Genet. Res., Camb. (1967), **10**, *pp.* 313–317
Printed in Great Britain

SHORT PAPERS

Developmental 'Noise' and a congenital malformation

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(*Received* 4 *July* 1967)

Developmental noise is the term given by Waddington (1957) to indicate asymmetry of paired organs. This inequality is presumably an environmental effect on genetically determined characteristics. Since the same genes determine characteristics of both sides of the body, asymmetry is presumably induced by the intrauterine environment. When the asymmetry in all subgroups of the population studied favors the same side of the body, it is designated directional; otherwise it is termed fluctuating. Fluctuating asymmetry thus reflects the degree of developmental stability or canalization.

The palm prints and dental casts considered in this study were obtained from individuals over age 5 years participating in a study of oral clefts carried out at the Lancaster Cleft Palate Clinic, Lancaster, Pennsylvania. A total of eighty-eight families having at least one member with an oral cleft and eighty-two families with no cleft history were examined. A total 657 persons are considered in the analysis. Families segregating for recognized genetic syndromes (of which oral clefts are a part) were not included. The comparison group was ascertained through children attending the same clinic for problems not related to oral clefts, such as functional articulation speech disorders, orthodontic treatment or general dental care.

Various anomalies of the palmar dermatoglyphic patterns and teeth have been reported as concomitants of this malformation (Silver, 1966; Jordan *et al.*, 1965). We did not identify any specific constellation of such defects as characteristic of our series.

Dermatoglyphic patterns are set in their final form during the organogenetic period of development and are not influenced by environmental stress after that time. They show strong familial correlations, indicating a degree of genetic control. They are continuously variable and the various patterns are themselves of no selective importance.

Variations in the development of the human hand are reflected in the palmar dermatoglyphics. Of particular interest in man, is the development of an opposable thumb. The degree of proximal migration and ventral rotation of the thumb and structures of the thenar eminence at the time of friction ridge formation is a prime determinant of the position of the axial triradius (Gall *et al.*, 1966), a commonly used dermatoglyphic landmark in the axis of the extremity at the base of the hand. Measurement of the position of the axial triradius is therefore an appropriate, if indirect, method of assessing variations in the development of the thumb and other structures of the hand.

An acceptable measurement of the position of this triradius, the *atd* angle, was described by Penrose (1954). The angle subtended at the axial triradius by the most medial digital triradius (*a*) and the most lateral digital triradius (*d*) on each hand was measured. This method, while perhaps the best available, has several limitations:

1. *Age.* There is a gradual decrease in the *atd* angle with age. This is due largely to the relatively greater longitudinal than transverse growth of the hand. Fortunately, the angle

does not change significantly after the fifth year. Children under this age were not included in the study.

2. *Sex*. Females are reported to have a higher mean *atd* angle and a somewhat higher variance than males (Penrose, 1954).

3. *Reproducibility*. Due to the elasticity of the skin, differences of approximately 1° may occur with repeated printing of the same hand.

4. *Independence*. In general, the *atd* angle is little influenced by other dermatoglyphic features of the hand. However, the presence or absence of a hypothenar pattern does influence the measurement. Hypothenar patterns represent a qualitative trait with a large genetic component. Secondly, the axial triradius may be absent from one or both hands. This is most frequently seen in combination with hypothenar patterns and may represent expression of the same trait. The individual was dropped from the analysis if he lacked an axial triradius on either hand—whether with or without a hypothenar pattern—or when asymmetry existed for hypothenar patterns on the two hands.

No difference in the frequency of qualitative characters (i.e., absent triradius or unilateral hypothenar pattern) in the cleft and comparison groups was apparent either by sex or cleft versus control.

Analysis of the *atd* angle of the cleft and control groups revealed the mean and variance of the *atd* angle to have no significant left-right directional asymmetry; there was no difference in the mean or variance of the *atd* angle of the affected versus control groups in any of the categories; and adult females of both groups had a somewhat greater variance than adult males.

The within-pair variance (between hands of a single individual) was used as a measure of symmetry (Waddington, 1957; Van Valen, 1962). Significant differences at the $P = 0{\cdot}05$ level occurred between the total sample of affected and comparison children. An attempt was made to determine if this increased asymmetry in the cleft propositi was due to a particular type of cleft. For this analysis the sample was divided into familial and sporadic cleft lip $\pm$ cleft palate and sporadic isolated cleft palate. This division was indicated in view of the many studies (Fogh-Anderson, 1942; Fraser, 1955; Woolf *et al.*, 1963) which have indicated that cleft lip $\pm$ cleft palate and isolated cleft palate are distinct entities. There were insufficient familial cases of isolated cleft palate for analysis. The results (Table 1) show an increased asymmetry of the propositi only in the familial cleft lip $\pm$ cleft palate cases, as indicated by the significant difference ($P < 0{\cdot}005$) of the within-pair variance between this group and the comparison group. This difference was not significant in the other two comparisons.

