INHERITANCE OF SUSCEPTIBILITY: LAMARCKISM REVISITED

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ABSTRACT

The familial nature of susceptibility to rheumatic fever has been known for nearly three quarters of a century but even after massive ascertainments of affected families in 5 major cities, viz Toronto, Belfast, London, Glasgow and New York, a consensus on the exact mode of inheritance could not be reached. Reduced penetrance was suggested 40 years ago and still cited today even though the fit is poor. However with the sampling bias of the observed data resolved in the recently formulated geometric continuum $v^{affected-1} x$ P(sibship) (where $O < v \rightarrow \infty$) all those published ascertainments clearly show a unilocal Mendelian recessive mode of inheritance. Since rheumatic fever is clearly associated with streptococcal sore throat, I have therefore demonstrated the inheritance of an acquired trait. This Larmarckian concept is explained using simple numerical examples.

Keywords: Recessive rheumatic fever, haemolytic streptococcal infection, gene to phene, gene to susceptibility and to phene, regressive segregation analysis.

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INTRODUCTION

A long embraced genetic concept[1] considers the genotype that fails to manifest the phenotype that is characteristically associated with it, 'incompletely penetrant'. That carries the assumption of direct commutability from genotype to phenotype, ie

genes → overt disease

Gary and Chase[2] stated this assumption when they declared that the possible cause for "the nonmanifestation may be programmed into the phenotype by genetic information", a typical neo-Darwinian perception. This 'gene-is-also-phene' perception sets the limits in family studies of Mendelian traits whereby detection of the affected genotype more frequently than random is possible but less than random detection is impossible. Thus when the genetic causation of the familial tendency of rheumatic fever[3] and its major sequela, rheumatic heart disease, is considered or cited as incompletely penetrant[4-6] it would appear to deny, perhaps unwittingly, their causal relationship with pharyngeal infection by Lancefield group A haemolytic streptococci[7-10], an environmental agent, by which non-infection would simply mean no rheumatic fever. There is however little doubt that rheumatic fever and rheumatic heart disease are acquired diseases consequent upon virulent streptococcal infection, and that prompt anti-microbial treatment or prophylaxis can avert the overt pathology[9-11]. The fact that observed ascertainment data of rheumatic families do not match expectations under the assumption of incomplete penetrance[12] shows that the assumption of direct gene-to-phene commutability is incorrect. Recently, however, Sit[13] has shown that if streptococcal infections were considered as a causal factor of the overt disease, then a unilocal Mendelian recessive transmission would match the segregation patterns of rheumatic families from all 4 large scale ascertainments of rheumatic fever families that are ever published. The analysis considers a 2 step cascade, viz

genes → susceptible phenotype → overt disease

where genes→ *susceptible phenotype* conversion depends on genetic segregation (hereditary) while *susceptible phenotype→ overt disease* conversion depends on streptococcal infection. Correlation of a definitive mode of genetic inheritance with the manifestion of an acquired disease breaks a long established barrier in genetic perception. It is also very clearly reminiscent of pre-Darwinian or Lamarckian ideas[14] concerning the inheritance of acquired diseases. In the post-Darwinian era, Lamarckism is taboo and very much distanced by neo-Darwinians. However, Lamarckian ideas, which had an early following in the eugenics movement on both sides of the Atlantic[15], may seem rationalizable as illustrated here based on Uchida's Toronto survey of rheumatic families[5] which I have shown to match recessive transmission at detection bias unrestricted by perceptions of gene-to-phene conversion[13]. Perhaps more important than the new-found ability to assigning risk ratios in families with rheumatic fever, a disease that continues to be a global problem with an estimated 15 to 20 million new cases a year[10], is the realization that one could in effect inherit an environmentally caused disease if the environmental agent will only produce the disease in persons who are sensitive, a heritable trait. This is Lamarckian.

RESULTS AND DISCUSSION

The binomial expansion of $(a + b)^s$, (where s = sibship size, $a = {}^3/_4$ the normals proportion and $b = {}^1/_4$ the affected proportion of recessive segregation from heterozygous parents), gives the expected proportions of the various combinations of affected and non-affected sibs. The first term of that expansion, a^s, represents the proportion of sibships with no affected members and therefore truncated off in a survey of affected families (an ascertainment) since such families are not distinguishable from normal true-bred matings.

