

Penetrance of a rare genetic defect

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(Received 5 June 1967)

1. INTRODUCTION

In recent years considerable attention has been given to genetic mechanisms responsible for phenotypic abnormalities whose incidence is characteristically low in the general population as well as among the relatives of affected individuals. The genetic mechanism attributed to one such trait, congenital tremor in White Leghorn chicks, poses an inconsistency with regard to the postulated levels of incidence and penetrance. In the only report of an occurrence in chickens known to us Hutt & Child (1934) described congenital tremor as a lethal neuromuscular defect which they observed in less than 5% of the sibs of affected chicks. Hutt and Child ruled out sex linkage and accepted a single recessive gene with unusually low penetrance as the most plausible cause of the disease, although they did consider the possibility that two pairs of recessives might be responsible. In his book, Hutt (1949) repeated his earlier conclusion which was adopted later by other reviewers (Koch, Fischer & Schumann, 1957; Wiesner, 1960).

The postulate of substantially decreased penetrance of this rare trait is at variance with evolutionary theory which, as a rule, predicts an inverse relation between penetrance and population incidence of harmful traits. This note presents the results of a new analysis of Hutt and Child's data under the hypothesis H that congenital tremor is caused not by one but by two pairs of recessive genes and that penetrance is complete.

2. ANALYSIS AND DISCUSSION

Hutt & Child (1934) observed the first cases of congenital tremor among the offspring of two closely related birds. Over a period of several years 39 tremor chicks were produced by a total of 23 female and 11 male parents all of which belonged to the same pedigreed flock of White Leghorns. Each of these parents had produced at least one tremor chick and was thus known, *a posteriori*, to have been a 'carrier'. The pedigree data consist of an array of full-sib families which represent all the offspring of matings between two known carriers. Some of the tremor-producers, particularly males, were mated to more than one carrier, so that the full-sib families may be arranged either by common dam into 23 maternal half-sib families or by common sire into 11 paternal half-sib families. Hutt and Child reported their observations in this manner as shown in Table 1. No infor-

Table 1. *Affected chicks/total chicks observed in 23 maternal and in 11 paternal half-sib families (after Hutt & Child, 1934)*

Maternal sibships

1/2, 1/5, 1/7, 2/7, 1/8, 2/9, 1/11, 1/12, 2/14, 2/14, 1/16, 1/19, 1/20, 2/20, 1/21, 2/21, 2/21, 2/22, 1/25, 1/28, 3/39, 3/51, 5/55. Sum = 39/447.

Paternal sibships

1/2, 1/5, 1/7, 1/7, 2/15, 2/35, 7/35, 3/63, 6/71, 6/91, 9/116. Sum = 39/447.

mation on remating of carriers and, consequently, on the composition of the half-sib families in terms of constituent full-sib families was given in the original paper.

The first step in the present analysis was to calculate the segregation ratio (p) from the data in Table 1. For this purpose it was assumed that carriers were double heterozygotes but that at the time of mating it was not known whether both parents were carriers or not. Matings between two carriers with no affected offspring could not be distinguished from non-carrier matings in the population; their absence from the data available for analysis (Table 1) necessitates a correction when p is estimated. The probability of two double heterozygotes producing a sibship without any affected chicks decreases with increasing family size (s); it becomes less than 5% in sibships of 47 or more chicks, i.e. $s = 46.4$ when $(15/16)^s = 0.05$. Most sibships in Table 1 are smaller than 47 chicks. Therefore, some correction must be applied for small family size in a manner that depends upon the mode of ascertainment of affected chicks and on the mating system.

In human genetics (Steinberg, 1959), ascertainment of full-sib families with one or more affected sibs is referred to as 'truncate', if every member of the population is observed. Hutt and Child did observe and classify every chick hatched in their flock of White Leghorns. Thus, analysis of the present data according to truncate selection seems in order, provided that it is performed on full-sib families. The reason for the restriction is that in correcting for small family size the expected number of affected individuals in one large family is somewhat less than twice the number expected in two families of half that size. Thus, mistaking two small full-sib families with one tremor chick each for one large half-sib family with 2 tremor chicks biases the expected number of tremor chicks downwards and the estimate of p upwards. Bias from this source is likely to be small in the case of the maternal sibships most of which are considered to consist of only one full-sib family.

Table 2 gives segregation values calculated for maternal sibships of two sizes by the maximum likelihood method pertaining to truncate ascertainment. Finney's (1949) tables were used to obtain iterative values of p for small families (≤ 20 sibs); tables for large families (≥ 21 sibs) were available from another study (Sittmann, 1967).

Small and large maternal families differed very little in their estimates of p . These two estimates are essentially independent of each other, and the agreement between them serves as an internal check of the consistency of the segregation

Table 2. *Proportion of tremor chicks in maternal and in paternal half-sib families before and after correction for small family size by maximum likelihood methods pertaining to two types of ascertainment**

Half-sib families			Phenotypes observed		Percentage of tremor chicks		
Type	Sizes	Number	Normal	Tremor	Uncorrec- ted data	Truncate selection	Single selection
Maternal	2-20	14	145	19	11.59	5.79 ± 2.36	3.33 ± 1.47
	21-55	9	263	20	7.07	5.96 ± 1.58	4.01 ± 1.19
	2-55	23	408	39	8.72	5.91 ± 1.31	3.77 ± 0.93
Paternal	2-116	11	408	39	8.72	7.84 ± 1.29	6.42 ± 1.17

*Data from Hutt & Child (1934).

ratio in these data. The overall estimate of 5.91% differed from the expected 6.25% by less than one standard error (Table 2). Thus, there is good agreement with the postulated double recessive mode of inheritance and complete penetrance of congenital tremor.

