

CHARACTER CHANGES CAUSED BY MUTATION OF AN
ENTIRE REGION OF A CHROMOSOME IN
DROSOPHILA.¹

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A female, just hatched, having wings serrated or notched at the end, was found in the purple stock bottle, October 7, 1918. In order to test whether this character was due to a new mutation the female was mated to males from an unrelated stock. The majority of her few F_1 daughters had typically "notch" wings quite like the females in the old stocks called notch (see MORGAN and BRIDGES 1916). Later crosses in which larger numbers were obtained always gave notch females, normal females, and normal males in equal numbers, but no notch males, showing that the mutant was a sex-linked dominant, acting in addition as a lethal in the male, precisely like the old notch. It was possible to ascertain that the purple stock had not been contaminated. The character was accordingly considered as due to a reappearance of the old notch gene. Notch was known to have reappeared six times since it first occurred.

In order to find out whether the location of the new notch ("notch₈") gene was identical with that of the earlier ones, two cultures were raised in which a red-eyed notch₈ female was crossed to males carrying the sex-linked recessive genes eosin (eye color) and crimson (eye color). These genes are located fairly near to the left and to the right respectively of the old notch gene.

When the F_1 flies hatched, a paradoxical result was obtained: All the notch₈ daughters, instead of being red-eyed as expected, had a yellowish eosin-like eye color. Since the normal-winged daughters did not show this exceptional eye color, the latter could not be due to a duplication of the eosin gene in the X chromosome received from the eosin crimson fathers, and it was at once regarded as probable that the appearance of F_1 eosin notch females was due to a "deficiency" (BRIDGES 1917) in the

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X chromosome containing the notch₈ gene. If a deficiency, i.e., loss or inactivation, of a piece of the X chromosome carrying the normal allelomorph for eosin were present in the notch₈ flies, notch₈ females heterozygous for eosin would be somatically eosin, or lighter, with regard to eye color.

An important support for the deficiency-explanation was found in the fact that males which received the notch₈ chromosome all died. BRIDGES (1917) had shown that bar-deficiency acted as a lethal for the male. Moreover, notch females from two of the earlier notch stocks, in crosses to males carrying the recessive sex-linked gene for facet (eyes), located near to the left of notch, had given notch-facet females in F₁ (METZ and BRIDGES 1917).

When it was taken into consideration that notch₈ which had a peculiar effect on eosin analogous to that previously obtained with facet, also agreed with old notches in a series of somatic respects, as will be pointed out later, it was regarded as probable that the character notch itself might be due to deficiency and not to a gene of the common kind. If this were true it was to be expected that the deficiency in the notch₈ flies covered a region extending at least from eosin (at 1.1) to the locus of the old notch (at 2.6), a distance of 1.5 units. This was an extraordinarily favorable case for further analysis, since the following mutant genes were present in this region of the X chromosome: White and its 8 allelomorphs, one of which is eosin (at 1.1), facet (at 2.2) and the gene for the dominant sex-linked character abnormal abdomen (at 2.4). Two of these characters, viz., eosin and facet, were in addition sex-limited, both being much more extreme in males than in females.

On the basis of the working hypothesis mentioned, it could be predicted that notch₈ females, when crossed to males carrying the recessive sex-linked genes just spoken of, would give F₁ notch₈ daughters which, in spite of being heterozygous, would show the characters. By crossing notch₈ females to males carrying other sex-linked genes to the left and to the right of this region it would be seen in F₁ if other loci also were included in the deficient region, and a preliminary measure of the extent of the deficiency could in this way be obtained.

The result of these crosses proved the hypothesis to be correct. White and all its allelomorphs manifested themselves in the heterozygous F₁ notch₈ females; so also did facet. Abnormal abdomen, being partially dominant, would be expected to appear to some extent anyhow. Special facts with regard to the latter cross will be given later. None of the other

sex-linked genes (those to the left and right) showed in the F_1 notch₈ females. The gene nearest eosin to the left is the recessive broad (wings), (at 0.4), the one nearest to the right of the old notch is the recessive echinus (eye), (at 5.6). It could accordingly be concluded that the deficient region was not long enough to cover this distance, 5.2 units.

The examination of the F_1 notch₈ females heterozygous for the allelomorphs of white or for facet or abnormal abdomen revealed a new and important fact. The notch₈ flies heterozygous for an allelomorph of white had a lighter eye color than the flies in the corresponding stocks. This exaggerating effect of deficiency was especially striking in notch flies heterozygous for the darker allelomorphs of white, such as cherry, coral or blood. Similarly heterozygous notch₈ facet females had much more extreme facet eyes even than the facet males. Also the notch₈ females heterozygous for abnormal abdomen had a more marked abnormal abdomen than their heterozygous abnormal-abdomen sisters, though this difference was less pronounced than was the case with regard to facet. This result indicated that the deficiency exaggerates the effect of all the mutant genes present in the corresponding region of the other X chromosome.

