

TWIN AND FAMILY STUDIES IN INHERITANCE OF CLEFT CHIN

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Abstract: In this paper an attempt has been made to test the probable genetic mechanism of cleft chin, a morphological character in man. The material consists of 107 pairs of twins, 132 families and 424 unrelated individuals collected from the Chitpavan Brahmins of Pune, Maharashtra. Analysis attempts to establish that cleft chin is dominant over absence of the trait and it depends on a single locus diallelic autosomal gene.

ON the lower margin of the chin of some individuals a fissure or a depression is some times observed. This is cleft chin. Its mode of inheritance is not yet fully established. Some pedigree studies indicate it to be an autosomal dominant (Winchester, 1967). Malhotra and Sarkar (1975) find the trait to be inherited as an autosomal, di-allelic and incompletely dominant. An attempt has been made in this paper to investigate further the pattern of inheritance of this trait.

The principal methods adopted for this study are twin, family and population. The material consists of 107 pairs of twins (53 MZ and 54 DZ), 132 families consisting of father, mother and at least two children per family (total number of children being 392 and parents 264) and 424 (216 males and 208 females) unrelated persons from general population. The individuals from family and population data are selected from the Chitpavan subcaste of Maharashtra.

The lower margin of the chin of each individual was observed and the presence or absence of the depression, dimple,

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June, 1977]

Guha : INHERITANCE OF CLEFT CHIN

171

fissure or cleft was recorded. Zygosity of the twins was diagnosed on the basis of serology, somatometry, somatoscopy, P.T.C. taste sensitivity, secretor factor, G-6-PD, colourblindness, dermatoglyphics and body weight (Details of diagnosis and importance of twin study is provided in the present investigator's thesis submitted to the Poona University, 1975).

The degree of concordance is total in both male-male and female-female series of MZ twins, being 100 per cent each. In DZ series they are 78.6 per cent, 82.6 per cent and 70.6 per cent in male-male, male-female and female-female series respectively. The heritability estimate calculated after Holinger (1929) is found to be 1. The results positively indicate that heredity is the chief factor in the incidence of this trait (Table 1).

Bisexual variation is observed in the data but there is no age variation. The four possible types of matings PXP, PXA, AXP and AXA do not differ statistically from the theoretical expected values ($\chi^2 = 1.05$, d.f. 3 $P > 0.10$). PXA and AXP matings were later combined as no difference was observed between them. Frequency distribution of children from different types of mating show that PXP yields 3.2 per cent of A children and AXA yields 1.2 per cent of P children. Rest in both matings resemble parents.

From the distribution of children from all mating types it appears that the trait is hereditary. Before testing the genetic hypothesis it is necessary to explain if a non-genetic chance hypothesis can explain the occurrence of the trait. Under chance hypothesis the ratio between the two types of children [present (P) and absent (A)] should come out to be the same irrespective of the mating type. The null hypothesis is that the number of A and P children in each of the mating types are equal. The test statistic is $(A - P)^2 / (A + P)$, which follows a chi-square distribution with appropriate degree of freedom under null hypothesis. The contingency chi-square for each of the 3×2 mating tables has also been calculated for testing the goodness of fit with the values expected under chance

TABLE I

TABLE 1
Degree of concordance in cleft chin in 53 pairs of MZ and 54 pairs of DZ twins

Both male N=23			Both female N=30			Both male N=14			Male-female N=23			Both female N=17		
Dizygotic pairs : 54														
++	--	+-	Deg. of	++	--	+-	Deg. of	++	--	+-	Deg. of	++	--	+-
			concor-				concor-				concor-			
			dance				dance				dance			
10	13	0	100%	11	19	0	100%	3	8	0	780%	6	13	4
++	++		represent	presence of cleft chin in both							82.6%	3	9	5
--	--		"	absence of cleft chin in both										70.6%
+-	+-		"	presence in one and absence in the other										

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hypothesis. The results are shown in Table 2. It shows that there might be some systematic forces behind the manifestation of the trait.