A different method of estimating *p* was required for the 11 paternal sibships, because they consisted on average of at least two full-sib families. The likelihood for a male parent to be recognized as a carrier is proportional to the number of carriers to which it had been mated. In human genetics, this corresponds to 'single' selection where the probability of ascertainment of a full-sib family is proportional to the number of affected sibs in that family (Steinberg, 1959). Some of the paternal half-sib families were composed of only one and others of several full-sib families, a situation intermediate between truncate and single selection but approaching more nearly the latter. It can be seen from the last column in Table 2 that *p* estimated from paternal half-sib families by the method pertaining to single selection is in good agreement with the hypothesis *H*.

The estimate of *p* derived from maternal sibships is considered more reliable than that from paternal sibships, because the former agree more closely with the conditions required by the method of analysis used. Both estimates are biased upwards for two reasons relating to the assumptions first that parents were recognized as carriers only after they had been mated, and secondly that all carriers were double heterozygotes.

With regard to the first source of bias, consider a dam that produced tremor and normal chicks with each of two sires, the first unknown and the second known to be a carrier at the time of mating. The correction for small family size should be applied only to the sibship produced by the former; if the correction is applied to the whole maternal sibship, then the expected number of tremor chicks is biased downwards and the estimate of *p* upwards. The magnitude of bias from this source is likely to be very small.

It is more serious to assume that all of the 34 male and female carriers were double heterozygotes. Little can be inferred from the original paper on the breeding

history of the flock, but it is likely that some carriers were homozygous at one of the two loci. Mated to double heterozygotes these carriers give rise to a segregation ratio of 1/8 (hypothesis H_1). A check of the individual sibships in Table 1 was performed to see whether they agreed more closely with H or with H_1 . In two maternal sibships, i.e. 2/7 and 2/9, the observed number of tremor chicks exceeded the number expected under both, H and H_1 . The smaller of the two sibships was the only maternal family that differed significantly from H at the 5% level of probability. Further, all maternal sibships with two or more tremor chicks and $s \geq 14$ had observed numbers of mutants intermediate between those expected under H and H_1 respectively. Of these sibships, only those with $s = 14, 20, 55$ agreed more closely with H_1 than with H . Among the paternal sibships, only one (i.e., 7/35) differed significantly from H . In all, the number of tremor chicks expected under H was lower than the observed number in 10 and higher in 13 of the 23 maternal sibships; analogous frequencies for the 11 paternal sibships were 5 and 6. Thus, bias from homozygosity of carriers is considered to be present but not to a serious extent. It may be cancelled to some extent, in that some tremor chicks may have been misclassified as normals (Hutt & Child, 1934).

Haldane (1949) suggested a test of homogeneity that provides an independent check of the hypothesis. For a given segregation ratio and family size there is a binomial probability that a family contains exactly one abnormal sib. This probability summed over all sibship sizes multiplied by their frequency gives the total number of sibships expected to contain exactly one mutant. Under the double recessive hypothesis 13.0 of the 23 maternal sibships are expected to include exactly one tremor chick as compared with 12 observed (Table 3). Next, the

Table 3. *Number of maternal sibships with exactly n affected chicks. Expectations are calculated for four segregation ratios (p) under the assumption of truncate ascertainment of affected individuals*

n	Observed number	Expected number			
		p = 0.0591	p = 0.0625	p = 0.1250	p = 0.2500
1	12	13.40	13.00	7.75	3.29
2	8	6.82	6.63	4.06	1.62
3	2	1.27	1.19	0.29	0.005
5	1	0.53	0.51	0.16	0.002

sample of families is truncated so as to exclude all families with one affected and to include only those with two or more affected sibs. Binomial probabilities for exactly two abnormals per family are summed over all remaining family sizes. Of the 11 maternal families with two or more tremor chicks 6.6 are expected to have exactly two as compared with 8 families observed (Table 3). This process is repeated with the distribution of families truncated so as to include only the families with three or more affected and finally only the one family with five affected sibs. Expected and observed frequencies agree closely when the underlying

segregation ratio is either the estimate calculated from the sample ($p = 0.0591$) or the theoretical value ($p = 0.0625$). Segregation ratios of 1/8 and 1/4 give grossly aberrant results which cannot be explained by incomplete penetrance.

Manifestation of the disease in terms of mean number of muscle contractions per second in affected Leghorn chicks was very similar to that observed by Dyrendahl (1958) in affected young of the common duck. Few segregating families of ducks were studied, but in these hereditary tremor appeared to be caused by only one pair of autosomal recessive genes (Dyrendahl, 1958). No anatomical defect has been found in affected young of either species.

SUMMARY

Contrary to the conclusion of earlier workers, penetrance of a very rare genetic defect, congenital tremor in White Leghorn chicks, was found to be complete. By appropriate correction of the original data for small family size it is shown that the defect is determined not by one but two pairs of autosomal recessive genes. In the terminology of human genetics, ascertainment of affected individuals corresponded to conditions of 'truncate' selection in the case of maternal sibships and more nearly to 'single' selection in the case of paternal sibships.

Preparation of tables used in this study was supported in part by Public Health Service grants TIGM701-04/05 and FR-0009 to the Genetics Department and the Computer Centre, respectively, at the University of California at Davis. Services of the Computing Center, McGill University, are gratefully acknowledged. The author expresses his sincere thanks to the editor for valuable suggestions.

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