# MORPHOGENETIC HOMEOSTASIS IN MICE

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*Summary*

The incidence of 29 minor bilateral skeletal variants is analysed in three inbred strains of mice and the hybrids between them. It was found that the frequency of asymmetrical mice (i.e. those with the variant present on one side only) was less than expected on the assumption of mice with variants on two, one, and neither sides occurring at random. This represents a form of morphogenetic homeostasis.

Splitting the asymmetrical mice into those with variants on the left- and right-hand sides, respectively, revealed a number of variants occurring significantly more frequently on the left compared with the right-hand side, and vice versa.

## I. Introduction

Cannon (1932) developed and elaborated the concept of physiological homeostasis. He defined homeostasis as the totality of steady states maintained in an organism through the co-ordination of its complex physiological processes. Thus homeostasis refers to the property of the organism to adjust itself to variable conditions (see Lerner 1954). Since the publication of Cannon's book, the term homeostasis has been used in various ways. For example, developmental homeostasis refers to the regulation of development to make it relatively invariant, and genetic homeostasis refers to a situation where the adaptive value of populations is relatively invariant. Various other terminologies have been used (see, for example, Waddington 1957).

In this paper we will present evidence showing the occurrence of homeostasis involving the skeleton of the mouse, which can be called *morphogenetic homeostasis*. Minor skeletal variants which occur on both sides of the mouse, on one side, or on none (bilateral variants) will be discussed.

In a population let the frequency of mice with a given variant on the left-hand side be $p_1$, and the frequency of mice without the variant on the left-hand side be $q_1$ such that $p_1+q_1 = 1$. Further, let $p_2$ and $q_2$ be the frequencies of mice with and without the variant on the right-hand side such that $p_2+q_2 = 1$. If the occurrence of mice with variants on two, one, or neither sides occurs at random for $n$ mice, $np_1p_2$ mice would be expected to have variants on both sides, $np_1q_2$ on the left-hand side only, $np_2q_1$ on the right-hand side only, and $nq_1q_2$ on neither side. This hypothesis will be tested for 29 minor bilateral variants that have been described by various

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authors (see Table 1 for details). If there are fewer mice with variants on one side (asymmetrical mice) observed than expected, then this would represent a form of morphogenetic homeostasis, since symmetry would be favoured at the expense of asymmetry.

TABLE 1

THE SKELETAL VARIANTS

| No. | Variant | Reference |
|---|---|---|
| | A: Variants of the skull | |
| 1 | Lower turbinal–premaxilla fusion | Deol (1955) |
| 2 | Inframaxillary crest | Deol (1955) |
| 3 | Maxillary foramen I absent | Berry (1963) |
| 4 | Maxillary foramen I double | Berry (1963) |
| 5 | Maxillary foramen II absent | Berry (1963) |
| 6 | Frontal foramen double | Berry and Searle (1963) |
| 7 | Preoptic sutures present | Truslove (1954) |
| 8 | Metoptic roots abnormal | Truslove (1954) |
| 9 | Foramen sphenoidale laterale ventrale present | Berry (1963) |
| 10 | Alae palatinae absent | Deol (1955) |
| 11 | Foramen ovale double | Deol (1955) |
| 12 | Foramen ovale open posteriorly | Deol (1955) |
| 13 | Processus pterygoideus | Deol (1955) |
| 14 | Foramen pterygoideum double | Berry (1963) |
| 15 | Foramen infra-ovale double | Berry (1963) |
| 16 | Foramen hypoglossi double | Deol (1955) |
| 17 | Mandibular foramen double | Berry (1963) |
| 18 | Accessory mental foramen | Deol (1955) |
| | B: Variants of the vertebral column* | |
| 19 | C III Double foramen | Weber (1950) |
| 20 | C III–C IV Dystopia of foramen | Grüneberg (1950) |
| 21 | C V Accessory foramen | Weber (1950) |
| 22 | C VI Accessory foramen | Weber (1950) |
| 23 | C VII Accessory foramen | Weber (1950) |
| 24 | Th I Accessory foramen | Weber (1950) |
| 25 | C VI Inflexion of tuberculum anterius | Grüneberg (1950) |
| 26 | C VI Absence of tuberculum anterius | Grüneberg (1950) |
| | C: Variants of the appendicular skeleton | |
| 27 | Accessory scapular foramen | Berry and Searle (1963) |
| 28 | Fossa olecrani perforata | Weber (1950) |
| 29 | Dyssymphysis ischio-pubica | Grüneberg (1952); Searle (1954) |

* C, cervical vertebrae; Th, thoracic vertebrae.

