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FAMILIAL SINISTRALITY: THE UTILITY OF CALCULATING EXACT GENOTYPE PROBABILITIES FOR INDIVIDUALS

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ABSTRACT

Measures of familial sinistrality are frequently used in neuropsychological research. However they suffer from the problem that they are essentially a global measure of *phenotypes* in the family, whereas they are interpreted as an indicator of the *genotype* of the individual concerned. In this paper it is shown how to calculate a precise probabilistic estimate of a proband's genotype, given a particular genetic model of handedness, using all of the information available in a family tree. Example calculations are provided for a range of families with one or two sinistral relatives. Genotype probabilities are also calculated for a large population data set (the National Childhood Encephalopathy Study) and it is shown that familial sinistrality does not account for all of the variability present in the genotype probabilities, and that genotype probabilities provide an additional prediction of individual sinistrality after taking familial sinistrality into account, whereas all of the information in familial sinistrality is accounted for by the genotype probabilities. Finally it is shown how genotype probabilities can be used to assess whether there is heterozygote advantage for a characteristic, and using this method it is suggested that there is no support for heterozygotes having higher intellectual ability than homozygotes.

Neuropsychological studies of functional lateralisation often divide subjects into those with and those without a history of *familial sinistrality* (FS). The logic is that although most individuals show left hemisphere dominance (LHD) for language, a minority show right hemisphere dominance (RHD) for language. Many RHD individuals are left-handed, although a majority are right-handed. Dating from the work of Foster Kennedy (1916) on "stock handedness", right-handers with RHD have been assumed to have more left-handed relatives than those with LHD; and that suggestion is compatible with the currently popular genetic models of handedness, right-handed RHD individuals being more likely to carry the C allele (McManus, 1985a) or the RS- allele (Annett, 1985). Classification of individuals as FS+ and FS− has been used either to reduce within group variability, as in studies of dichotic or lateral tachistoscopic presentation (Birkett, 1981; Bryden, 1988; McKeever, 1990; O'Boyle and Benbow, 1990; McKeever, 1986; van Eys and McKeever, 1988; Searleman, Tweedy and Springer, 1979), or as a clue to aetiology, as in studies of autism, stuttering, dyslexia and mental retardation (Pipe, 1987).

Measurement and definition of FS is a difficult problem, and studies differ in their usage. Many studies simply ask whether *any* known relatives are left-handed (*broad familial sinistrality*, FS_{broad}). However this criterion confounds family size with FS_{broad}, since the greater numbers of relatives increase the

likelihood of being $FS_{broad}+$ (Bishop, 1980); and asymptotically all individuals must be $FS_{broad}+$, since all humans share ancestors if the family tree is taken back far enough. The problem is partly circumvented by considering only *first-degree relatives* (*narrow familial sinistrality*, FS_{narrow}), that is, individuals sharing 50% or more of an individual's genes — parents, children, siblings, or monozygotic twins. Although the criterion does not have the problem of all individuals asymptotically being positive, it is still confounded with family size, and makes the dubious assumption that first-degree relatives all have the same effect upon the likelihood of RHD.

The interpretation of FS is also controversial. Often it is used to infer the cause of left-handedness, FS+ left-handers being assumed to be genetically sinistral, whereas FS− left-handers are seen as implying environmental or pathological causes. As has been clearly pointed out by Bishop (1990), such an association is too weak to be of practical utility.

Despite such criticisms of FS there is a strong argument that the information in a family history of sinistrality should inform about an individual's genetic organisation, and, if handedness and cerebral dominance share a genetic origin, then FS or other measures should be useful. In this paper I suggest that measures such as FS cannot extract the full information in a proband's kindred. A more satisfactory measure will not apply arbitrary definitions of FS, construed as a binary variable of limited sensitivity and power, but will give continuous measures about an individual's likely genotype. Such measures can then be used as a benchmark for assessing simpler criteria for FS.

For FS be to be a useful measure it must be partitioned into two separate types of information: information about an individual's likely genotype given their family tree; and information concerning shared social or cultural influences, by processes such as imitation, social learning, or cultural influence. Cultural inheritance, by horizontal, vertical and oblique transmission is complex but can be analysed (see e.g. Cavalli-Sforza and Feldman, 1981). The difference between genetic and cultural processes is that one acts via the *genotypes* of family members, whereas the other acts via their *phenotypes*. Although genotypes cannot presently be observed directly, they can be inferred from phenotypes and an explicit genetic model. This paper will concentrate on assigning genotypic probabilities to probands, and will only briefly consider the separate and potentially useful information remaining in the environmental components.

The assignment of genotype probabilities to probands has advantages over mere categorisation into classes of FS+ and FS−. Firstly, the measures are continuous, and hence are more powerful than discrete measures; and secondly that power arises in part because all specifically *genetic* information is extracted, because of the explicit genetic model (and indeed the method cannot be applied without a genetic model). Also the assignment of genotype probabilities attaches *several* numbers to each individual, one for each genotype (although one is statistically redundant), allowing one to distinguish individuals with high or low probability of a particular genotype; in principle this allows double dissociation to be applied in genotypically equivalent individuals (see McManus, 1987). It also provides an attack upon the problem of the balanced polymorphism which almost certainly underpins handedness. Stable polymorphisms must be balanced,

typically by heterozygotes showing an advantage over heterozygotes. Annett (e.g. Annett and Manning, 1989, 1990a, 1990b; Annett, 1991a, 1991b, 1991c) argues the advantage can be investigated by examining phenotypic differences between heterozygotes and homozygotes; the method appears however to be flawed (McManus, Shergill and Bryden, 1993), although see Annett (1993). The present method allows a more direct assignment of heterozygote probabilities, allowing comparison of subjects with high and low probabilities.

Assignment of genotypic probabilities requires an explicit genetic model. Here I restrict the analysis to the McManus model, described extensively elsewhere (McManus, 1984, 1985a, 1991; McManus and Bryden, 1992, 1993). Although it differs from the Annett model in many details (McManus, 1985b, 1991), it is broadly equivalent in its ability to fit familial data (McManus, 1985a; McManus and Bryden, 1992).

The McManus genetic model in its original form assumes that there are two alleles, *D* (Dextral) and *C* (Chance), at a single locus. There are two phenotypes, *R* (right) and *L* (left), with *L* manifesting in 50% of *CC* genotypes, 25% of *DC* genotypes, and 0% of *DD* genotypes. The frequency of the *C* allele in the gene-pool is estimated to be about 0.155, resulting in a "true" incidence of left-handedness of 7.75%, a value compatible with the overall value in a meta-analysis of the incidence of left-handedness (Seddon and McManus, 1993; McManus, 1991). The incidence of RHD is calculated by assuming that it also occurs in 0% of *DD* genotypes, 25% of *DC* genotypes and 50% of *CC* genotypes, the probability being independent of being left-handed. The McManus model has undergone a minor revision in recent years in order to explain the sex differences in the incidence of handedness, and the maternal effect (McManus and Bryden, 1992); however the modified model, with a sex-linked modifier gene, is more complex than the original model and, as will be seen in subsequent analyses, is more difficult to analyse on computational (but not theoretical) grounds.

In this paper I describe the application of the statistical model to the simple case of a child and two parents, and then generalise it to complex family trees. The model is then used to explore the influence of different forms of familial sinistrality in a series of "model families" of different size and structure. The method is then applied to a large, population-derived series of families, and is used to ask whether "pathological" left-handedness is genetic in origin; it is used to explore the sensitivity of the method; and it is used to ask whether there are different patterns of intellectual ability in heterozygotes.