The dentition offers an additional area in which to study asymmetry of paired organs. To overcome the difficulty of missing or malformed teeth, the lower first molar was measured because it is generally the first permanent tooth to erupt and therefore the permanent tooth most frequently present in the younger children. It is also remote from the site of the defect and not likely to be directly affected by the cleft. The maximum diameter in the region of the buccal and lingual grooves was recorded. Measurements were made with vernier calipers to the nearest 0·1 mm. The error involved in this procedure is tolerable (Hunter & Priest, 1960).

Analysis of these data is presented in Table 2. The means and variances are not significantly different for any of the four groups. As was the case for the dermatoglyphics, the familial cleft lip $\pm$ cleft palate propositi show greater asymmetry than the controls ($F = 1{\cdot}79$, $P < 0{\cdot}025$). Neither of the other two groups differ from the comparison group.

The dermatoglyphic and dental measurements examined in this study are continuously variable and to a greater or lesser degree bilaterally symmetrical. The means of the right and left sides are not significantly different, indicating no appreciable directional asymmetry. Thus the asymmetry that occurs is of the fluctuating type.

Fluctuating asymmetry results from the failure of the organism to duplicate perfectly a bilateral structure. It is reasonable to assume the identity of the genetic information relevant to the development of the two hands. Likewise it is improbable that the teeth on both sides of the mouth are independently controlled. The amount of fluctuating asymmetry is therefore a measure of the lack of precision in development.

Fluctuating asymmetry is a characteristic of all continuously variable bilateral characters. It is undoubtedly a consequence of the interaction of environmental influences with polygenic developmental sequences. In a uniform (or randomly variable) environment,

Table 1. *Analysis of the* atd *angle of palmar dermatoglyphics: propositi*

		Measurement in degrees				
		Left hand		Right hand		Intra pair
	N	Mean	Variance	Mean	Variance	variance
Familial cleft lip ± cleft palate	24	45·7	26·8	44·0	19·1	16·5*
Sporadic cleft lip ± cleft palate	24	44·2	26·8	46·6	25·8	9·6
Sporadic isolated cleft palate	17	42·6	39·6	43·7	27·4	10·5
Comparison group	67	43·0	25·2	43·9	28·1	7·9

* Significantly different from comparison group at the 0·005 level, $F = 2{\cdot}09$.

Table 2. *Analysis of the buccal-lingual diameter of lower first molars: propositi*

		Measurement in millimeters				
		Left molar		Right molar		Intra pair
	N	Mean	Variance	Mean	Variance	variance
Familial cleft lip ± cleft palate	26	10·09	0·256	10·18	0·338	0·0385*
Sporadic cleft lip ± cleft palate	24	10·08	0·343	9·98	0·418	0·0271
Sporadic isolated cleft palate	15	10·26	0·303	10·14	0·366	0·0207
Comparison group	62	10·02	0·313	10·08	0·251	0·0215

* Significantly different from comparison group at the 0·025 level, $F = 1{\cdot}79$.

increased asymmetry will be an indication of the inability of the genetic information to control development effectively in the presence of disturbing factors. Several studies have confirmed a genetic basis for variation in developmental buffering of this type (Bader, 1965; Waddington, 1960).

The finding of increased fluctuating asymmetry (=decreased developmental buffering) in familial cases of a common congenital malformation would therefore suggest that there had been a deficiency in the stabilization of development which resulted, in this case, in the faulty fusion of the lip and palate. It is possible that an overwhelming environmental stress (i.e., teratogen) could have caused both the defect and the increased asymmetry; however, the fact that this increase occurred only in familial cases and not in sporadic cases makes this less likely.

Increased asymmetry has not been previously demonstrated in congenital malformations; however, various authors have suggested that complex genetic systems may be the basis of certain congenital defects (Waddington, 1957; Lerner, 1954; Neel, 1958). All have presumed this predisposition to be polygenic and most have assumed there was interaction with environmental agents. A model of polygenic predisposition based upon quasi-continuous (threshold) effect was postulated by Grüneberg (1952). Several investigators (Edwards, 1960; Carter, 1964; Falconer, 1960) have extended the model and presented evidence for its applicability in several congenital defects.

Direct evidence of polygenic inheritance and estimates of its relative importance have been difficult to obtain. However, several tests have been developed. Edwards (1960), for instance, has asserted that the risk among sibs of patients, as compared to the population frequency of p, is increased by a factor $1/\sqrt{P}$. Carter's (1964) data for cleft lip $\pm$ cleft palate are in excellent agreement with expected values.

The hypothesis may be restated as follows: Evidence available on the etiology of cleft lip $\pm$ cleft palate is suggestive of a polygenic basis. Normally these polygenic systems adequately buffer the development of the organism against adverse environmental influences. Substitution of deleterious genes in these systems lowers the developmental stability. A discontinuity of response (malformation) may occur when the level of buffering becomes too low to compensate for the degree of environmental variability acting to disturb development.

SUMMARY

Non-directional asymmetry of paired organs is attributed to developmental 'noise'. The level of asymmetry is inversely correlated to the degree of developmental stability. Children affected with familial cleft lip $\pm$ cleft palate have an increased asymmetry of their dermatoglyphics and molar teeth. The action of polygenes with a quasi-continuous distribution is consistent with this observation.

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