In not all cases do the asymmetrical mice have the variant on the left- and right-hand sides with equal frequencies. Thus polydactyly of the hind feet tends to affect the right foot more frequently than the left in one set of data (Holt 1945). This will be investigated for the 29 variants, and merely involves testing the equality of the number of mice with the variant on the left-hand side only and on the right-hand side only.

## II. Method

The skeletons were prepared by a modification (Searle 1954) of Luther's (1949) technique for the digestion of non-osseous tissue by the proteolytic enzyme papain. The skeletons were in fact those considered by Howe and Parsons (1967) in a study of the relative importance of genotype and environment in the control of minor skeletal variants. Detailed data are given for two of the three inbred strains employed in this previous study, namely C57BL and BALB/c and the hybrid between them. Fewer mice were scored for the third inbred strain C3H and the hybrids between this strain and the other two strains, so that detailed results will not be presented for these genotypes. Some of the variants analysed by Howe and Parsons (1967) are considered in the present study, but a number of additional variants are included.

## III. Results

In Tables 2, 3, and 4 the frequencies of the variants $p_1$ and $p_2$ are given for strains C57BL and BALB/c and the hybrid between them respectively. Expected numbers were computed as described above, and the agreement of expected and observed tested by a $\chi_1^2$ test. In some cases certain of the expected values for each variant were low and where they were $<2$, $\chi_1^2$ values were not calculated. The observed number of mice with a variant on one side only was compared with the expected number of $n(p_1q_2+p_2q_1)$. In all cases where $\chi_1^2$ values were significant at the 0·05 level or less, the expected number was greater than the observed number (Tables 2–4), and also in most cases where the $\chi_1^2$ values were not significant. There is therefore a general tendency for a deficiency of asymmetrical compared with symmetrical mice, which argues for the type of morphogenetic homeostasis postulated. In Table 5, those variants showing significant morphogenetic homeostasis for the third inbred strain, C3H, and the hybrids between this and the other two strains are given. In total, combining information from Tables 2, 3, 4, and 5, there are 47 $\chi_1^2$ values significant at $P<0{\cdot}05$ all showing morphogenetic homeostasis.

The variants in Table 1 are classified roughly into anatomical groups. It can therefore be asked if there are any groups of variants which tend to show morphogenetic homeostasis more than others. The various foramina of the vertebral column (variants 19–24) form the only obvious group. For this group there are 19 $\chi_1^2$ values significant at the 0·05 level or less, showing that there is particularly strong selection against asymmetry, compared with the various other variants under analysis.

Tables 2–4 also split the asymmetrical mice into the number with variants on the left- and right-hand sides respectively, with $\chi_1^2$ values testing the equality of these numbers. Including the data in Table 5, there are 23 $\chi_1^2$ values significant at $P<0{\cdot}05$, of which 12 are for variants affecting the left side more frequently than the right, and 11 for the reverse situation. Even though there are enough significant $\chi_1^2$ values to show that the deviations from equality are not just a matter of chance, no definite pattern emerges. More data on more variants, perhaps restricted to one strain, are needed before further comment may be made on the biological significance of asymmetry of this type.