The Statistical Model

The Calculations for the Basic Family of Two Parents and One Child

Consider a family in which there are two parents (*m*: mother, *f*: father) and a single child (*c*). The handedness phenotypes of the family members are symbolised h_m, h_f and h_c respectively. The phenotypes are known and for the present can be considered as right-handed (*R*), left-handed (*L*) or unknown (*U*). Each individual can have one of three possible genotypes, *DD*, *DC* and *CC*;

the particular genotypes of parents and children will be symbolised as g_m, g_f and g_c respectively. The symbols g_x and h_x are used to refer to the genotype and phenotype of individuals in general, irrespective of whether they are parents or children.

The specific problem is to calculate the set of conditional probabilities that a particular individual has each of the possible genotypes, *DD*, *DC* and *CC*; thus $p(g_c = DD/h_m,h_f,h_c)$ is the conditional probability that the child has the genotype *DD*, given that the phenotypes of the family are h_m, h_f and h_c.

Three separate sets of information are required to calculate such probabilities:

a. The likelihood that parents of a particular genotype could produce a child of a particular genotype. This is summarised in the Mendelian function, which contains the transmission probabilities for offspring genotypes given parental genotypes. The function, symbolised as $M(g_c|g_m,g_f)$, takes two arguments, and provides the probability of a child with particular genotype arising from parents of particular genotypes. Thus if the mother is *DD* and the father is *DC* then $M(DD|DD,DC)=.5$, $M(DC|DD,DC)=.5$, and $M(CC|DD,DC)=0$; and so on for other combinations. A probability of zero indicates an outcome incompatible with Mendelian transmission.

b. The likelihood that an individual of a particular genotype, g_x, will have a particular phenotype, h_x. The phenotypic function, $Q(h_x|g_x)$, results directly from the genetic model itself. Thus for the McManus model of the genetics of handedness, $Q(R|DD)=1$, $Q(L|DD)=0$, $Q(L|DC)=0.25$, etc.

c. The likelihood that the parents have each of the three possible genotypes, symbolised by $R(g_x)$. These are calculated from the gene-frequency in the population and the Hardy-Weinberg equilibrium. Thus if $p(C)=0.155$ (see McManus, 1985a), then $R(DD)=(1-.155)^2=0.714$, $R(DC)=2\times.155\times(1-.155)=0.262$, and $R(CC)=0.155^2=0.024$. Note, these likelihoods are not required for the child since his or her genes must have been transmitted from the parents; to use the nomenclature to be introduced later, the parents are exogenous to the system, whereas the child is endogenous.

It is now possible to calculate the basic equation for the family, which shows the *relative likelihood* that the child has genotype g_c, given that the parents have genotypes g_m and g_f, and that the phenotypes of the parents and child are h_m, h_f and h_c.

$$L(g_c \mid h_c,h_m,h_f,g_m,g_f) = M(g_c \mid g_m,g_f)\cdot Q(h_c \mid g_c)\cdot Q(h_m \mid g_m)\cdot Q(h_f \mid g_f)\cdot R(g_m)\cdot R(g_f)$$

This equation assumes that the parental genotypes, g_m and g_f, are known. However they are not, and each parent may be any of the three genotypes, i.e. *DD*, *DC* and *CC*. The *likelihood* that the child is a particular genotype, given only the phenotypes of the family members, can be calculated by summing the basic equation across all possible parental genotype combinations:

$$L(g_c \mid h_c,h_m,h_f) = \sum_{\substack{g_m=DD,DC,CC \\ g_f=DD,DC,CC}}\sum \left[\begin{array}{c} M(g_c \mid g_m,g_f)\times Q(h_c \mid g_c)\times Q(h_m \mid g_m) \\ \times Q(h_f \mid g_f)\times R(g_m)\times R(g_f) \end{array}\right]$$

Table I shows a worked example of the calculation for the situation in which one parent is right-handed, the other is left-handed and the child is right-handed.

The *probability* that the child is of genotype g_c, can be calculated from the likelihood that the child is of that genotype divided by the summed likelihoods of the child being all of the possible genotypes (*DD*, *DC* and *CC* in this case), i.e.:

$$p(g_c \mid h_c,h_m,h_f) = \frac{L(g_c \mid h_c,h_m,h_f)}{\sum_{g_c = DD,DC,CC} L(g_c \mid h_c,h_m,h_f)}$$

For the example shown in Table I, the likelihoods of *DD*, *DC* and *CC* are 0.0266, 0.0300 and 0.0025 respectively, giving probabilities that the child is *DD* of 0.4501, *DC* of 0.5076 and *CC* of 0.0423. These probabilities are substantially different from those for a right-hander for whom no family history is known (*DD*: .7740, *DC*: .2130, *CC*: .0130).

It should be noted that the method can readily be modified to obtain the genotype probabilities for each parent, also conditional upon the total information provided by the family tree. Specifically, to find the probability that the mother is of a particular genotype, then the equations are:

$$L(g_m \mid h_c,h_m,h_f) = \sum_{\substack{g_c = DD,DC,CC \\ g_f = DD,DC,CC}} \sum M(g_c \mid g_m,g_f) \cdot Q(h_c \mid g_c) \cdot Q(h_m \mid g_m) \cdot Q(h_f \mid g_f) \cdot R(g_m) \cdot R(g_f)$$

$$p(g_m \mid h_c,h_m,h_f) = \frac{L(g_m \mid h_c,h_m,h_f)}{\sum_{g_m = DD,DC,CC} L(g_m \mid h_c,h_m,h_f)}$$

The equations for the father are similar except for the swapping of the *m* and *f* subscripts.

Development of the Model to Extended Families

The model can readily be elaborated to cope with extended families, in which there are grandparents, great-grandparents, aunts and uncles, cousins, and children; indeed any combination of relatives is acceptable, including half-siblings and monozygotic twins, and in-breeding also presents no problems.

Let the family tree consist of N individuals. The constraints on the tree are that:

a. All individuals must be connected through the tree. If necessary one should introduce "dummy" individuals with unknown handedness to link all individuals into the tree. Thus if a proband has cousins with known handedness then the proband's aunt and uncle must be included as dummy members to make the tree fully connected.

b. If an individual has one parent in the tree then the second parent must also be in the tree; if necessary they must be a dummy individual marked as of "Unknown" phenotype.

The general problem is to calculate the probabilities of a particular individual (the proband) having each of the three possibile genotypes, conditional upon the known genetic relationships and the known phenotypes of the entire family tree. In practice the proband can be any member of the kindred, so that conditional genotypic probabilities can be calculated for all family members.

It is necessary to distinguish two different types of family member, *endogenous* and *exogenous* [the terms have analogous usage in structural equation modelling (Kenny, 1979)]. Endogenous members arise from within the tree itself, so that their parents are also part of the tree; their genes therefore come from other individuals in the tree. In contrast, exogenous members are not descended from other members of the tree; it must be assumed that they

are unrelated to one another and that their genes are randomly drawn from the population gene-pool, conditional upon their own phenotype and the rest of the family tree.

Let there be m individuals endogenous to the tree and n exogenous individuals (where $m+n=N$); for convenience endogenous individuals have index number $1...m$, and exogenous individuals have index numbers $m+1...m+n$. Let h_i be the handedness phenotype of the *ith* individual, and let g_i be a hypothesised genotype for the *ith* individual, where $i=1...N$. For convenience assume the proband is endogenous (which in general they will be) and has subscript 1, and hence phenotype h_1 and genotype g_1. In the rare cases of an exogenous proband there are minor changes necessary to the equations. Let $f(i)$ and $m(i)$ be the father and the mother of the *ith* individual, so that $h_{f(1)}$ is the handedness of the father of the proband, etc. It should be noted that a complete listing of the parents of each individual completely defines a family tree.

