and may have relevance to distinguish phenocopies in genetic research of AD.

Risk factors and familial aggregation of seizures and epilepsy. S.S. Rich[1], W.A. Hauser[2] and V.E. Anderson[1]. [1]University of Minnesota, Minneapolis, MN, and [2]Columbia University, New York, NY, U.S.A.

Epilepsy patients present with an array of clinical features and phenotypes. These heterogeneous phenotypes may be clarified by grouping families into "homogeneous" subsets on the basis of increased sibling risk with respect to relevant clinical variables. We present data that provides increased familial aggregation that may assist in defining subgroups of families suitable for mapping seizure susceptibility genes.

In our population, potential cases of seizure were ascertained through a surveillance system to identify patients presenting for evaluation of newly identified seizures. Interviews obtained medical, neurologic, family and social history.

A total of 1047 probands were ascertained. Life-table analyses of seizure risk to siblings uncovered no significant effect due to sex, intake etiology, or recurrence in the proband. Factors that led to an increased sibling risk were: early onset of seizures (< 25 yrs.: 3.4%; > 25 yrs.: 1.9%), parental history (none: 2.7%; positive: 3.3%), seizure type (partial 1.3%; generalized 3.6%), and EEG pattern (focal: 1.4%, generalized: 4.0%). Thus, selection for mapping studies should center on patients with early onset seizures with generalized seizure type and EEG pattern.

Gestational seizures and congenital malformations in offspring of probands with epilepsy. J.H. Lee, R. Ottman, and D. Warburton. Columbia Univ., New York, NY, USA.

Intrauterine exposure to antiepileptic drugs (AEDs) is known to cause congenital malformations (CMs) in offspring. However, among exposed offspring, the proportion with CMs is small; thus it is important to identify factors associated with differential susceptibility to CMs.

We obtained information on CMs and epilepsy in 1,831 offspring of probands with epilepsy via telephone interview. Verbatim descriptions of CMs were reviewed by a clinical geneticist, and only those confirmed to be major CMs were included in the analysis.

Univariate logistic regression showed AED polytherapy (odds ratio=1.8), gestational seizures (OR=3.5), idiopathic (vs. symptomatic) epilepsy in the proband (OR=2.8), CM in the proband (OR=9.8) and epilepsy in at least 2 offspring of the proband (OR=3.9) to be significant predictors of CMs in offspring. A stratified analysis showed that AEDs and gestational seizures were independent risk factors. When confounding was controlled using multivariate logistic regression, gestational seizures (OR=5.8), CMs in the proband (OR=10.1), and idiopathic epilepsy in the proband (OR=3.2) were significant, and the increased risk associated with AEDs disappeared. The increased risk of CMs associated with gestational seizures was similar regardless of whether or not the gestational seizures occurred in the first trimester.

These results indicate that gestational seizures are a risk factor for CMs, independent of AEDs, and this increased risk is not explained entirely by an increased dose of AEDs following uncontrolled seizures. The observed elevated risk may represent metabolic problems and/or severity of the epilepsy.

Measured genotype analysis of age at peak height velocity and a Bgl II chorionic somatomammotropin RFLP. B. Towne[1], J.S. Parks[2], M.R. Brown[2], T.C. Murphy[2], R.M. Siervogel[1]. [1]Wright State University School of Medicine, Yellow Springs, OH, and [2]Emory University School of Medicine, Atlanta, GA.

Growth hormone (GH) variation influences growth in stature during childhood, but the effects of GH variation on the timing of maturational events such as the pubertal growth spurt measured by age at peak height velocity (APHV) are less understood.

A GH cDNA was used to probe the GH/chorionic somatomammotropin (CS) gene cluster at 17q22-24. Presence of a Bgl II site 3' to the CS-1 gene produces a 10.5 kb fragment, while its absence produces a 12.7 kb fragment. Allele frequencies in 543 participants in the Fels Longitudinal Study were p (10.5 kb) = 0.715 and q (12.7 kb) = .285, with gene and genotype frequencies in Hardy-Weinberg equilibrium. APHV was calculated for 333 of these individuals who are from 112 kindreds.