TABLE 2

INCIDENCE OF SKELETAL VARIANTS ($p_1$ AND $p_2$) ON THE LEFT- AND RIGHT-HAND SIDES OF MICE OF THE INBRED STRAIN C57BL

Number of mice scored = 190. Observed frequencies of mice with the variant on both sides, on the left and right sides, and on neither side are given. $\chi_1^2$ values testing agreement of expected and observed frequencies (see text) and $\chi_1^2$ values for asymmetry (see text) are also given

| Variant | $p_1$ | $p_2$ | Frequency of Mice with Variant Present on | | | | $\chi_1^2$ for Agreement of Expected and Observed | Expected >, =, or < Observed for Variants Present on One Side | $\chi_1^2$ for Asymmetry |
|---|---|---|---|---|---|---|---|---|---|
| | | | Both Sides | Left Side | Right Side | Neither Side | | | |
| 1 | 0·479 | 0·511 | 63 | 28 | 34 | 65 | 23·08*** | > | 0·58 |
| 2 | 0·711 | 0·679 | 109 | 26 | 20 | 35 | 35·33*** | > | 0·78 |
| 3 | 0·200 | 0·242 | 13 | 25 | 33 | 119 | 2·58 | > | 1·10 |
| 4 | 0·384 | 0·316 | 29 | 44 | 31 | 86 | 3·64 | > | 2·25 |
| 5 | 0·332 | 0·374 | 30 | 33 | 41 | 86 | 4·23* | > | 0·86 |
| 6 | 0·032 | 0·032 | 1 | 5 | 5 | 179 | — | > | 0 |
| 7 | 0·116 | 0·116 | 16 | 6 | 6 | 162 | 90·45*** | > | 0 |
| 8 | 0·016 | 0·011 | 1 | 2 | 1 | 186 | — | > | — |
| 9 | 0·747 | 0·653 | 98 | 44 | 26 | 22 | 3·49 | > | 4·63* |
| 10 | 0·063 | 0·026 | 5 | 7 | 0 | 178 | — | > | 7·00** |
| 11 | 0·984 | 0·979 | 185 | 2 | 1 | 2 | — | > | — |
| 12 | 0·379 | 0·474 | 38 | 34 | 52 | 66 | 1·36 | > | 3·77 |
| 13 | 0·063 | 0·089 | 4 | 8 | 13 | 165 | — | > | 1·19 |
| 14 | 0·268 | 0·232 | 19 | 32 | 25 | 114 | 7·79** | > | 0·86 |
| 15 | 0·058 | 0·021 | 1 | 10 | 3 | 176 | — | > | 3·77 |
| 16 | 0·747 | 0·737 | 108 | 34 | 32 | 16 | 1·63 | > | 0·06 |
| 17 | 0·142 | 0·168 | 11 | 16 | 21 | 142 | 13·06*** | > | 0·68 |
| 18 | 0·747 | 0·732 | 109 | 33 | 30 | 18 | 3·72 | > | 0·14 |
| 19 | 0·406 | 0·456 | 46 | 27 | 36 | 71 | 15·09*** | > | 1·29 |
| 20 | 0·236 | 0·258 | 27 | 16 | 20 | 119 | 40·23*** | > | 0·44 |
| 21 | 0·536 | 0·645 | 73 | 25 | 45 | 40 | 9·23** | > | 5·71* |
| 22 | 0·644 | 0·750 | 99 | 17 | 36 | 28 | 18·61*** | > | 6·81** |
| 23 | 0·478 | 0·429 | 47 | 40 | 31 | 64 | 8·48** | > | 1·14 |
| 24 | 0·681 | 0·730 | 99 | 27 | 36 | 23 | 6·29* | > | 1·29 |
| 25 | 0·315 | 0·427 | 16 | 12 | 22 | 39 | 3·48 | > | 2·94 |
| 26 | 0·306 | 0·272 | 13 | 42 | 36 | 89 | 0·51 | < | 0·46 |
| 27 | 0·495 | 0·600 | 59 | 35 | 55 | 41 | 0·59 | > | 4·44* |
| 28 | 0·642 | 0·632 | 90 | 32 | 30 | 38 | 16·51*** | > | 0·06 |
| 29 | 0·235 | 0·364 | 31 | 13 | 37 | 106 | 28·90*** | > | 11·52*** |

*$P < 0·05$. **$P < 0·01$. ***$P < 0·001$.