The fundamental equation for the analysis gives the relative likelihood that the proband has genotype g_1 (where g_1 can be *DD*, *DC* or *CC*), conditional upon the proband being of handedness h_1, the other relatives (individuals $2...N$) having handedness phenotypes $h_2...h_N$ given their genotypes $g_2...g_N$, the endogenous relatives being descended through Mendelian mechanisms with likelihoods $M(g_j|g_{m(j)},g_{f(j)})$, where $j=2...n$, and the exogenous relatives being drawn from the population gene-pool with likelihoods $R(g_k)$, where $k=m+1,m+n$. The likelihood can be expressed as:

$$L(g_1 \mid h_1,h_2,...h_N,g_2,...g_N) = \left[\begin{array}{l} M(g_1 \mid g_{m(1)},g_{f(1)}) \times M(g_2 \mid g_{m(2)},g_{f(2)})...M(g_m \mid g_{m(m)},g_{f(m)}) \\ \times Q(h_1 \mid g_1) \times Q(h_2 \mid g_2)...Q(h_N \mid g_N) \times R(g_{m+1})...R(g_{m+n}) \end{array}\right]$$
$$= \prod_{j=1,m} M(g_j \mid g_{m(j)},g_{f(j)}) \cdot \prod_{k=1,m+n} Q(h_k \mid g_k) \cdot \prod_{l=m+1,m+n} R(g_l)$$

This equation can be summed across all genotypes for individuals 1 through N to give the likelihood of the proband having genotype g_1.

$$L(g_1|h_1,h_2,...h_N) = \sum_{g_2=DD,DC,CC} \cdots \sum_{g_{m+n}=DD,DC,CC} \left[\prod_{j=1,m} M(g_j|g_{m(j)},g_{f(j)}) \cdot \prod_{k=1,m+n} Q(h_k|g_k) \cdot \prod_{l=m+1,m+n} R(g_l) \right]$$

The probability that the proband is of a particular genotype given the proband's handedness (*PH*) and the family handedness (*FH*) can then be calculated as:

$$p_{FH+PH}(g_1) = p(g_1 \mid h_1,h_2...h_N) = \frac{L(g_1 \mid h_1,h_2...h_N)}{\sum_{g_1=DD,DC,CC} L(g_1 \mid h_1,h_2...h_N)}$$

It should be noted that sometimes it is useful to calculate the probability of a proband having a particular genotype, conditional upon the entire family tree, *but without taking the handedness of the proband into account.* This is useful either if the handedness of the proband is not known or if it is suspected that the handedness of the proband may be pathological. There is also a sense in which such estimates are the direct equivalents of conventional measures of FS;

they provide a summary measure of the history of sinistrality within the individual's family, without taking any account of the individual's own sinistrality. For such calculations one needs to estimate the probability of the genotypes from the equations:

$$L(g_1 \mid h_2 \ldots h_N) = \sum_{g_2 = DD,DC,CC} \cdots \sum_{g_{m+n} = DD,DC,CC} \left[\prod_{j=1,m} M(g_j \mid g_{m(j)}, g_{f(j)}) \cdot \prod_{k=2,m+n} Q(h_k \mid g_k) \cdot \prod_{l=m+1,m+n} R(g_l) \right]$$

$$p_{FH}(g_1) = p(g_1 \mid h_2 \ldots h_N) = \frac{L(g_1 \mid h_2 \ldots h_N)}{\sum_{g_1 = DD,DC,CC} L(g_1 \mid h_2 \ldots h_N)}$$

Extensions of the Model

The model as stated is very general, and copes with a wide range of different types of family tree, with any Mendelian or quasi-Mendelian genetic characteristic. In particular there are several potentially useful variations:

i. *Multiple genotypes.* The model can cope with any number of genotypes, and a genotype can be broadly defined as *any* combination of alleles, at one or more loci, so that epistatic effects can readily be accommodated, as also can modifier genes.

ii. *Sex-linked effects.* Although the model as presented is similar for males and females, it readily copes with different genetic transmission between the sexes (by modifying the Mendelian transmission model), or with different phenotypic expression in the two sexes (as in sex-limited effects).

iii. *Secular trends.* There is suggestive evidence that the manifest incidence of left-handedness may have increased through the twentieth century. This process can be modelled by allowing the phenotypic expression from genotypes (the function Q) to differ between cohorts. Similarly, real growth in the frequency of the C allele in the gene-pool could be modelled by the function R differing between cohorts.

iv. *Age-dependent effects.* Just as in some diseases (e.g. schizophrenia or Huntington's chorea) the probability of phenotypic expression depends on an individual's age, so the likelihood of an individual being left-handed may depend on age. By making the Q function conditional upon age it is possible to model such effects.

v. *Twins.* Dizygotic twins are readily modelled as ordinary siblings (which genetically they are). Monozygotic twins are genetically identical and are therefore modelled *as a single individual.* The difference from singletons is that the phenotype consists not just of R or L, but instead is one of the pairs, RR, RL or LL. The function Q then contains the binomial probabilities of obtaining these phenotypic combination from a genotype, calculated from the probability of a singleton being right or left-handed.

vi. *Inbreeding.* All genetic relationships are specified entirely in terms of which individuals are the parents of other individuals in the kindred, and therefore inbred relationships (as for instance in cousin marriages) present no problems at all to the method of calculation.

The Combinatorial Problem

The general equation is in essence very simple (and can be programmed very economically in FORTRAN as nested DO loops). However the formula has computational problems with large number of individuals. If there are $m+n$ individuals, then the equation requires $m.n.(m+n)$ multiplications, which must be summed across all genotypic combinations of the $m+n=N$ individuals.

Therefore $3^{(m+n)}.m.n.(m+n)$ multiplications must be carried out. The computational cost of the multiplications can partly be reduced by summing logarithms acquired from look-up tables, thereby solving the modified equation:

$$L(g_1|h_1,h_2...h_N)=\sum_{g_2=DD,DC,CC}\cdots\sum_{g_{m+n}=DD,DC,CC}\left[\exp\left(\sum_{j=1,m}\log(M(g_j|g_{m(j)}))+\sum_{k=1,m+n}\log(Q(h_k|g_k))+\sum_{l=m+1,n}\log(R(g_l))\right)\right]$$

Nevertheless, as N increases so the number of operations is dominated by the exponent of *3*, resulting in a combinatorial explosion. The consequences can clearly be seen in a simple calculation. A family tree with $N=11$ took about 20 seconds to calculate on a MicroVax computer. Scaling up suggests that a family with 12 members would take about 60 seconds, a family of 18 would take 12 hours, a family of 21 would take 13.7 days, and families of 24 and 27 would take 1 year and 27 years respectively. In practice it is therefore not possible to examine large kindreds unless one has access to a super-computer, or a superior algorithm is found. To some extent the algorithm is improvable by eliminating pathways known early on to result in zero products due to containing at least one zero (as for instance in many of the rows in Table I), but even such devices cannot solve the basic problem of a calculation which expands exponentially. Effectively the problem is that of a "travelling salesman" (see Penrose, 1990, pp. 181-187) — and might perhaps be soluble by methods currently being found for that problem. For the present, although the equations can be solved they can only be solved for relatively small family trees (and in this paper that means with 19 or less members).

Application to Example Family Trees

The influence of sinistrality in different members of a pedigree will be demonstrated in example families, chosen to assess the effect of different types of relative, the effect of family size, and the effect of including great-grandparents.

Three family trees are considered (see Figure 1). The first, NF, is typical of a modern nuclear family, consisting of proband, one sibling, two parents, one maternal sibling, one paternal sibling, and four grand-parents. There are two offspring from each parental pair, and the handedness of nine core members is known. The second family type, NFSS, contains the same nine core members as NF but with two additional siblings from each parental pair, making a total of fifteen members. The third family tupe, NFGGP, is similar to NF but also includes an extra generation of individuals, the eight great-grandparents, making seventeen individuals altogether. Comparison of NF and NFSS assesses the effect of family size, whereas comparison of NF with NFGGP assesses the effect of knowing about an additional generation.