A maximum likelihood method was used to estimate for APHV, genotype specific means for males (μ_{pp}, μ_{pq}, μ_{qq}), their female displacements (β_{pp}, β_{pq}, β_{qq}), sex specific heritabilities (h^2_M, h^2_F) and phenotypic standard deviations (σ_M, σ_F), and the additive genetic correlation between the sexes (ρ_G). The best model posited $\mu_{pp} \neq \mu_{pq} = \mu_{qq}$, $\beta_{pp} \neq \beta_{pq} \neq \beta_{qq}$, $h^2_M \neq h^2_F$, $\sigma_M \neq \sigma_F$, and $\rho_G = 1.0$.

This model suggests a dominance effect of the rarer (q) allele on APHV of males (μ_{pp} = 13.04 ± 0.17, μ_{pq} and μ_{qq} = 13.49 ± 0.17), and measured genotype by sex interaction on APHV of females (β_{pp} = -1.29 ± 0.20, β_{pq} = -2.32 ± 0.22, β_{qq} = -1.87 ± 0.32). These results indicate a complex effect of GH/CS variation on sex differences in APHV.

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Genetic susceptibility to Leprosy in a Brazilian population sample. M.F. Feitosa[1,2], I. Borecki[2], H. Krieger[3], B. Beiguelman[4], D.C. Rao[2]. [1]Dept. Genetica-FIOCRUZ, Rio de Janeiro, RJ, Brazil; [2]Div. Biostatistics-Washington Univ. School Medicine, St. Louis, MO, USA; [3]Dept. Parasitologia-USP, Sao Paulo, SP, Brazil; [4]Dept. Genetica Medica-UNICAMP, Campinas, SP, Brazil.

Leprosy is an infectious disease, caused by *Mycobacterium leprae*, which affects about 15 million individuals world-wide. The variation of the host's resistance to infection has been shown to be genetically controlled in animal models, and there is accumulating evidence that genetic factors also play a significant role in human Leprosy (Beiguelman, *Acta Genet.Med.Gemellol*,1972, *21*:21; Abel and Demenais, *Am. J. Hum. Genet.*., 1988, *42*:256). The majority of individuals exposed to bacillus develop effective immunity without disease. Others present a wide spectrum of clinical manifestations. At one pole of this spectrum are Tuberculoid (T) patients displaying a positive, acquired cell-mediated immunity against the bacillus; at the other pole are Lepromatous (L) patients who show an absence of specific cell-immune response to *M. Leprae*. Borderline (B) patients present variable degrees of the pole forms and Indeterminate (I) ones are transitional to all other Leprosy types.

Data on Leprosy patients have been obtained from "Dispensario de Lepra de Campinas", Sao Paulo State-Brazil, where records on practically all cases of Leprosy in the Campinas region during the period 1960-70 are filed. The whole sample comprises 10,886 individuals, distributed among 1,568 families with sibship size ranging from 1 to 15. Information was collected on sex, age at examination, age of onset, vital state (live or dead) and type of individual's disease (L, T, I, B or type unknown). To determine the nature of the genetic factors that may operate on the Leprosy and its subtypes, complex segregation analysis (Lalouel et al., *Am. J. Hum. Genet.*, 1983, *35*:816) was utilized. The results are consistent with the presence of a recessive major gene controlling susceptibility to Leprosy *per se*, and the gene frequency is estimated as approximately 0.05. Similar results are obtained for Tuberculoid - Leprosy, with evidence for a Mendelian gene (either recessive or codominant), with a frequency of 0.02. The results for Lepromatous - Leprosy also suggest a recessive major gene, although the estimation of the transmission parameters is inconsistent with a simple Mendelian mechanism.

Preferential zygotic assortment of the HLA-A2,Cw1,B56,DR4,DQ8 haplotype contributes to the high incidence of insulin-dependent diabetes mellitus (IDDM) in Finland. E. Tuomilehto-Wolf, J.Tuomilehto and the DiMe Study Group. Department of Epidemiology, National Public Health Institute, Helsinki, Finland.

Since 1950 - 25 years after the introduction of insulin - the incidence of IDDM has steadily increased in Finland (2.5% per year). It was 40/100,000/yr in the age group 0-14 years in 1991; three times higher than in 1950 and the highest in the world. We have carried out the first population-based prospective HLA family study in IDDM nationwide in Finland (801 families). We have already reported a new IDDM susceptibility haplotype HLA-A2,Cw1,B56,DR4,DQ8 only seen in Finnish IDDM patients that carries the highest absolute risk (218/100,000/yr).