TABLE 3

INCIDENCE OF SKELETAL VARIANTS ($p_1$ AND $p_2$) ON THE LEFT- AND RIGHT-HAND SIDES OF MICE OF THE INBRED STRAIN BALB/c

Number of mice scored = 252. Observed frequencies of mice with the variant on both sides, on the left and right sides, and on neither side are given. $\chi_1^2$ values, testing agreement of expected and observed frequencies (see text) and $\chi_1^2$ values for asymmetry (see text) are also given

| Variant | $p_1$ | $p_2$ | Frequency of Mice with Variant Present on | | | | $\chi_1^2$ for Agreement of Expected and Observed | Expected >, =, or < Observed for Variants Present on One Side | $\chi_1^2$ for Asymmetry |
|---|---|---|---|---|---|---|---|---|---|
| | | | Both Sides | Left Side | Right Side | Neither Side | | | |
| 1 | 0·171 | 0·155 | 16 | 27 | 23 | 185 | 18·65*** | > | 0·32 |
| 2 | 0·008 | 0·008 | 0 | 2 | 2 | 248 | — | = | — |
| 3 | 0·091 | 0·091 | 3 | 20 | 20 | 209 | 0·47 | > | 0 |
| 4 | 0·429 | 0·266 | 43 | 65 | 24 | 120 | 16·93*** | > | 18·89*** |
| 5 | 0·175 | 0·151 | 13 | 31 | 25 | 183 | 8·68** | > | 0·64 |
| 6 | 0·317 | 0·333 | 37 | 43 | 47 | 125 | 8·81** | > | 0·18 |
| 7 | 0·534 | 0·382 | 59 | 75 | 37 | 80 | 4·07* | > | 12·89*** |
| 8 | 0·964 | 0·956 | 237 | 5 | 3 | 6 | — | > | 0·50 |
| 9 | 0·321 | 0·464 | 57 | 24 | 60 | 111 | 27·54*** | > | 15·43*** |
| 10 | 1·000 | 0·992 | 250 | 2 | 0 | 0 | — | > | — |
| 11 | 0·694 | 0·730 | 133 | 42 | 51 | 26 | 2·59 | > | 0·87 |
| 12 | 0 | 0 | 0 | 0 | 0 | 252 | — | = | — |
| 13 | 0·790 | 0·790 | 168 | 31 | 31 | 22 | 17·00*** | > | 0 |
| 14 | 0·083 | 0·079 | 4 | 17 | 16 | 215 | — | > | 0·03 |
| 15 | 0·048 | 0·056 | 1 | 11 | 13 | 227 | — | > | 0·17 |
| 16 | 0·540 | 0·393 | 60 | 76 | 39 | 77 | 2·89 | > | 11·90*** |
| 17 | 0·623 | 0·687 | 114 | 43 | 59 | 36 | 3·04 | > | 2·51 |
| 18 | 0·849 | 0·825 | 180 | 34 | 28 | 10 | 2·43 | > | 0·58 |
| 19 | 0·224 | 0·249 | 20 | 35 | 41 | 149 | 4·99* | > | 0·47 |
| 20 | 0·650 | 0·683 | 120 | 40 | 48 | 38 | 9·51** | > | 0·73 |
| 21 | 0·052 | 0·065 | 2 | 11 | 14 | 221 | — | > | 0·36 |
| 22 | 0·167 | 0·195 | 12 | 29 | 36 | 169 | 2·98 | > | 0·75 |
| 23 | 0·070 | 0·066 | 0 | 17 | 16 | 209 | — | < | 0·03 |
| 24 | 0·293 | 0·264 | 34 | 38 | 31 | 143 | 22·65*** | > | 0·71 |
| 25 | 0·004 | 0·016 | 1 | 0 | 3 | 241 | — | > | — |
| 26 | 0·008 | 0 | 0 | 2 | 0 | 245 | — | < | — |
| 27 | 0·813 | 0·861 | 179 | 26 | 38 | 9 | 1·33 | > | 2·25 |
| 28 | 0·004 | 0·008 | 0 | 1 | 2 | 248 | — | = | — |
| 29 | 0·008 | 0·012 | 0 | 2 | 3 | 246 | — | < | 0·20 |

*$P < 0·05$. **$P < 0·01$. ***$P < 0·001$.