The influence of familial sinistrality was explored by setting all individuals as right-handed, and then allowing one or two individuals to be left-handed. Table II shows, separately for families in which the proband is right or left-handed, the probability (p_{FH+PH}) of the proband being DD, DC or CC, and of

TABLE I

Worked Example of the Equations for a Simple Family. The child is right-handed, the mother left-handed and the father right-handed. The likelihood, the total of the products in the final column, is calculated separately for each possible genotype of the child i.e. DD, DC and CC)

Parental genotype combinations		Mendelian transmission	Phenotype probabilities			Parental genotype probabilities		Product of probabilities in each row
Mother	Father		Child	Mother	Father	Mother	Father	
Child = DD								
g_m	g_f	$M(DD \mid g_m,g_f)$	$Q(R \mid DD)$	$Q(L \mid g_m)$	$Q(R \mid g_f)$	$R(g_m)$	$R(g_f)$	
DD	DD	1.	1.	0.	1.	.714	.714	0.
DD	DC	.5	1.	0.	.75	.714	.262	0.
DD	CC	0.	1.	0.	.5	.714	.024	0.
DC	DD	.5	1.	.25	1.	.262	.714	0.0234
DC	DC	.25	1.	.25	.75	.262	.262	0.0032
DC	CC	0.	1.	.25	.5	.262	.024	0.
CC	DD	0.	1.	.5	1.	.024	.714	0.
CC	DC	0.	1.	.5	.75	.024	.262	0.
CC	CC	0.	1.	.5	.5	.024	.024	0.
							Total = L(DD | R,L,R) = 0.0266	
Child = DC								
g_m	g_f	$M(DC \mid g_m,g_f)$	$Q(R \mid DC)$	$Q(L \mid g_m)$	$Q(R \mid g_f)$	$R(g_m)$	$R(g_f)$	Product
DD	DD	0.	.75	0.	1.	.714	.714	0.
DD	DC	.5	.75	0.	.75	.714	.262	0.
DD	CC	1.	.75	0.	.5	.714	.024	0.
DC	DD	.5	.75	.25	1.	.262	.714	0.0175
DC	DC	.5	.75	.25	.75	.262	.262	0.0048
DC	CC	.5	.75	.25	.5	.262	.024	0.0003
CC	DD	1.	.75	.5	1.	.024	.714	0.0064
CC	DC	.5	.75	.5	.75	.024	.262	0.0009
CC	CC	0.	.75	.5	.5	.024	.024	0.
							Total = L(DC | R,L,R) = 0.0300	
Child = CC								
g_m	g_f	$M(CC \mid g_m,g_f)$	$Q(R \mid CC)$	$Q(L \mid g_m)$	$Q(R \mid g_f)$	$R(g_m)$	$R(g_f)$	Product
DD	DD	0.	.5	0.	1.	.714	.714	0.
DD	DC	0.	.5	0.	.75	.714	.262	0.
DD	CC	0.	.5	0.	.5	.714	.024	0.
DC	DD	0.	.5	.25	1.	.262	.714	0.
DC	DC	.25	.5	.25	.75	.262	.262	0.0016
DC	CC	.5	.5	.25	.5	.262	.024	0.0002
CC	DD	0.	.5	.5	1.	.024	.714	0.
CC	DC	.5	.5	.5	.75	.024	.262	0.0006
CC	CC	1.	.5	.5	.5	.024	.024	0.0001
							Total = L(CC | R,L,R) = 0.0025	

having RHD for language. The first two rows show the *a priori* probability of an individual being of the three genotypes or being RHD without any knowledge of family history, and if they are right-handed, left-handed, or their handedness is not known. These probabilities are a baseline for assessing the impact of information about other family members. Right and left-handers will be considered separately.

Right-handers

Three-quarters of right-handers are of the DD genotype, and only about 1% are of the CC genotype.

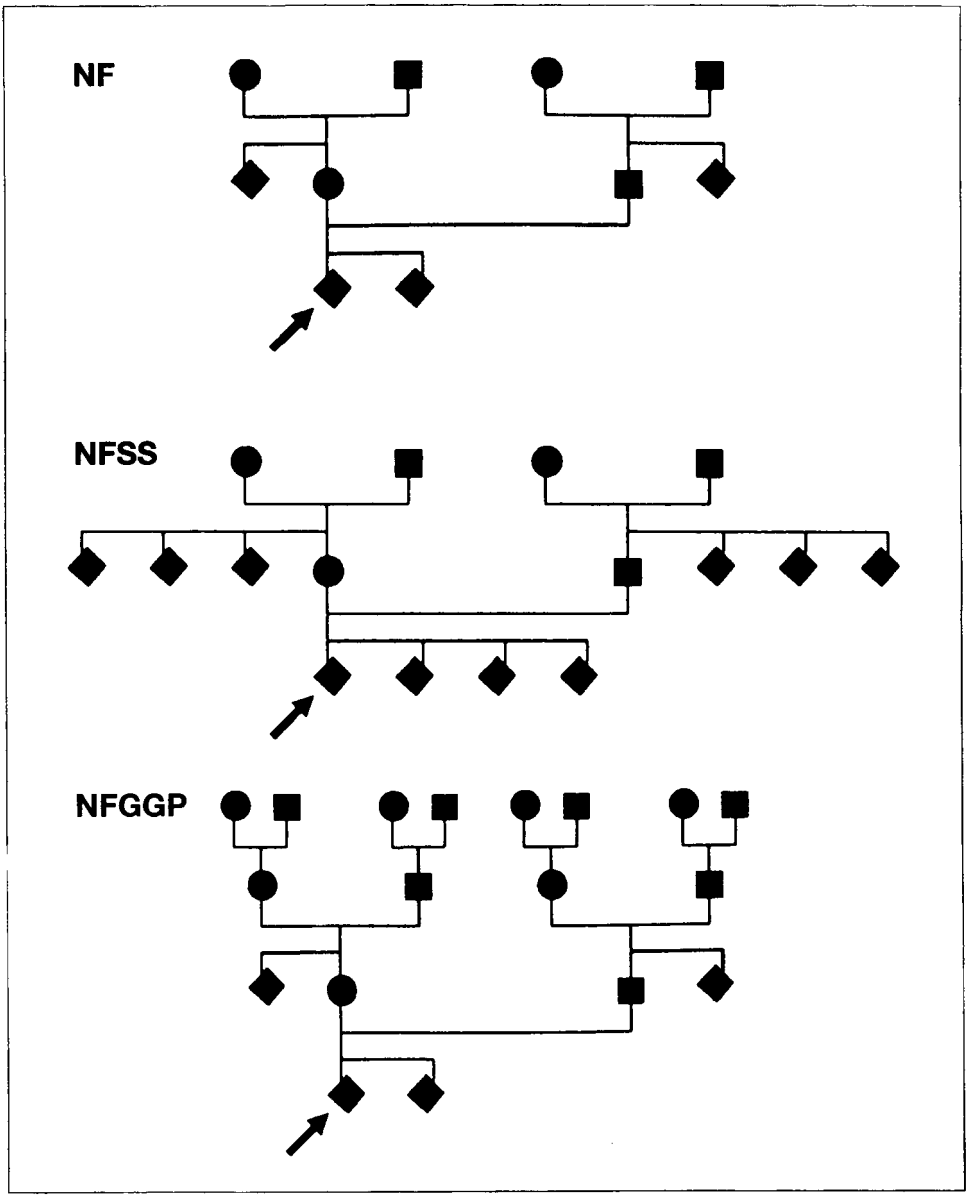

Fig. 1 – *The family trees of the three family types, NF, NFSS and NFGGP, used in the calculations for Table II. Circles represent females, squares represent males, diamonds represent individuals of either sex, and the arrow shows the proband.*

No Sinistral Family Members

Knowing that *all* family members in the NF, NFSS or NFGGP families are right-handed results in 90% of right-handers being of the DD genotype — two and a half-times more likely than in an individual drawn at random from the

TABLE II

The probability of an individual right- or left-hander having each of three genotypes [p(DD), p(DC), p(CC)] and of being right-hemisphere dominant for language [p(RHD)] according to the number of left-handed relatives in the family, the identity of those left-handed relatives, and the size and structure of the family tree