After excluding all the diabetic index cases as they had been consecutively ascertained for the presence IDDM, we analyzed how often the A2,Cw1,B56,DR4,DQ8 haplotype was transmitted compared to the alternative parental haplotype to 99 siblings in 75 informative families. In 52 siblings from 41 families where the father had one A2,Cw1,B56,DR4,DQ8 haplotype it was transmitted to 24 offspring (46%)(3 with IDDM). In 47 siblings from 34 families where the mother had one A2,Cw1,B56,DR4,DQ8 haplotype it was transmitted to 29 offspring (62%)(3 with IDDM). Mothers transmitted the A2,Cw1,B56,DR4, DQ8 haplotype 23% more often than the alternative maternal haplotype. A sex-associated effect in the transmission of the A2,Cw1,B56,DR4,DQ8 haplotype was seen as 33 siblings (62%) were of the same sex as the parent from whom they had inherited it. Our data provide empirical evidence that the A2,Cw1,B56,DR4,DQ8 haplotype contributes to the high and increasing incidence of IDDM in Finland by enlarging the pool of susceptible individuals through preferential zygotic assortment.

Is there a major gene for the HDL-C/LDL-C ratio? K.A. Weissbecker[1,2], G.S. Berenson[2], A.F. Wilson[1], S.R. Srinivasan and R.C. Elston[1]. [1]L. S. U. Medical Center and [2]Tulane Univ. School of Public Health, New Orleans, LA.

The ratio of high density lipoprotein cholesterol levels (HDL-C) to low density lipoprotein cholesterol levels (LDL-C) is a known risk factor for cardiovascular disease. Previous segregation analysis has suggested evidence for a single major gene that determines a linear function that is approximately the log of (HDL-C/LDL-C) with the effects of sex, age, body mass index, and cigarette and alcohol use removed by regression. We examined a similar linear function in three large, randomly selected white families obtained through the Bogalusa Heart Study. A mixture of three normal distributions fitted the data significantly better than either one or two normal distributions, and the maximum likelihood parameter estimates of the models were similar to those reported previously. However, all Mendelian models were rejected when compared to the general model which estimated transmission probabilities. Although a multifactorial model could not be rejected, it did not fit the data significantly better than a three distribution, environmental model. Furthermore, the assumption of Hardy-Weinberg equilibrium proportions for the distributions was rejected. Thus, although there is evidence for more than one distribution of the HDL-C/LDL-C ratio in these data, our analyses were unable to corroborate the previous report of single major gene inheritance. Sib-pair analysis, however, did suggest evidence for linkage between the linear function and the orosomucoid (ORM) marker on chromosome 9q34 ($p = 0.05$). Possible explanations for the discrepancy between our findings and the previous report will be discussed.

Genetic epidemiology of lung cancer: I. Familial risk of lung cancer among non-smokers. A.G. Schwartz and P. Yang. University of Pittsburgh, Pittsburgh, PA, USA.

To study familial risk of lung cancer in a group likely to have risk associated with genetic susceptibility, we selected population-based non-smoking lung cancer cases aged 40-84 from the Metropolitan Detroit Cancer Surveillance System (a SEER registry). Detailed information on family history of cancer and environmental exposures was collected for the 256 lung cancer cases and their 2,236 family members and for 263 controls and their 2,261 family members. Preliminary findings from multivariate logistic regression models adjusting for age, race, gender, passive tobacco smoke exposure, occupation, and other respiratory diseases, suggest that non-smoking cases are twice as likely as non-smoking controls to have a first-degree relative with lung cancer ($p=0.04$). A positive first-degree family history of lung cancer was associated with a 2.2-fold increased risk of lung cancer in non-smoking females ($p=0.02$), but not in non-smoking males. First-degree family history of lung cancer ($OR=1.9$, $p=0.046$), passive tobacco smoke exposure at work ($OR=1.6$, $p=0.04$), and history of chronic obstructive pulmonary disease ($OR=6.63$, $p=0.009$) were significant predictors of risk of adenocarcinoma of the lung. Mean age of lung cancer diagnosis among non-smoking relatives of cases (57.5 years) was less than that for non-smoking relatives of controls (64.1 years). Risk of cancer among first-degree relatives was analyzed using logistic regression to take into account age, sex, race, smoking history, and passive tobacco smoke exposure for each relative. Highest risk of lung cancer was seen among offspring of the non-smoking cases when compared with offspring of controls ($OR=6.7$, $p=0.08$). Excess risk of all cancers combined was found for first-degree relatives of cases ($OR=1.2$, $p=0.04$). These results suggest that familial risk of lung and other cancers is present for at least a subset of families identified through non-smoking lung cancer cases. Analyses which incorporate other risk factors for the relatives and use newer logistic regression methods which take into account dependence among relatives are underway.

