Developmental ‘Noise’ and a congenital malformation
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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 \(\text{atd}\) angle and a somewhat higher
variability than males (Penrose, 1954).

3. Reproducibility. Due to the elasticity of the skin, differences of approximately \(1^\circ\)
may occur with repeated printing of the same hand.

4. Independence. In general, the \(\text{atd}\) 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 uni-
lateral hypothenar pattern) in the cleft and comparison groups was apparent either by sex
or cleft versus control.

Analysis of the \(\text{atd}\) angle of the cleft and control groups revealed the mean and variance
of the \(\text{atd}\) angle to have no significant left-right directional asymmetry; there was no
difference in the mean or variance of the \(\text{atd}\) 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 \(P = 0.05\)
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 + 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 + 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 + cleft
palate cases, as indicated by the significant difference \((P < 0.005)\) of the within-pair vari-
ance 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 per-
manent 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 toler-
able (Hunter & Priest, 1960).

Analysis of these data is presented in Table 2. The means and variances are not sig-
nificantly different for any of the four groups. As was the case for the dermatoglyphics,
the familial cleft lip + cleft palate propositi show greater asymmetry than the controls
\((F = 1.79, P < 0.025)\). 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 asym-
metry. 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, 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Left hand</th>
<th>Right hand</th>
<th>Intra pair variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>Variance</td>
</tr>
<tr>
<td>Familial cleft lip ± cleft palate</td>
<td>24</td>
<td>45.7</td>
<td>26.8</td>
</tr>
<tr>
<td>Sporadic cleft lip ± cleft palate</td>
<td>24</td>
<td>44.2</td>
<td>26.8</td>
</tr>
<tr>
<td>Sporadic isolated cleft palate</td>
<td>17</td>
<td>42.6</td>
<td>39.6</td>
</tr>
<tr>
<td>Comparison group</td>
<td>67</td>
<td>43.0</td>
<td>25.2</td>
</tr>
</tbody>
</table>

* Significantly different from comparison group at the 0.005 level, $F = 2.09$.

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

<table>
<thead>
<tr>
<th></th>
<th>Left molar</th>
<th>Right molar</th>
<th>Intra pair variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>Variance</td>
</tr>
<tr>
<td>Familial cleft lip ± cleft palate</td>
<td>26</td>
<td>10.09</td>
<td>0.256</td>
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<tr>
<td>Sporadic cleft lip ± cleft palate</td>
<td>24</td>
<td>10.08</td>
<td>0.343</td>
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<tr>
<td>Sporadic isolated cleft palate</td>
<td>15</td>
<td>10.26</td>
<td>0.303</td>
</tr>
<tr>
<td>Comparison group</td>
<td>62</td>
<td>10.02</td>
<td>0.313</td>
</tr>
</tbody>
</table>

* Significantly different from comparison group at the 0.025 level, $F = 1.79$. 

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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 Grünberg (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 \( \frac{1}{\sqrt{p}} \). 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.

REFERENCES