		Right-handers				Left-handers		
	Type	p(DD)	p(DC)	p(CC)	p(RHD)	p(DC)	p(CC)	p(RHD)
No family data:								
Handedness not known	—	.7140	.2619	.0240	.0775	—	—	—
Handedness of proband only	—	.7740	.2130	.0130	.0598	.8450	.1550	.2888
No left-handed relatives:								
All right-handed	NF	.8944	.1030	.0258	.0387	.9300	.0700	.2675
	NFSS	.9360	.0630	.0009	.0162	.9595	.0404	.2601
	NFGGP	.9197	.0788	.0015	.0212	.9469	.0531	.2633
One left-handed relative:								
Parent	NF	.5000	.4776	.0245	.1317	.8763	.1236	.2809
	NFSS	.5305	.4571	.0123	.1204	.9252	.0748	.2687
	NFGGP	.5170	.4663	.0166	.1332	.9037	.0963	.2741
Sibling	NF	.5043	.4700	.0255	.1303	.8595	.1404	.2851
	NFSS	.5331	.4526	.0142	.1203	.9141	.0859	.2715
	NFGGP	.5206	.4604	.0189	.1340	.8899	.1101	.2725
Parental sibling	NF	.7480	.2419	.0009	.0609	.8900	.1100	.2775
	NFSS	.8100	.1855	.0045	.0486	.9329	.0671	.2668
	NFGGP	.7710	.2219	.0071	.0626	.9130	.0870	.2718
Grandparent	NF	.7468	.2431	.0010	.0613	.8898	.1102	.2776
	NFSS	.8084	.1870	.0045	.0490	.9327	.0672	.2668
	NFGGP	.7699	.2229	.0071	.0593	.9128	.0872	.2718
Great-grandparent	NFGGP	.8668	.1296	.0035	.0342	.9260	.0740	.2685
Two left-handed relatives:								
Both parents	NF	.2856	.5112	.2031	.2294	.4562	.5437	.3859
	NFSS	.3077	.5069	.1853	.2194	.4767	.5232	.3808
	NFGGP	.2970	.5090	.1939	.2242	.4667	.5332	.3833
Parent and sibling	NF	.4303	.5210	.0486	.1546	.7811	.2188	.3047
	NFSS	.4853	.4872	.0273	.1355	.8558	.1441	.2860
	NFGGP	.4598	.5036	.0365	.1442	.8212	.1788	.2947
Two grandparents (same side)	NF	.5918	.3905	.0177	.1065	.8803	.1197	.2799
	NFSS	.6796	.3124	.0079	.0824	.9290	.0710	.2678
	NFGGP	.6131	.3740	.0129	.1000	.9065	.0936	.2734
Two grandparents (opposite sides)	NF	.6263	.3345	.0392	.1032	.7401	.2598	.3149
	NFSS	.7018	.2752	.0229	.0803	.7997	.2003	.3001
	NFGGP	.6473	.3183	.0343	.0967	.7554	.2445	.3111
Two great-grandparents (same side)	NFGGP	.8140	.1805	.0054	.0478	.9173	.0827	.2707
Two great-grandparents (opposite sides)	NFGGP	.8175	.1743	.0081	.0476	.8775	.1225	.2806
G/parent and parental sib (same side)	NF	.6969	.2905	.0125	.0851	.8855	.1145	.2786
	NFSS	.7732	.2212	.0054	.0580	.9309	.0691	.2673
	NFGGP	.7287	.2626	.0086	.0700	.9103	.0897	.2724
G/parent and parental sib (opposite sides)	NF	.6273	.3338	.0389	.1029	.7409	.2590	.3147
	NFSS	.7031	.2741	.0227	.0799	.8008	.1991	.2998
	NFGGP	.6482	.3176	.0341	.0965	.7562	.2438	.3110
Parent and parental sib (same side)	NF	.4695	.5065	.0239	.1505	.8759	.1240	.2810
	NFSS	.5116	.4756	.0127	.1251	.9253	.0746	.2686
	NFGGP	.4838	.4983	.0177	.1334	.9035	.0965	.2741
Parent and parental sib (opposite sides)	NF	.4216	.4898	.0884	.1667	.6485	.3514	.3378
	NFSS	.4640	.4719	.0640	.1500	.7108	.2892	.3223
	NFGGP	.4377	.4817	.0805	.1607	.6661	.3338	.3334
Two siblings	NFSS	.4905	.4782	.0312	.1352	.8364	.1636	.2909
Two parental siblings (same side)	NFSS	.7761	.2184	.0053	.0573	.9312	.0688	.2672
Two parental siblings (opposite sides)	NFSS	.7044	.2730	.0225	.0795	.8019	.1981	.2995
	NFGGP	.6490	.3169	.0339	.0962	.7568	.2432	.3108

population. The likelihood of being a heterozygote is also substantially reduced by a similar amount in all three family types, and the likelihood of being CC is also reduced in NFSS and NFGGP families (but not in NF families). The impact on RHD is to reduce the probability of RHD from about 6% to about 2-3%.

One Sinistral Relative

The model was fitted for a single sinistral relative who was a parent, sibling, parental sibling, grand-parent or great-grandparent. A single left-handed parent or sibling reduces the likelihood of being DD to only about 50%, and doubles the likelihood of being a heterozygote to almost 50%, with little effect upon the likelihood of being CC. A single sinistral parental sibling or grandparent has about half the effect upon the likelihood of being DD or DC. A single sinistral great-grandparent doubles the likelihood of being a heterozygote, with relatively little effect upon the other probabilities. A single first-degree sinistral relative doubles the likelihood of being RHD and a sinistral second-degree relative doubles the likelihood.

Two Sinistral Relatives

Not all possible combinations have been presented in Table II. Nevertheless several features are clear. Firstly, not all combinations of relatives are equivalent. Thus although parents and siblings are both first-degree relatives, two sinistral parents have a much larger effect than a sinistral parent and a sinistral sibling, primarily because of the possibility of inheriting C alleles independently from both parents. The effect of having sinistral relatives on the same or different sides of the family differs by genotype; it hardly affects the likelihood of being a heterozygote, but has a substantial effect upon the likelihood of being of the CC genotype (compare, for example, a sinistral parent and parental sib on same and opposite sides). The presence of two sinistral relatives always increases the likelihood of being RHD, often substantially, so that the children of two left-handed parents have over a 20% likelihood of RHD; however even two sinistral great-grandparents doubles the likelihood of being RHD as compared with the case of them being dextral.

Left-handers

Left-handers can only be of genotypes DC or CC, with five out of six left-handers in the general population being heterozygotes. Over a quarter are expected to show RHD. The impact of familial sinistrality upon left-handers is far less than that for right-handers. Of particular importance is that the likelihood of being RHD is hardly altered by familial sinistrality. In general the more sinistral relatives then the higher the likelihood of being CC, with a particularly high incidence if two sinistral relatives are on opposite sides of the family.

The Effect of Family Size

Comparison of the NF and NFSS families, which differ according to the size of the sibship, shows only minor differences in almost all cases. It must be concluded that although different sibship sizes are a theoretical problem in assessing the effect of familial sinistrality, in practice they have relative little impact, mainly because on average the additional members are additional dextrals, who have little effect on genotype frequencies. There is perhaps some evidence that the effect of family size is greater upon the likelihood of being CC than of being DC or DD.

The Utility of Great-grandparents in a Family Tree

Many studies do not collect data on great-grandparents, and it is therefore of practical use to assess their impact by comparing families of type NF with those of type NFGGP. In general the effects of knowing great-grandparental handedness are relatively small except in the case where the great-grandparents are the only sinistral relatives, and then the effect is principally upon the CC likelihood.