TABLE 2

Cleft chin in 132 Chitpavan Brahman families of Maharashtra

Mating type	No. of families	Present		Absent		chi-square	
		Male	Female	Male	Female	Male	Female
P × P	10	15	15	0	1	11.58*	55.13*
P × A & A × P	40	50	28	15	15	29.84*	4.78*
A × A	82	3	0	109	141	75.93*	105.75*
Total	132	68	43	124	157	39.86*	58.39*

Contingent chl-square

Male : 182.04*, d.f. 2, $P < .001$

Female : 205.52*, d.f. 2, $P < .001$

* Indicates significance at 5% level of probability

The data are further analysed for the same hypothesis. The probability (t) that an individual is 'present' is computed from the parental data as follows :

$$t = \frac{2N_{AA} + N_{Aa}}{2(N_{AA} + N_{Aa} + N_{aa})}, \quad \text{where } N_{AA} = \text{No. of } \bar{A} \times \bar{A} \text{ families}$$

$$N_{Aa} = \text{No. of } \bar{A} \times \bar{a} \quad ,$$

$$N_{aa} = \text{No. of } \bar{a} \times \bar{a} \quad ,$$

($\tilde{a}$ = absent, $\bar{A}$ = present)

c. Under chance hypothesis, the probability that such a family has atleast one $\bar{a}$ child is given by the following expression :

$$\pi_c = 1 - t^c$$

Let, N_c = Observed number of families (of all mating types)
of size c .

R_c = Observed number of families (of all mating types) of size c , each family containing at least one $\bar{a}$ child.

Then, for each value of c , provided that the numbers

involved are large enough, the statistic of testing the validity of the chance hypothesis is given by

$$(R_c - N_c \pi_c)^2 / [N_c \pi_c (1 - \pi_c)],$$

which follows a chi-square distribution with 1 d.f. The results, as shown in Table 3, reveal that the trait is genetically controlled.

TABLE 3

Analysis of 132 families under non-genetic chance hypothesis
 $t = .2273$ (proportion of present)

Sibship size c	π_c	N_c	$N_c \pi_c$	R_c	$N_c \pi_c (1 - \pi_c)$	Chi ²	d.f.
2	0.9483	57.0	54.0558	44.0	2.7921	36.2156	1
3	0.9883	44.0	43.4835	33.0	0.5105	215.3000	1
4	0.9973	16.0	15.9573	13.0	0.0426	205.4212	1
5	0.9994	12.0	11.9927	11.0	0.0073	135.5197	1
6	0.9999	1.0	0.9999	1.0	0.0001	0.0001	1
7	1.0000	2.0	2.0000	1.0	0.0000	70242.9507	1
Totals	—	132.0	128.4891	103.0	3.3526	70835.4073	6

Chi-square for totals : 193.789, d.f. 1. $P < .001$

All possible sib-pairs are extracted from the family data. A sibship of size c gives rise $c(c-1)/2$ sibpairs, which are classified as follows.

$\bar{A}\bar{A}$ = both sibs 'present'

$\bar{A}\bar{a}$ = elder sib 'present' and younger 'absent'

$\bar{a}\bar{A}$ = elder sib 'absent' and younger 'present'

$\bar{a}\bar{a}$ = both sibs 'absent'

The probabilities of the four sibpair types under the chance hypothesis are derived as follows : let ' t ' denote the proportion of absent individuals in a random sample. Now, if the chance hypothesis were to be true, the probability that an individual is 'absent' is estimated from family data by ' t '. Then the probabilities of the various sibpairs are obtained as follows :

$$P(\bar{A}\bar{A}) = (1 - t)^2$$

$$P(\bar{A}\bar{a}) = (1 - t)t = P(\bar{a}\bar{A})$$

$$P(\bar{a}\bar{a}) = t^2$$

This analysis also provides strong evidence against chance hypothesis (Table-4).