Genetic Epidemiology of Lung Cancer: II. Complex segregation analysis of families of non-smoking lung cancer probands. P Yang and AG Schwartz. University of Pittsburgh, Pittsburgh, PA, USA.

As part of a genetic-epidemiologic study of lung cancer among non-smokers, we investigated the role of a possible Mendelian genetic factor (one locus, two alleles) in observed familial aggregation. Population based cases were identified from the Metropolitan Detroit Cancer Surveillance System (a SEER registry). Information on lung cancer occurrence, smoking habits and other environmental factors was obtained for 2,059 first-degree relatives of 259 non-smoking probands with lung cancer (74 males, 185 females). Lung cancer was reported in 11 female and 29 male relatives. We observed a striking difference in mean age of onset between female smoking and non-smoking lung cancer relatives, 55 years and 72 years, respectively. We performed complex segregation analyses using two different approaches, REGD (Under a Class A Regressive Logistic Model, V2.1) and REGTL (For a Truncated Trait, V2.0, Model I) implemented in the SAGE program. REGD incorporates unobserved "type" effects (e.g., genotypes) into the logistic regression. For each individual, the probability of having lung cancer for a given age and sex (based on SEER data) was included in all models. REGTL models the putative predisposition as having a type-dependent age of onset and a susceptibility parameter common to all types. The effects of cigarette smoking were evaluated simultaneously while testing for the presence of a major genetic factor. From both approaches, an environmental model with homogeneous risk best explained the observed data. Two competing hypotheses were rejected: I) the occurrence of lung cancer among first-degree relatives is sporadic; and II) there is a genetic predisposition to lung cancer (Mendelian recessive, dominant or codominant locus). These preliminary results suggest that the pattern of occurrence of lung cancer in families of non-smoking lung cancer patients differs from that in families of smoking lung cancer patients. Despite the profound effect of smoking on lung cancer risk, other environmental and/or non-Mendelian genetic risk factors need to be identified.

A logistic random-effects model for estimation of gene-environment interaction under heterogeneity: application to early-onset bilateral breast cancer data. S.A. Ingles[12], R.W. Haile[2], R.C. Millikan[2], V.K. Cortessis[2], and R.M. Elashoff[1]. [1]Department of Biomathematics, School of Medicine and [2]Department of Epidemiology, School of Public Health, University of California at Los Angeles, U.S.A.

A logistic model is presented which allows estimation of: the effect of a

putative high risk genotype, the effect of an observed covariate, the gene-covariate interaction, and the proportion of families linked. A family-specific random effect represents the linkage status of the family, and an optional sibship-specific random effect represents unmeasured risk factors shared by sibs. The genotype may be modeled as an observed or as a latent variable.

The model was applied to data from 63 multiplex early-onset bilateral breast cancer families in which BRCA1 genotypes were inferred from 17q haplotypes. For the covariate oral contraceptive use (ever/never), several variations of the model were fit by Gibbs sampling. The estimated OC use-BRCA1 interaction odds ratio is approximately 2 for all models, but the estimated effect of the BRCA1 gene depends on assumptions about the age of onset distribution. Approximately 40% of families are estimated to be linked to BRCA1.

Somatic alterations in HER-2/neu and p53 in familial breast cancer. S.A. Ingles,[1] R.C. Millikan,[2] L.B. Ramos,[3] D.J. Slamon,[3] R.W. Haile.[2] [1]Department of Biomathematics, School of Medicine, [2]Department of Epidemiology, School of Public Health, and [3]Department of Medicine, School of Medicine, University of California at Los Angeles, U.S.A.

Immunohistochemical methods were used to evaluate HER-2/neu and p53 overexpression in over one hundred formalin-fixed, paraffin-embedded breast tumors from members of 48 multiple case families. Somatic alterations in HER-2 and p53 are believed to contribute to breast tumor development and confer a worse prognosis in patients with sporadic tumors.

Overall prevalence and distribution by histopathologic type and stage did not differ from those reported for sporadic breast tumors. Subgroups were also analyzed: individuals from families linked versus unlinked to markers on chromosome 17q, as well as individuals reporting exposure to one or more risk factors for breast cancer.