To summarise, the comparison of specific family types suggests that:

i. Familial sinistrality has much less impact upon genotype probabilities in left-handers than in right-handers.

ii. First-degree relatives are not all equivalent in their impact upon genotype probabilities.

iii. Two sinistral relatives have a greater impact if they come from opposite sides of the family, rather than the same.

iv. The likelihood of showing RHD for language is greatly affected by having sinistral relatives in right-handers, but has almost no impact in left-handers.

An Empirical Example

In this section the method of calculation is applied to data obtained from the UK National Childhood Encephalopathy Study (NCES). The study originally investigated the relationship between pertussis immunisation and encephalopathy, and included all cases of serious acute neurological illness in children aged between 2 months and 35 months of age admitted to British hospitals during 1976-79 (Miller et al., 1981; Miller, Wadsworth and Ross, 1988). Age and sex matched controls were obtained for each case from the local birth register. Follow-up took place in 1986-89 when children were 10-12 years older (age range 7-15 years) (Madge et al., 1993; Miller et al., 1993), and as part of that study a questionnaire was given to parents of all cases and one control for each case, concerning the handedness of the proband and the biological family.

The questionnaire asked handedness of the proband, and their mother and father, on a five-point scale, which was collapsed to a two-point scale for analysis; and it asked how many of the proband's siblings, the mother's siblings, and the father's siblings were right-handed or left-handed, and about the handedness of the mother's parents and the father's parents (i.e. the proband's

grandparents). It was stressed that information should only be given if the respondents were fairly certain of its correctness, and should only be given for biological relatives.

Information on familial handedness was available for 1384 families, in 582 of which the proband was a case, and in the other 802 the proband was a control. Left-handedness was not ascertainable for all probands, particularly those who were cases, but was more common in the probands (25.5%; N = 523) than in the controls (12.4%; N = 799%), a highly significant difference ($\chi^2 = 34.36$, 1 df, $p < .001$).

Familial handedness was reported for an average of 11.87 relatives (mode = 10, median = 11, SD 4.24, range = 0-43). Probands had a mean of 0.964 left-handed relatives (mode = 0, median = 1, SD = 1.168, range = 0-9), with 44.6% of probands having no left-handed relatives at all. 55.4% of families could therefore be classified as showing FS_{broad} whereas 27.0% of families showed FS_{narrow}.

Genotype probabilities were calculated for the probands (both cases and controls), based on the family tree alone (p_{FH}) and on the family tree in conjunction with the proband's own handedness (p_{FH+PH}). For computational reasons family trees were limited to three proband's siblings, three maternal siblings and three paternal siblings. If there were more than three siblings then since additional left-handed siblings have a demonstrable effect upon genotype probabilities, whereas additional dextral siblings have little effect upon genotype probabilities (see Table II), sinistral siblings were preferentially included in the calculations; this situation applied to only a very small number of cases.

Comparison with Conventional Measures of FS

Figures 2a, 2b and 2c shows probabilities of the genotypes based only upon the family tree (i.e. p_{FH}). There is a wide-range of probabilities, particularly for DD and DC; the rarer CC genotype shows a more restricted range, although substantial variability is present, maximum values reaching about 0.4. Figures 2a, 2b and 2c also classify individuals as FS_{broad} and FS_{narrow}, FS + + individual showing broad and narrow FS, FS + − individuals showing only broad familial sinistrality, and FS − − not meeting either criterion. For each genotype the three FS categories show different ranges of probabilities, although there is moderate overlap, and within classes there is still much remaining variance not explained by FS. The three-fold classification of FS accounts for 86.6% of variance in $p_{FH}(DD)$, 88.4% of the variance in $p_{FH}(DC)$ and 34.8% of the variance in $p_{FH}(CC)$. FS_{narrow} alone (i.e. combining FS + − and FS − −) is almost as successful, accounting for 76.8% of $p_{FH}(DD)$, 77.5% of $p_{FH}(DC)$, and 32.8% of $p_{FH}(CC)$, whereas FS_{broad} on its own (i.e. combining FS + + and FS + −) accounts for only 54.0% of variance in $p_{FH}(DD)$, 56.5% of $p_{FH}(DC)$ and 18.3% of $p_{FH}(CC)$. Of the conventional criteria, FS_{narrow} alone is superior to FS_{broad} alone, but the three-fold classification is more successful; nevertheless with each genotype there is much variance unaccounted by conventional FS measures, particularly for $p_{FH}(CC)$. It should also be emphasised that $p_{FH}(DD)$, $p_{FH}(DC)$

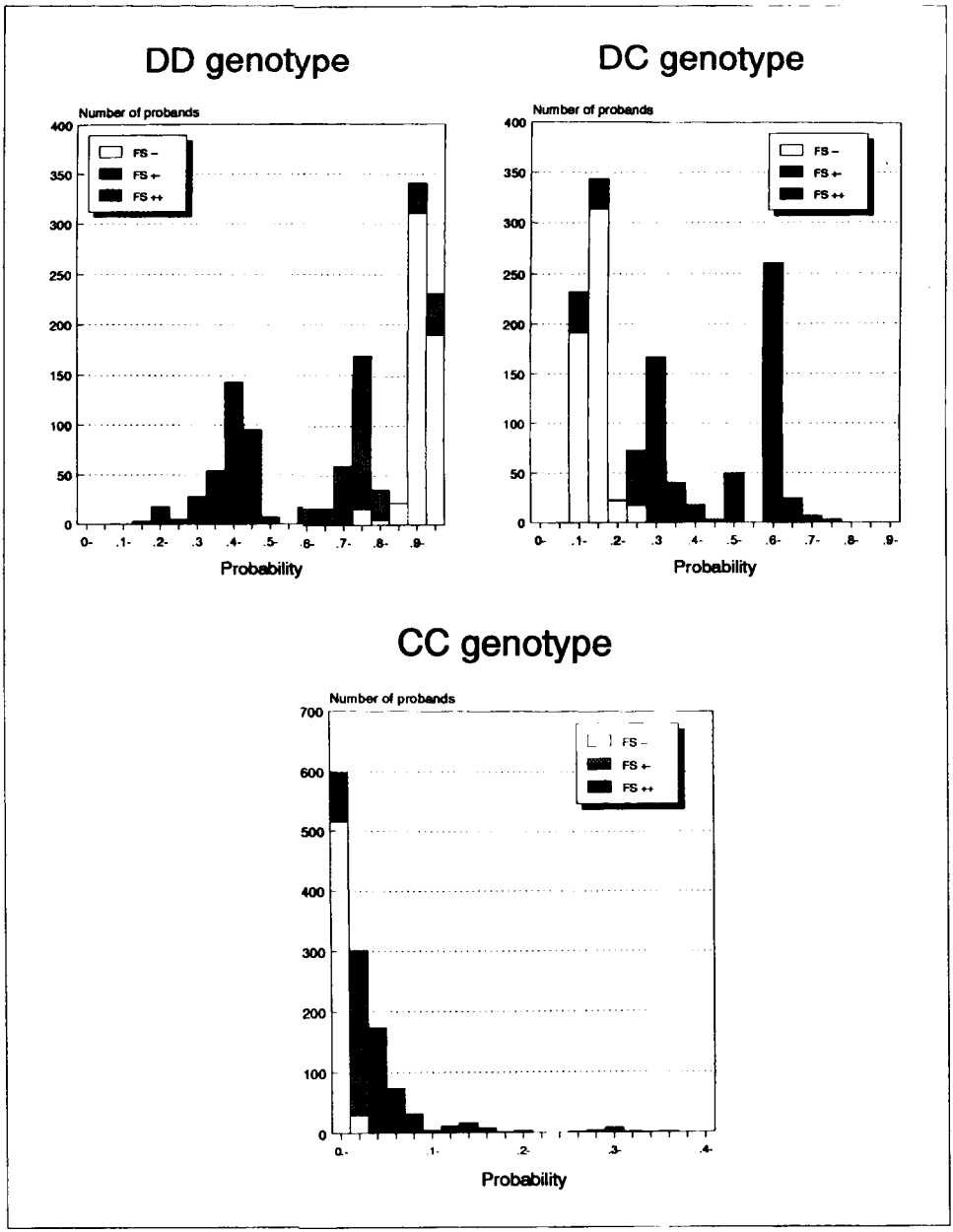

Fig. 2 – *The probability that individual probands are of (a) the DD genotype, (b) the DC genotype and (c) the CC genotype, conditional upon the entire family tree. They are divided according to whether on the basis of the history they show* FS_{narrow} *(FS++),* FS_{broad} *only (FS+−) or are FS− (FS−−).*

and $p_{FH}(CC)$ are multivariate (strictly bivariate) measures, partitioning the genetic component into orthogonal components, whereas FS measures are univariate and do not separate genetic from environmental influences.

