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1

Maximum likelihood generalized heritability estimates for blood pressure among Nigerian families.

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Elevated blood pressure is more common in relatives of hypertensives than in relatives of normotensives indicating familial resemblance of the blood pressure phenotypes. However, most published studies were conducted in families in westernized societies. We examined familial patterns of blood pressure in a population-based sample of 510 nuclear families, including 1552 individuals (320 fathers, 370 mothers, 475 sons and 387 daughters) from Ibadan, Nigeria. The prevalence of obesity is this community is low (body mass index: fathers = 21.6, mothers = 23.6, sons = 19.2 and daughters = 21.0, kg/m^2). The blood pressure phenotype used in all analyses was created from the best regression model by standardizing the age-adjusted systolic blood pressure and diastolic blood pressure to zero mean and unit variance. Heritability was estimated using SEGPATH from the most parsimonious model of no spouse and no sex nor generation difference as 45% for systolic blood pressure and 43% diastolic blood pressure. The lack of a significant spouse correlation suggests little or no effect of common familial environmental influence. However, a strong non-shared environmental effect is also suggested given the heritability estimate of less than 50% for both systolic and diastolic blood pressures.

2

The necessity of individual approach to segregation analysis of some complex diseases.

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The transmission probability approach is usually used to detect the major gene effect. It has been shown that this approach prevents false inference of major gene. However a false rejection of a major gene effect

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may occur due to imperfection of genetic model or misspecification of the disease status. Therefore, to infer a major gene effect one has to pay a special attention to the selection of genetic models and the accuracy of disease status identification.

We performed the segregation analysis of adolescent idiopathic scoliosis using the regressive logistic models with different ways of age-of-onset description and ascertainment correction. We applied two approaches to define the affected status. First, when it has been prescribed to persons with all forms of disease; second, when it has been done for individuals with only pronounced forms of disease. Only in the second case we found the major gene control. The unique method of describing the age dependence of penetrance function allows to detect major-gene effect. This method introduced by Elston and George (1989) corresponds to adolescent nature of disease. It seems that often the segregation analysis of complex diseases requires the special information on the diagnosis and the manifestation of disease. Constructing the genetic models based on this information may be helpful for detecting the major-gene effect.

3

Inflation of Sibling Recurrence Risk Ratio Due to Ascertainment Bias and/or Over-Reporting

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One widely used measure for familial aggregation is the sibling recurrence risk ratio, which is defined as the ratio of risk of disease manifestation given that one's sibling is affected as compared with the disease prevalence in the general population. Known as lambda, now it has been used extensively in the mapping of complex diseases. In this paper, I will show that for a fictitious disease that is strictly non-genetic and non-environmental, lambda can be dramatically inflated due to misunderstanding of the original definition of lambda, ascertainment bias, and over-reporting. Therefore, for a disease of entirely environmental origin, the inflation of lambda due to ascertainment bias and over-reporting is expected to be more prominent if the risk factor also is familially aggregated. This suggests that, like segregation analysis, the estimation of lambda also is prone to ascertainment bias and should be performed with great care. This is particularly important if we use lambda for exclusion mapping, for discriminating between different genetic models, and for association studies, as these practices hinge tightly on an accurate estimation of lambda.

4

Tests and Estimates of Allelic Association in Complex Inheritance

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Family-based procedures like the transmission disequilibrium test (TDT) were motivated by concern that sample-based methods to map disease genes by allelic association are not robust to population stratification, migration, and admixture. Other factors to consider in designing a study of allelic association are specification of gene action in a weakly parametric model, efficiency, diagnostic reliability for hypernormal individuals, interest in linkage and imprinting, and sibship composition. Compared with cases and normal controls the TDT is the method of choice for family data, which are not the data of choice for allelic association. The TDT has an efficiency of ½ for parent-offspring pairs, and 2/3 for father-mother-child trios. Against cases and hypernormal controls the efficiency is only 1/6 on the null hypothesis. Although dependent on marker gene frequency and other factors, efficiency for hypernormal controls is never less than for random controls. Efficiency is increased in multiplex families and by inclusion of normal sibs, approaching a case-control design with normal but not hypernormal controls. Isolated cases favour unrelated controls, and only in exceptional populations would avoidance of stratification justify a family-based design to map disease genes by allelic association.