Linkage analysis of chromosome 1p36 using 64 multiple case breast or breast-ovarian cancer pedigrees. R.C. Millikan,[1] S.A. Ingles,[2] A.T. Diep,[1] R.A. Sparkes,[3] R.W. Haile.[1] [1]Department of Epidemiology, School of Public Health, [2]Department of Biomathematics and [3]Department of Medicine, School of Medicine, University of California at Los Angeles, U.S.A.

Studies of sporadic tumors suggest that one or more loci on chromosome 1p may be involved in breast tumor progression, and at least one previous linkage analysis (Ferrell, 1989) implicates 1p36 as a possible susceptibility locus for familial breast-ovarian cancer. Using 64 breast or breast-ovarian cancer pedigrees in which the proband had early onset bilateral breast cancer, linkage to 1p36 was assessed using two highly polymorphic DNA markers, D1S160 (MIT-A115) and D1S170 (COS37).

Linkage analyses were performed using MENDEL for each marker separately and in combination as a 1p36 haplotype. Under the assumption of homogeneity, strong evidence against tight linkage was obtained. However, a subgroup of families with positive lod scores under a variety of models merit further attention. Issues of model dependence were addressed (including mode of transmission), and non-parametric approaches (Affected Pedigree Member method) were utilized as well.

A linkage method for joint estimation of effects of environmental factors with the recombination fraction. V. Cortessis[1], S.A. Ingles[12], W.J. Gauderman[3], R.W. Haile[1]. [1]Department of Epidemiology, School of Public Health, [2]Department of Biomathematics School of Medicine, University of California at Los Angeles, U.S.A. [3]Department of Preventive Medicine, School of Medicine, University of Southern California, U.S.A.

We extended the standard lod score linkage method to incorporate measured factors. Three free parameters of interest are estimated jointly with the recombination fraction, θ: odds ratios for the measured covariate and the high-risk genotype, and an interaction term. We perform sensitivity analyses on allelic frequency at the disease locus, which remains fixed. We address age and sex effects by using age-, sex-specific disease rates as constraints. We implemented the method using the program MENDEL. The new parameters reduce potential model misspecification and resultant bias in estimating θ, while supporting inferences about the effects of measured covariates and their influence on the expression of disease genotypes. We apply the model to a BRCA1 linkage problem using mfd188 as a marker and history of oral contraceptive use as a covariate in multiplex breast cancer families ascertained through premenopausal, bilateral probands.

Behavioral difficulties of young girls with fragile X syndrome.
D.V. Dawson and A.M. Lachiewicz. Duke University Medical Center, Durham, North Carolina, USA.

Young girls with fragile X syndrome are reported to have a high incidence of abnormal behaviors that are believed to be associated with the fragile X genetic abnormality. The Connors Parent's Questionnaire, a behavioral checklist commonly used by pediatricians, was used to evaluate sixty fragile X girls with respect to six behavioral factors reflecting conduct, learning, psychosomatics, impulsiveness-hyperactivity, anxiety and hyperactivity. Ages ranged from 35-152 months, and IQ scores from <50 to 114. Measures were also collected for a comparison group of 58 girls with other genetic and developmental disorders, similar in composition with respect to age and IQ. Indices of anxiety and hyperactivity were markedly elevated among fragile X girls, both relative to published reports in normal children, and with respect to the non-fragile X comparison group (p=.0001). The proportion of fragile X girls with factor scores exceeding the 98th percentile was significantly greater than in the comparison group (23% vs 2% for anxiety, 38% vs 10% for hyperactivity). Significance persisted after adjustment for IQ and age group by the Cochran-Mantel-Haenszel test (p=.0005 for both factors).

Using a genetic algorithm to search for good pedigree plots.
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The author has described a plotting algorithm for general pedigrees which first enumerates possible conceptual plots to determine how good they are, before fixing actual co-ordinates. Many parts of human pedigrees are trees of certain types, for which a locally best sub-plot forms part of any overall best plot of the pedigree. Downward or upward divergent trees, with a single marriage-node at the top or bottom, are handled as special sub-plots, but the algorithm as programmed takes a time at least exponential in n for arbitrarily complex pedigrees.

Thomas (1988) has used a stochastic simulated annealing algorithm to give good marriage-node graphs. The nature of conventional plotting, however, suggests that use of a 'genetic algorithm' (so called because parts of different possible solutions are regarded as alleles on 'chromosomes' (bit-strings which represent complete possible solutions) in an evolving pool with stochastic crossover and mutation) might work well. These algorithms are robust; parametrization of the various subparts is easier; and known best solutions to subproblems, and problem-specific knowledge, can both be used to modify the initial pool and the genetic operators (crossover, etc) which are used.