TABLE 4

INCIDENCE OF SKELETAL VARIANTS ($p_1$ AND $p_2$) ON THE LEFT- AND RIGHT-HAND SIDES OF HYBRID MICE FROM THE CROSS C57BL × BALB/c

Number of mice scored = 86. Observed frequencies of mice with the variant on both sides, on the left and right sides, and on neither side are given. $\chi_1^2$ values testing agreement of expected and observed frequencies (see text) and $\chi_1^2$ values for asymmetry (see text) are also given

| Variant | $p_1$ | $p_2$ | Frequency of Mice with Variant Present on | | | | $\chi_1^2$ for Agreement of Expected and Observed | Expected >, =, or < Observed for Variants Present on One Side | $\chi_1^2$ for Asymmetry |
|---|---|---|---|---|---|---|---|---|---|
| | | | Both Sides | Left Side | Right Side | Neither Side | | | |
| 1 | 0·198 | 0·093 | 3 | 14 | 5 | 64 | — | > | 4·26* |
| 2 | 0·186 | 0·128 | 4 | 12 | 7 | 63 | 2·62 | > | 1·32 |
| 3 | 0·023 | 0·058 | 0 | 2 | 5 | 79 | — | < | 1·29 |
| 4 | 0·733 | 0·616 | 41 | 22 | 12 | 11 | 1·19 | > | 2·94 |
| 5 | 0·244 | 0·140 | 3 | 18 | 9 | 56 | 0 | > | 3·00 |
| 6 | 0·058 | 0·047 | 1 | 4 | 3 | 78 | — | > | 0·14 |
| 7 | 0·163 | 0·140 | 4 | 10 | 8 | 64 | — | > | 0·22 |
| 8 | 0·581 | 0·349 | 21 | 29 | 9 | 27 | 2·66 | > | 10·53** |
| 9 | 0·779 | 0·733 | 53 | 14 | 10 | 9 | 5·31* | > | 0·67 |
| 10 | 0·872 | 0·791 | 65 | 10 | 3 | 8 | 20·47*** | > | 3·77 |
| 11 | 0·965 | 0·965 | 81 | 2 | 2 | 1 | — | > | 0 |
| 12 | 0 | 0·012 | 0 | 0 | 1 | 85 | — | > | — |
| 13 | 0·802 | 0·872 | 64 | 5 | 11 | 6 | 9·60** | > | 2·25 |
| 14 | 0·035 | 0 | 0 | 3 | 0 | 83 | — | > | — |
| 15 | 0·023 | 0·012 | 1 | 1 | 0 | 84 | — | > | — |
| 16 | 0·744 | 0·640 | 44 | 20 | 11 | 11 | 2·49 | > | 2·61 |
| 17 | 0·384 | 0·442 | 21 | 12 | 17 | 36 | 8·21** | > | 0·86 |
| 18 | 0·837 | 0·756 | 58 | 14 | 7 | 7 | 5·93* | > | 2·33 |
| 19 | 0·361 | 0·398 | 19 | 11 | 14 | 39 | 10·90*** | > | 0·36 |
| 20 | 0·631 | 0·714 | 44 | 9 | 16 | 15 | 9·46** | > | 1·96 |
| 21 | 0·475 | 0·525 | 29 | 9 | 13 | 29 | 16·46*** | > | 0·73 |
| 22 | 0·549 | 0·537 | 30 | 15 | 14 | 23 | 6·79** | > | 0·03 |
| 23 | 0·463 | 0·390 | 21 | 17 | 11 | 33 | 7·85** | > | 1·29 |
| 24 | 0·458 | 0·602 | 26 | 12 | 24 | 21 | 1·96 | > | 4·00* |
| 25 | 0·075 | 0·013 | 0 | 6 | 1 | 73 | — | < | 3·57 |
| 26 | 0 | 0·024 | 0 | 0 | 2 | 80 | — | < | — |
| 27 | 0·895 | 0·977 | 75 | 2 | 9 | 0 | — | < | 4·45* |
| 28 | 0·419 | 0·442 | 22 | 14 | 16 | 34 | 7·19** | > | 0·13 |
| 29 | 0 | 0·023 | 0 | 0 | 2 | 84 | — | < | — |

*$P < 0·05$. **$P < 0·01$. ***$P < 0·001$.