5

Possible departure from Holman's triangle constraints

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Holmans (1993) showed that, for any genetic models, the proportions of affected sibs sharing 2, 1 or 0 Identical By Descent parental marker alleles are constrained to belong to a specific " triangle ". Theses constraints are indeed valid as long as in all pairs the phenotypes of the two sibs are underlied by a same model (same probability for a given genotype to be affected). We show in this study that the triangle constraints do not hold anymore in many realistic situations where the sib phenotypes may correspond to different models. It is the case if the two sibs differ for a variable on which the penetrance function depends and which is not taken into account in the phenotype. This variable may be a caracteristic of the trait itself,

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eg severe vs. mild form, or the presence/absence of an associated trait or of an environnemental factor. In such situations, relaxing the constraints will improve the power of risk factor detection. In addition, rejection of Holman's constraints will imply that sib phenotypes are underlied by different models and give evidence for an hidden effect of a variable. It is possible to test if the observed heterogeneity is due to a candidate variable by a predivided sample test.

6

Natural Selection for the MTHFR Gene: Mating Type Distortion

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Heterozygote advantage of the 5, 10-methylenetetrahydro-folate reductase gene (MTHFR) was reported (Weitkamp et al, Lancet, in press) in unaffected first degree male relatives of neural tube defect (NTD) probands (n =258, p = 0.000002) and not in unaffected female relatives (n = 258, p = 0.51). The opposite sex effect on increased MTHFR C677T heterozygosity was observed in spina bifida probands (33 males, p = 0.58; 50 females, p = 0.011). To investigate the mechanism of sex-dependent MTHFR heterozygote advantage in individuals with NTD susceptibility polygenes, we compared MTHFR mating type frequencies in the 167 NTD families and also in 90 random fecund Caucasian couples with expectation based on Hardy-Weinberg equilibrium and observed C and T allele frequencies (0.651 and 0.349; 0.664 and 0.336, respectively). Matings in each cohort were grouped according to whether the probability that an offspring would be heterozygous was 100%, 50%, or 0%. Both cohorts showed mating type distortion (NTD, p = 0.022; random, p = 0.002). However, the distortion was opposite in the two cohorts: e.g., couples that could produce only heterozygous offspring were 7/167 in the NTD families (17.2 expected) and 17/90 in the random couples (9.0 expected). In 69 NTD families of the mating type heterozygote by C/C homozygote the mother was heterozygous in 21 and homozygous in 48 rather than the equal numbers expected (p = 0.001), suggesting an interaction between maternal and fetal genes in fetal survival. Indeed, from these 69 matings, 28 of 36 spina bifida offspring were heterozygous (18 expected, p = 0.0009). These results provide unusual and striking evidence of natural selection.

7

The $(GGN)_n$ polymorphism in the androgen receptor gene is associated with time to relapse and overall survival in men with prostate cancer.

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Androgens are required for the growth and function of the prostate gland as well as for the early stages of prostate cancer (PC). US studies suggest that a subset of alleles at one or both of the trinucleotide repeat polymorphisms in the first exon of the androgen receptor gene may be associated with increased risk of PC. Alleles with fewer repeated CAG triplets have been associated with a higher risk of more aggressive disease as well as with increased *in-vitro* activity of the gene product. The other polymorphism, a repeated GGN sequence, has been less studied. We have genotyped 162 British Caucasian PC patients along with geographically matched controls to assess the roles of the $(CAG)_n$ and $(GGN)_n$ polymorphisms in both risk and clinical course of the disease.

We found no association of either polymorphism with PC risk. Significant associations were seen between $(GGN)_n$ alleles with = 17 repeats and shorter disease free survival, DFS, (RR= 1.74, 95% CI= 1.08-2.79) as well as decreased overall survival, OS (RR= 1.98, 1.13-3.45). After adjusting for stage and grade, these effects remained high but became only marginally significant (RR_{DFS}=1.60, p= 0.052; RR_{OS}= 1.60, p= 0.088, respectively). The greatest effects were in early stage, T1-T2 (RR_{DFS}= 3.56, 1.13-11.21) and grade 1, well differentiated (RR_{DFS}= 6.47, 0.57-72.8) tumors.

We conclude that $(CAG)_n$ allele length is not universally associated with PC risk and in this population the $(GGN)_n$ polymorphism is a significant predictor of DFS and OS with longer alleles conferring worse prognosis. Additionally, the $(GGN)_n$ effect is likely to be restricted to the early stages of tumor progression. We hypothesize that although the androgen receptor is universally required for PC development, the nature of its involvement may be variable.