In the first instance we shall take the view point that rheumatic fever occurs only in those who are susceptible which is an inherent disposition of the person[6,11] and that virulent haemolytic streptococci is the necessary causal factor in rheumatic fever. If the infection is treatable in its early stages with antimicrobial therapy then the number of persons per family succumbing with the rheumatic pathology could differ from

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Table I - Expected distribution of susceptible (recessive) and rheumatic sibs in $(a + b)^3$ given that streptococcal infection modulates the susceptible to rheumatic conversion producing only a minimum number of affected per sibship, (the first term of $(a + b)^3$ is truncated)

$(a + b)^3 =$	$3a^2b$	$3ab^2$	b^3	Total
Normal sibs	2	1	0	
Recessive sibs	1	2	3	
Bias, $v^{r-1} =$	v^0	v^1	v^2	
Proportion of family	$v^0 3\left(\frac{3}{4}\right)^2\frac{1}{4}$	$v^1 3\left(\frac{3}{4}\right)^1\left(\frac{1}{4}\right)^2$	$v^2\left(\frac{1}{4}\right)^3$	
If $v = 0.245$	$= \frac{27}{64}$	$= \frac{2.205}{64}$	$= \frac{0.060025}{64}$	$\frac{29.265025}{64}$
Proportion of rheumatics	$\frac{1}{3} \times \frac{27}{64}$ $= \frac{9}{64}$	$\frac{2}{3} \times \frac{2.205}{64}$ $\frac{1.47}{64}$	$\frac{3}{3} \times \frac{0.060025}{64}$ $\frac{0.060025}{64}$	$\frac{10.530025}{64}$

the number of sensitive persons. Let us consider families who are sensitive to rheumatic fever. If in these 3 sib families (sibship of size 3) only one sib per familiy is affected with rheumatic fever, then the average number of rheumatics per sibship is

$$\frac{\text{rheumatic total}}{\text{total ascertained}} \times \text{sibship size} = \left(\frac{37}{192} / \frac{37}{64}\right) \times 3 = 1$$

See Table I.

Now, in the second instance, we shall consider a direct gene-to-phene commutability whereby the recessive genotype is also the rheumatic, overtly affected, phenotype in similar 3 sib families but qualified by the detection bias[16,17] ($v = 0.245$) which I have previously derived[13] from the rheumatic fever families in the Toronto survey reported by Uchida[5]. The expected average number of affected per sibsip which is

$$\frac{\text{affected total}}{\text{total ascertained}} \times \text{sibship size} = \frac{(10.530025)}{(29.265025)} \times 3 = 1.079448$$

See Table II.

One step (direct) gene-to-phene conversion, qualified only by the detection bias $v = 0.245$ will satisfy neo-Darwinian per-

Table II - Expected distribution of rheumatic sibs in $(a + b)^3$ in Uchida's rheumatic fever ascertainment in Toronto[5], (the first term of $(a + b)^3$ is truncated)

$(a + b)^3 =$	$3a^2b$	$3ab^2$	b^3	Total
Normal sibs	2	1	0	
Susceptible sibs	1	2	3	
Proportion of family	$3\left(\frac{3}{4}\right)^2\frac{1}{4}$	$3\frac{3}{4}\left(\frac{1}{4}\right)^2$	$\left(\frac{1}{4}\right)^3$	
	$= \frac{27}{64}$	$= \frac{9}{64}$	$= \frac{1}{64}$	$\frac{37}{64}$
Rheumatic sibs	1	1	1	
Proportion of rheumatics	$\frac{1}{3} \times \frac{27}{64}$	$\frac{1}{3} \times \frac{9}{64}$	$\frac{1}{3} \times \frac{1}{64}$	
	$= \frac{9}{64}$	$= \frac{3}{64}$	$= \frac{1}{192}$	$\frac{37}{192}$

ceptions of what inheritance should be. This calculated average number of affected is in complete conformity with observed data[13]. The question now is what is the reason behind a detection bias that is less than unity. The explanation is given in the result presented in Table I which is similiar to that of Table II. In other words, it happens when the number of rheumatics is dissociated from the expected number of recessives, due to early treatment of the infection, better awareness, hygiene or social conditions. Thus if one does not deny the fact that rheumatic fever is a direct consequence of streptococcal sore throat then I have demonstrated the inheritance of an acquired disease.

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