## IV. Discussion

Little discussion is needed since development is clearly canalized against asymmetry, so providing evidence for morphogenetic homeostasis, which is one aspect of developmental homeostasis. Other anatomical consequences such as in the muscular, nervous, and vascular systems would be of interest, even though they would be more difficult to study. This would particularly apply to the various foramina of the vertebral column, for which the evidence for morphogenetic homeostasis was found to be very convincing. We have done a re-analysis (Howe and Parsons, unpublished data) of some published data for various traits in man, involving the muscular and vascular systems, as well as the skeletal system, showing very significant morphogenetic homeostasis. The analysis of these data, together with some original data of our own in man, will be published elsewhere.

Table 5

VARIANTS SHOWING SIGNIFICANT MORPHOGENETIC HOMEOSTASIS AND ASYMMETRY AT A LEVEL OF SIGNIFICANCE OF $P < 0{\cdot}05$

| Strain or Hybrid | No. of Mice | Variants Showing Significant Morphogenetic Homeostasis | Variants Showing Significant Asymmetry | |
|---|---|---|---|---|
| | | | Left > Right | Right > Left |
| C3H | 73 | 21, 22, 23, 28 | 16 | 3, 13, 19 |
| C57BL × C3H | 33 | 10, 13, 17, 18, 21, 28 | 28 | 9 |
| BALB/c × C3H | 76 | 9, 22, 28 | 4, 14, 19 | |

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## VI. References

Berry, R. J. (1963).—Epigenetic polymorphism in wild populations of *Mus musculus*. *Genet. Res. Camb.* **4**, 193–220.

Berry, R. J., and Searle, A. G. (1963).—Epigenetic polymorphism of the rodent skeleton. *Proc. Zool. Soc. Lond.* **140**, 577–615.

Cannon, W. B. (1932).—"The Wisdom of the Body." (W. W. Norton & Co., Inc.: New York.)

Deol, M. S. (1955).—Genetical studies on the skeleton of the mouse. XIV. Minor variations of the skull. *J. Genet.* **53**, 498–514.

Grüneberg, H. (1950).—Genetical studies on the skeleton of the mouse. I. Minor variations of the vertebral column. *J. Genet.* **50**, 112–41.

Grüneberg, H. (1952).—Genetical studies on the skeleton of the mouse. IV. Quasi-continuous variations. *J. Genet.* **51**, 95–114.

Holt, S. B. (1945).—A polydactyl gene in mice capable of nearly regular manifestation. *Ann. Eugen.* **12**, 220–49.

Howe, W. L., and Parsons, P. A. (1967).—Genotype and environment in the determination of minor skeletal variants and body weight in mice. *J. Embryol. exp. Morph.* **17**, 283–92.

Lerner, I. M. (1954).—"Genetic Homeostasis." (John Wiley and Sons, Inc.: New York.)

Luther, P. G. (1949).—Enzymatic maceration of skeletons. *Proc. Linn. Soc. Lond.* **161**, 146.

SEARLE, A. G. (1954).—Genetical studies on the skeleton of the mouse. IX. Causes of skeletal variation within pure lines. *J. Genet.* **52**, 68–102.

TRUSLOVE, G. M. (1954).—Genetical studies on the skeleton of the mouse. XIII. Variations in the presphenoid. *J. Genet.* **52**, 589–602.

WADDINGTON, C. H. (1957).—"The Strategy of Genes." (George Allen and Unwin, Ltd.: London.)

WEBER, W. (1950).—Genetical studies on the skeleton of the mouse. III. Skeletal variations in wild populations. *J. Genet.* **50**, 174–8.