TABLE III

Comparison of the median probabilities that right-handed and left-handed probands show the DD, DC and CC genotypes, based entirely on the handedness of the individuals in the family tree, (a) for all NCES controls, (b) for NCES controls for whom both parents are right-handed, and (c) for NCES controls in which at least one parent is left-handed

a) All controls

Median genotype probability	Right-handers (N = 698)	Left-handers (N = 99)	Sig. (one-tailed)
DD	.771	.675	<.0005
DC	.215	.306	<.0005
CC	.011	.020	<.0005

b) Both parents right-handed

Median genotype probability	Right-handers (N = 571)	Left-handers (N = 68)	Sig. (one-tailed)
DD	.850	.712	<.025
DC	.144	.274	<.025
CC	.006	.013	<.025

c) One or more parents left-handed

Median genotype probability	Right-handers (N = 127)	Left-handers (N = 31)	Sig. (one-tailed)
DD	.410	.355	<.05
DC	.540	.535	NS
CC	.041	.043	NS

$p_{FH}(DD)$, $p_{FH}(DC)$ and $p_{FH}(CC)$ as Predictors of Left-handedness

Based on information in the family history of sinistrality, left-handers are more likely to be of genotypes DC and CC than are controls, and less likely to be DD. This was tested in the control subjects of the NCES, comparing 698 right-handers with 99 left-handers. The median genotype probabilities are shown in Table IIIa and all are significantly different in the expected direction (using a Mann-Whitney U test). A more exacting test of the hypothesis can be carried out by comparing right and left-handers who are the offspring of two right-handed parents, and once again the effects are significant and in the expected direction (Table IIIb). A more exacting test, comparing the offspring of parents at least one of whom is left-handed (Table IIIc) shows a significant effect for DD but not for DC or CC. Taken overall these results suggest that measures of $p_{FH}(DD)$, $p_{FH}(DC)$ and $p_{FH}(CC)$ can differentiate right- and left-handers as theory predicts.

FS_{narrow}, FS_{broad}, $p_{FH}(DD)$, $p_{FH}(DC)$ and $p_{FH}(CC)$ Compared as Predictors of Left-handedness

If measures derived from a knowledge of the family tree are to be useful then they should predict the presence of left-handedness in individual subjects.

The ability of the various measures to do this was tested in the 799 control subjects from the NCES data set. Handedness (right or left) was the dependent variable in a multiple logistic regression carried out using the package GLIM (Healy, 1988). A series of hierarchical models was compared to test various hypotheses. *A priori* it was predicted that FS_{narrow} would be a better predictor than FS_{broad} and that $p_{FH}(CC)$ would contribute more to prediction than $p_{FH}(DD)$ and $p_{FH}(DC)$ after FS was taken into account.

FS_{narrow} and FS_{broad} Compared

Together FS_{narrow} and FS_{broad} were significant predictors of left-handedness ($\chi^2 = 11.06$, 2 df, $p < .005$). On its own, FS_{narrow} was a significant predictor of left-handedness ($\chi^2 = 8.41$, 1 df, $p < .005$); subsequent addition of FS_{broad} to the model did not result in a further improvement in fit ($\chi^2 = 2.65$, 1 df, NS). Similarly FS_{broad} alone was a significant predictor of left-handedness ($\chi^2 = 8.57$, 1 df, $p < .005$), and subsequent addition of FS_{narrow} to the model did not result in a significant improvement in fit ($\chi^2 = 2.49$, 1 df, NS). There is therefore no significant difference in either FS_{narrow} or FS_{broad} in their ability to predict left-handedness. In view of its theoretical advantages, FS_{narrow} will therefore be used for the next section.

$p_{FH}(DD)$, $p_{FH}(DC)$, $p_{FH}(CC)$ Compared

Together the three measures are significant predictors of left-handedness ($\chi^2 = 14.33$, 3 df, $p < .005$). Each of them alone is also significant [$p_{FH}(DD)$: $\chi^2 = 9.75$, 1 df, $p < .005$; $p_{FH}(DC)$: $\chi^2 = 11.77$, 1 df, $p < .001$; $p_{FH}(CC)$: $\chi^2 = 10.39$, 1 df, $p < .005$]. On their own the three measures of genotype probability show only small differences which are probably of little consequence.

FS_{narrow} and $p_{FH}(DD)$, $p_{FH}(DC)$ and $p_{FH}(CC)$ Compared

A series of models was compared to assess whether either set of measures contributed any additional prediction after the other had been taken into account. In the first model $p_{FH}(DD)$, $p_{FH}(DC)$ and $p_{FH}(CC)$ were fitted, and then at the next step FS_{narrow} was added to the model; the lack of a significant improvement in fit (χ^2-square = 0.20, 1 df, NS) suggests that FS_{narrow} contains no additional information to that contained within the genotype probabilities themselves. In the second model FS_{narrow} was entered into the equation and then $p_{FH}(CC)$, $p_{FH}(DD)$ and $p_{FH}(DC)$ were entered in that order (reflecting the a priori prediction of the additional variance that each was likely to contribute). $p_{FH}(CC)$ showed a significant improvement in fit ($\chi^2 = 4.04$, 1 df, $p < .05$), but no additional improvement was shown by adding in $p_{FH}(DD)$ ($\chi^2 = 1.62$, 1 df, NS) or $p_{FH}(DD)$ ($\chi^2 = 0.46$, 1 df, NS). The implication is that the calculation of genotype probabilities provides additional information over and above that provided by FS_{narrow}, particularly due to $p_{FH}(CC)$, which shares least variance with FS_{narrow}, whereas there is no additional information in FS_{narrow} which is not already implicit in the genotype probabilities.

FS as a Predictor of Language Dominance

The McManus genetic model of handedness allows one to predict the probability, given an individual's genotype, that they show right-hemisphere dominance for language. In it simplest form (McManus, 1985a) the model predicts that 0%, 25% and 50% of individuals with genotypes *DD*, *DC* and *CC* will show RHD. If the probabilities have been calculated that an individual is of those genotypes then the probability of them being RHD can be calculated as $p(DC)/4 + p(CC)/2$, where $P(DC)$ and $p(CC)$ can be calculated based on FH alone or based on both *PH* and *FH*. Figure 3 shows, separately for right and left-handed controls, the probability, conditional on both *PH* and *FH*, that the probands show RHD. It is clear that within the right-handers there is a wide range of probabilities, whereas there is a much smaller range within the left-handers. It is also clear, as Bishop has previously emphasised (Bishop, 1990), that FS provides little differentiation between left-handers, although there is useful differentiation between right-handers. Familial sinistrality therefore provides useful information for differentiating between right-handers but is much less useful for left-handers.