8

Evidence of Linkage Disequilibrium Between POF and FRAXAC1

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In Western European populations, mean age of menopause is 51 years. Early menopause or early ovarian failure (EOF) prior to age 47 occurs in 10% of the population, while premature menopause or premature ovarian failure (POF) prior to age 40 occurs in 1%. A genetic influence in menopause has been inferred from studies of women who report a family history of EOF. Cytogenetic analysis of the X chromosome indicates that deletions and translocations co-segregate with POF. Two regions on the X chromosome appear to be critical for normal ovarian function. One is situated between Xq26-28 (POF1). FMR1, the gene responsible for fragile X [fra(X)] syndrome, is also located within POF1 at Xq27.3. Studies have suggested that fra(X) carriers are at increased risk for POF but not EOF. Moreover, the mutation co-segregates with POF in some fra(X) families. Kenneson et al (1997) proposed that the association between fra(X) mutations and POF may result from linkage disequilibrium between FMR1 and a mutation producing POF, and not from the FMR1 mutation itself. Previous studies have shown that FMR1 is in linkage disequilibrium with nearby loci, one of which is labelled FRAXAC1. FRAXAC1 is a polymorphic dinucleotide repeat about 7 kb upstream from the FMR1 repeat region. There are 5 distinct alleles in FRAXAC1, identified simply as A, B, C, D, and E. To test the hypothesis that POF is in linkage disequilibrium with FMR1, 10,600 women, ages 45-54 years, were surveyed. From this sample, 344 cases of EOF were recruited for further analysis, along with 344 age-matched controls who were menopausal from age 47 onward. Of these, 295 women were genotyped for FRAXAC1, producing a total of 590 alleles. Subjects were separated into three distinct groups: A "familial group" of menopausal women with a family history of EOF (N=14); a "sporadic group" of women with no family history of EOF (N=15); two control groups, one of which was composed of women with EOF occuring between ages 40 and 47 (N=164). A second control group consisted of women who were menopausal after age 47 (N=102). To determine if age was a factor in menopause, the frequency of alleles from the two control groups were compared with one another. Results indicated no difference in proportions (χ^2=2.17; ns). Consequently, allele frequencies from controls were pooled. Allele type frequencies were compared among the 3 groups. Given the sparse 3X5 matrix, pseudo-Bayes estimators were computed to smooth the data in the table. Although it appears in only 6% of the population, the B allele in the familial group occurred unusually often. Thus, odds ratios (OR) were computed to compare the frequency of the B allele with A, C, and D, in the familial versus control groups. Similarly, ORs were computed for the B allele in the sporadic versus control groups. Results show large and significant ORs for the B allele in the familial group compared to controls. ORs of the B allele in the sporadic group compared to controls were not significant. These results suggest that POF is in linkage disequilibrium with FMR1 at the FRAXAC1 locus.

9

Radiation hybrid (RH) mapping: selective models and analysis of a small number of genes

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We developed special statistical methods for mapping of combined group of genes including both isozyme and DNA markers. Our models simulating biological process of obtaining RH clones allow stringent and weak retention of a selective gene in the clone. These models have pseudo-Markovian and additive properties and are applicable for analysis of an arbitrary number of genes. In a number of cases (especially in analysis of mammals poorly studied genetically), we collide with a problem of RH mapping of a small number (3, 4 or 5) of genes. At the decision of this problem, localization of structural genes coding for known protein products is of special interest.

The problem of mapping of a small number of genes needs to be considered as a independent statistical problem, as far as there is a number of difficulties in estimating of relative distances between the genes (with which we do not collide at localisation of a large (6 and more) number of genes) and, on the contrary, there is a opportunity of use of criteria for choice of the correct order, not acceptable for a large number of genes. At the analysis of 3, 4 and 5 genes under stringent selection, the number of various types of clones is not enough, that leads to low informativity of an empirical material. In this case, it is impossible to estimate distances between the genes without introducing additional restrictions on the model parameters. However, due to introducing these restrictions, the model may don't reflect the real situation. We have analysed each of possible orders of 3 and 4 genes and solved analytically the problem on ordering genes. Besides, we have obtained analytically estimates of functional dependencies formed by parameters at the description of the model. Thus, the problem of mapping of a small number of genes contracts to ordering genes and to qualitative comparison of distances between genes.

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