TABLE 4

Sib-pair analysis for testing non-genetic chance hypothesis
 $t = 0.71884$ (proportion of absent)

Sib-pair type	Observed frequency	Expected frequency
$\bar{A}\bar{A}$	111.0	38.1
$\bar{A}\bar{a}$	18.0	96.2
$\bar{a}\bar{A}$	16.0	96.2
$\bar{a}\bar{a}$	331.0	244.2

chi-square (with 3 d.f.) : 172.556, $P < .001$

From the above analyses it could be presumed that cleft chin is under genetic control. Hence it was decided to fit simple, single-locus, diallelic model to the observed proportions of cleft chin type. The model gives a very good fit. ($\chi^2 = 0.47$, when 'present' is dominant over 'absent' and $\chi^2 = 20.13$, when 'absent' is dominant over 'present').

Analysis of simple model of inheritance reveals that presence of cleft chin is dominant over absent. It would be of interest, therefore, to examine if the recessive hypothesis for absence of cleft chin can be established by applying segregation analysis as suggested by Smith (1956). An agreement, if found, will further strengthen the results obtained by fitting simple model. This analysis is restricted to those families each of which has at least one 'absent' child. The results provide very good evidence in favour of the recessive hypothesis for absence of cleft chin. The results are provided in Tables 5 & 6.

TABLE 5

Number of $\bar{a}$ children in $\bar{A} \times \bar{a}$ (including $\bar{a} \times \bar{A}$) families each containing at least one $\bar{a}$ child

Sibship size c	No. of sibships m_c	Observed $\bar{a}$ children (R_c)	Expected $\bar{a}$ children (E_c)	Variance (V_c)	Chi ²	d.f.
1	—	—	—	—	—	—
2	10	11	13.83	2.222	2.45	1
3	8	14	13.71	3.918	0.02	1
4	2	5	4.27	1.565	0.34	1
5	—	—	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	—	—	—
8	—	—	—	—	—	—
Totals	20	30	31.31	7.705	2.81	3

Chi-square for totals : 0.228, d.f. 1, $P > 0.1$

TABLE 6

Number of children in $\bar{A} \times \bar{A}$ families each containing at least one $\bar{A}$ child

Sibship size c	No. of sibships M_c	Observed $\bar{A}$ children R_c	Expected $\bar{A}$ children E_c	Variance V_c	Chi ²	d.f.
1	—	—	—	—	—	—
2	—	—	—	—	—	—
3	1	1	—	—	—	—
4	—	—	1.29	0.270	0.311	1
5	—	—	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	—	—	—
8	—	—	—	—	—	—
Totals	1	1	1.29	0.270	0.311	1

Chi-square for totals : 0.311, d.f. 1, $P > 0.1$

Bisexual variation is present in the population data, whereas age variation is absent. The data are distributed in groups of 5 years and frequency in each group are recorded. The trait is more frequent among males (34.3%) than in females (21.2%). The observed frequencies as found in the family and population data are compared by applying χ^2 and found to be insignificant ($\chi^2 = 0.80$, d.f. 1 in males and 0.12, d.f. 1 in females). The frequency of P (dominant gene) in the family data is calculated to be 0.141 and in population it is 0.151.

Discussion: The above analyses suggest that the trait, cleft chin, is inherited by a single locus diallelic autosomal dominant gene. There are, however, a few departures from the ideal expectations: firstly, the trait had shown bisexual differences. This may be due to the influence of 'modified gene' or may be due to incomplete penetrance of the gene. Secondly, it is observed that 1.2 per cent of P children are found to be born from $X A \times A$ mating. Under autosomal diallelic dominant hypothesis no P child should arise. This may be due to (i) incomplete penetrance, (ii) illegitimacy, and (iii) due to misclassification. However, probability of misclassification is extremely low. The first reason, incomplete penetrance seems to be the major source. The present

exhaustive study therefore establishes single locus diallelic autosomal dominant mode of inheritance of this trait. It may be pointed out that the trait shows marked degree of manifestation from small dimple to Y-shaped deep depression. It is, therefore not unlikely that more than one allele are involved. We suggest to carry out further investigations to establish relationship between various phenotypic forms of this trait.

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