Current progress in implementing such an algorithm will be described.

Evidence for a common genetic source of variance in the use of tobacco, alcohol, and caffeine.
Lon R. Cardon, Gary E. Swan, and Dorit Carmelli. SRI International, Menlo Park, California.

Previous studies have addressed the contribution of genes in the use of tobacco, alcohol, and caffeine as if they occur independently of each other. Such treatment does not address the possibility of a common genetic etiology for these substances. To explore this possibility, we developed a multivariate genetic path model for the joint use of alcohol, tobacco, and caffeine reported by 173 monozygotic and 183 dizygotic male twin pairs of the National Heart, Lung, and Blood Institute Twin Study. The model postulates two overlapping sets of polygenes for evaluation of the extent to which polysubstance use results from multiple, single, or no common genetic causes. Environmental contributions are treated similarly. Results strongly suggest that the covariation of these substances is genetically mediated, and may be attributable to a single set of polygenes. Environmental factors are all specific and not shared among twin brothers.

Estimating the probability for major gene Alzheimer disease. L.A. Farrer and L.A. Cupples. Boston University School of Medicine, Boston, Massachusetts, U.S.A.

Alzheimer disease (AD) is neuropsychiatric illness caused by multiple etiologies. Prediction of whether AD is genetically based in a given family is problematic because of censoring bias among unaffected relatives owing to the late onset of the disorder, diagnostic uncertainties, heterogeneity and limited information in a single family. We have developed a method based on Bayesian probability to compute values for a continuous variable that ranks AD families as having a major gene form of AD (MGAD). In addition, we have compared the Bayesian method with a maximum likelihood approach. These methods utilize information from the best fitting genetic model derived from segregation analysis of a large consecutive series of families, sex and

age adjusted risk estimates obtained from a maximum likelihood procedure, and data on cumulative incidence of AD in the general population. Our procedures also allow for phenocopies and familial clustering of age at onset. Agreement is high between the two approaches for ranking families as MGAD (Spearman rank = .92). Using either method, the numerical outcomes are sensitive to assumptions of the gene frequency and cumulative incidence of the disease in the population. Consequently, risk estimates should be used cautiously for counseling purposes; however, there are numerous valid applications of these procedures in genetic and epidemiological studies.

Genetic Relationship between Depression and Other psychiatric Disorders:Results of Complex Segregation Analysis. H. Ameli[1], J.E. Bailey-Wilson[2], R.A. Remick[1], A.D. Sadovnick[1], M.A. Spence[3], P. Flodman[3], and I.M.L. Yee[1]. [1]University of British Columbia, Vancouver, BC, Canada, [2]Louisiana State University,New Orleans, LA, [3]University of California, Irvine, CA.

Some family studies have provided evidence for the existence of a major locus that may be responsible for bipolar disorder and recurrent depression when the "affected" status of relatives has included other psychiatric diagnoses as well as bipolar disorder and recurrent depression.

Data from the Mood Disorder Service Genetic Database comprising 487 probands with a diagnosis of bipolar disorder and recurrent depression and over 2,000 of the first-degree relatives were analyzed using Complex Segregation Analysis. Previously we reported evidence for a major locus in this dataset when "affected" status for relatives was limited to bipolar disorder and recurrent depression. In this analysis, first degree relatives of probands were considered affected if they had any of the following diagnoses: bipolar disorder, recurrent depression, alcoholism, drug abuse, completed suicide, antisocial behaviour, schizophrenia according to RDC and FHRDC diagnostic criteria.

Transmission probability models allowing for a logistically distributed age of onset and including genotype-dependent susceptibilities were used. The age of onset distribution depended on a baseline parameter, an age coefficient and birth cohort as a covariate. Using the program REGTL (S.A.G.E.) and fixing the regressive familial effects to zero, we tested single major locus (SML), random transmission and no transmission hypotheses.

When we included suicide, antisocial behaviour, alcoholism and drug abuse in the "affected" status with depression, evidence still existed for a SML in these families and non-genetic models were rejected. However, when "schizophrenia" was included, all the genetic and non-genetic models were strongly rejected ($P < 0.025$). These results are consistent with the reports in the literature that the mood disorders and some other psychiatric disorders such as alcoholism may both be the result of a SML.