Using Genotype Probabilities to Test Annett's Theory of a Balanced Polymorphism

Annett and Manning (1989, 1990b) proposed that heterozygotes are intellectually advantaged compared with homozygotes, and that this explains the maintenance of handedness as a balanced polymorphism. The present analysis allows a more direct test of this hypothesis calculating the probability that an individual is of the DD, DC and CC genotypes. It is assumed for present purposes that the three genotypes are broadly similar to Annett's RS++, RS+− and RS−− genotypes, although it is accepted that the two models do show differences in the expected population of heterozygotes — 49% in the Annett model compared with 26% in the McManus model. If the model is correct then individuals with a higher probability of being DC (and a lower probability of DD or CC) should show increased intellectual ability; i.e. ability should be correlated positively with $p_{FH+PH}(DC)$ and negatively with $p_{FH+PH}(DD)$ and $p_{FH+PH}(CC)$. Table IV shows such correlations for 460 NCES controls for whom data were available on five standardised psychometric tests, and six derived measures obtained from them (McManus and Mascie-Taylor, 1983; Madge et al. 1993). There is no association between overall intellectual ability (G) and $p_{FH+PH}(DD)$, $p_{FH+PH}(DC)$ and $p_{FH+PH}(CC)$. The only significant result is significant only at the 0.05 level. Given repeated significance testing, and the resultant inflation of the alpha level, that result is probably not truly significant. A canonical correlation relating genotype probabilities to the five psychometric tests was not significant (Wilk's Lambda = .967, p = .138). Given the effect for reading is in the opposite direction to that predicted by Annett (Annett and Manning, 1990b; Annett, 1991a) then the present data provide no support for heterozygotes being of greater intellectual ability. They do however show that the method can be used for testing hypotheses concerning the balanced

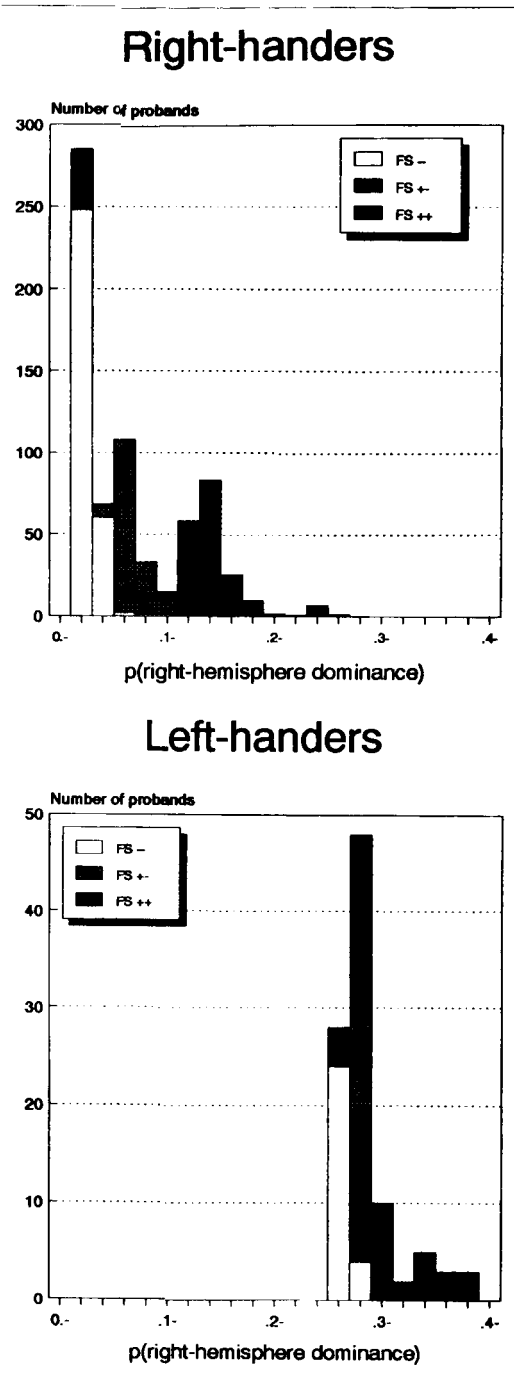

Fig. 3 – *The probability, conditional upon proband and family sinistrality, that control probands are right-hemisphere dominant for language, based on the McManus (1985a) genetic model. Results are shown separately for a) right-handers and b) left-handers. Individuals are also classified according to whether they show* FS_{narrow} *(FS++),* FS_{broad} *only (FS+−) or are FS− (FS−−).*

TABLE IV

Correlations, for control subjects in the NCES, between the probability of being of genotype DD, DC or CC, and ability on five psychometric tests, and six derived measures ('G': Principal component of the five measures; M_3, V_3, R_3 and A_3: residuals for the matrices test, verbal ability test, reading test and arithmetic test after taking each of the other three variables into account; S_4: the residual on the spelling test after taking all four other psychometric tests into account. N varies from 453 to 471)

	P_{FH+PH} (DD)	P_{FH+PH} (DC)	P_{FH+PH} (CC)
Raven's Progressive Matrices	−.0014	.0006	.0040
Mill Hill Vocabulary Test	.0187	−.0268	.0205
Graded Word Spelling Test	.0396	−.0368	−.0372
Wide-span Reading Test	.1070	−.1143	−.0396
	(p=.022)	(p=.014)	
Graded Arithmetic-Mathematics Test	.0749	−.0822	−.0191
		(p=.075)	
G	.0636	−.0686	−.0211
M_3	−.0504	.0564	.0083
V_3	−.0590	.0546	.0562
S_4	−.0464	.0598	−.0238
R_3	.1013	−.1035	−.0567
	(p=.031)	(p=.027)	
A_3	.0554	−.0596	−.0189

polymorphism which must surely underlie handedness.

The Environmental Information in Familial Sinistrality

Table II shows that not all trees with the same number of left-handers affect equally the genotype of the proband. The implication is that genetic components do not account for all the variance in the family tree, so that remaining variance must be not-genetic, and hence environmental in some sense (including genotype-environment interaction). This variance could be used to determine whether there are learned, non-genetic processes involved in lateralisation or other phenomena, by using the calculated genotype probabilities as covariates in an ANOVA or regression analysis in which family phenotypes of family members have been entered as variates. Any remaining effect of phenotype must result from non-genetic influences.

Discussion

A family tree contains a large amount of information, much of which is not adequately summarised by measures of familial sinistrality. Comparison of narrow and broad FS for predicting handedness suggests that they do not differ significantly; tinkering with them further is therefore unlikely to produce other superior measures. The problems with FS lie in its lack of a specific genetic model, and therefore its confounding of genetic information with non-genetic or environmental information, and in its reduction of all information to a single categorical measure instead of multi-dimensional continuous measures.

This paper describes a method for extracting specifically genetic information from a family tree, calculating the probability that each individual is a particular

genotype. Information present in FS and not in estimates of genotype probability can be considered as non-genetic. In the case of predicting handedness of a proband, the analyses suggest that FS contains no additional information over and above that in the genotype probabilities, implying that there is little useful non-genetic information in the family tree for predicting handedness. In contrast, genotype probabilities seem to contain information not present in FS, and this is particularly information on the CC genotype.

Calculation of genotype probabilites allows the testing of hypotheses that are not testable by measures of FS, particularly concerning other attributes correlated with genotypes rather than phenotypes. In particular the method allows testing of the hypothesis that heterozygotes have increased intellectual ability (Annett and Manning, 1989); but it could also be used to test whether any other variables are correlated with heterozygosity. Although Annett's balanced polymorphism model may not be empirically correct (McManus, Shergill and Bryden, 1993), in theoretical terms there seems little doubt that left-handedness must be maintained in the population by heterozygote advantage, and the search for that advantage will be facilitated by the present methodology.

As described the method for calculating genotype probabilities is computationally expensive. Nevertheless that will provide less problems as computational power continues to decline in price, particularly if more efficient algorithms are found for solving the equations.

Finally, it should be noted that although the method as described allows the calculation of genotype probabilities based on a particular genetic model, the method can also be reversed, using the total likelihood based on a set of family trees as a measure of the goodness of fit of a genetic model of handedness, and using differences in goodness of fit to compare contrasting models, or to estimate free parameters within a single model.

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