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INTRAFAMILIAL ASSOCIATION ANALYSES AS AN EFFICIENT ALTERNATIVE FOR POPULATION ASSOCIATION STUDIES TO MAP DISEASE GENES – A POOR MAN’S ANSWER TO EXPENSIVE SCIENCE

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One of the great expectations of the human genome project voiced in the mid 90s was that availability of high densities of SNPs would lead to identifying many genes involved in complex disorders or traits using population based association strategies. Now 10 years further on it is clear that this expectation has not been fulfilled despite enormous sample sizes and expenditure; this is probably due to much higher genetic and phenotypic heterogeneity than originally anticipated. One of the large disadvantages of population as opposed to family studies is that all genotype-phenotype associations are based on the total variability within the population as a whole, where as variation within families is much more restricted, rendering it easier to detect statistically significant associations. This conclusion stems from my experience of the much greater power of associating *FMR1* alleles with changes in the menopause phenotype within families than at the population level. This depends on the fact that differences in phenotype between individuals within a family are much more likely to depend on observed genotypic differences for given markers than within a population, since both the phenotypic and genotypic variance is reduced by ~50% within families due the common genetic predisposition present in family members. A simple additive or subtractive model of gene interaction is assumed and there is circumstantial evidence that this assumption might be true for menopause and other traits such as height and IQ that exhibit continuous Gaussian variation. However, traits with a phenotypic thresh-hold, such as involved in disease onset, may be less amenable to this approach. The analysis involves associating marker alleles with changes in phenotype within families. Only families are analysed where genotypic differences for a given marker are present; any increases or decreases of the phenotypic value associated with a given genotype relative to the family mean are measured. Following, the phenotypic means for all families are normalised to zero and the phenotype differences to the mean summated for given genotypes across all individuals from informative families. From then on the phenotypic means for individual families are further ignored and we are only interested in the difference to the mean for each family (λ). For the usual bi-allelic markers, in the majority of families this mainly results in just two genotype classes, namely AA and AB, and occasionally BB where B is the minor allele. Minimally there must be at least two individuals per family studied, but ideally the more individuals the better since this establishes a far more reliable estimate of the average family predisposition to a disease than the average of just two individuals. The prediction is that the family approach will require far less genotyping than population samples and deliver far more information than population studies; the approach is much more suitable for studying a selection of candidate genes rather than a chip based genome wide screen. The *FMR1*- menopause association will be used to exemplify the principle of this method. It is a sobering fact that the association of the *FMR1* premutation with POF would probably not have been detected in a genome wide association analysis based on a population study because of the low allele frequency.