To test this point under optimal conditions, deficiency notch₈ females heterozygous for white or the allelomorphs of white were back-crossed in pair matings to males from the white or to the corresponding white-allelomorph used in the cross. The not-notch females among the progeny were homozygous for the allelomorph of white used, and direct comparison was made between them and the eye colors modified by notch. The result of this experiment fully confirmed the earlier observation. The notch₈ flies always had lighter and more transparent eyes than their homozygous sisters. This effect of deficiency could be detected even in notch flies heterozygous for the lighter eye colors belonging to the white-allelomorph series.

An exaggerating effect of deficiency on other light eye colors was observed in other experiments. When the deficiency notch₈ was present in flies homozygous for the sex-linked genes vermilion and garnet, these eye colors were markedly lighter than in the not-notch sisters. Likewise notch₈ females homozygous for pink, the gene of which is in the third chromosome, showed a lighter eye color than homozygous pink flies. No similar effect on the darker eye color sepia in the third chromosome could be observed.

From these tests it was seen that deficiency notch₈ acted very much

like the factor for white itself. For, not only are compounds of white with its allelomorphs lighter than the later allelomorphs when homozygous, but the gene for white when present in heterozygous condition has also a diluting effect on some other eye colors, such as pink (MORGAN and BRIDGES 1913).

It was found, however, in the course of the above experiment, that deficiency seemed to have an even more pronounced effect than white itself was known to have. To ascertain this point, notch₈ females heterozygous for white were back-crossed in pair matings to males carrying the different allelomorphs of white. This would be a decisive experiment since the F₁ notch₈ daughters would have deficiency in one chromosome and the allelomorph of white in question in the other, while their sisters would have white in one chromosome and the same allelomorph in the other. The comparison could in this way be carried out under absolutely equal conditions, since the flies to be compared were raised in the same culture and derived from the same parents.

The result of this experiment proved the correctness of the above supposition. The deficiency-allelomorph compound was always somewhat lighter and more transparent than the corresponding white-allelomorph compound. Even in the lighter eye colors of the allelomorphic series the females could be separated on the basis of this difference in eye color. Deficiency notch₈ acts accordingly as a sub- or infra-white.

The marked exaggerating influence of the deficiency notch₈ on the effect of all the mutant genes located in the corresponding region of the other X chromosomes, could hardly be brought into accord with the earlier conception that deficiency represented a physical loss or a total inactivation. It was accordingly regarded highly desirable to be able to compare a notch₈ female heterozygous for one of the darker allelomorphs of white with a non-disjunctional XO male carrying the same allelomorph in its X chromosome. Such a male would show the effect, if any, of the total loss, since it has only one X chromosome, the entire Y chromosome being absent. No such effect in the XO males had previously been recorded, but much attention could hardly have been paid to this special point.

By chance, a non-disjunctional XO cherry male occurred in a cross between a notch₈ female and a cherry abnormal-abdomen male. This male could accordingly be compared with his own notch sisters heterozygous for cherry. That the male in question really was of the above non-disjunctional type could be ascertained by the fact that though tested

with six females, he proved to be sterile, since BRIDGES (1916) has demonstrated that non-disjunctional XO males are always sterile. This XO cherry male had the ordinary dark eye color of regular cherry males, much darker than that of his heterozygous deficiency-cherry sisters.

An analogous exaggerating effect of deficiency was, as mentioned, observed with regard to facet. Heterozygous facet-notch₈ females have a rough eye much more extreme than that of facet males, which in turn show the facet character much more pronounced than homozygous facet females. Moreover, the wings of the heterozygous notch-facet females were always very much modified, being constantly very markedly notched at the ends and in addition along the sides, so that the whole wing had a spade-like form. These squared-off wings were in addition extended, forming an angle with each other. When the facet stock was looked over it was observed that facet flies showed a tendency to a slight notching of the ends of the wings, most frequent in the males. The modified wing of heterozygous notch₈-facet females was accordingly regarded as an expression of this tendency to notching produced by the ordinary facet gene, exaggerated, in this case, by its combination with the deficiency notch₈.

With regard to the notch₈ × abnormal-abdomen crosses it should be noticed that the dominant character abnormal abdomen demands special conditions in the culture bottle to manifest itself (MORGAN 1915). It would be regarded *a priori* as fairly probable that the deficiency, exaggerating the effect of the genes in the opposite region, would cause a dominant character of this type, which had its gene within this region, to manifest itself in F₁ notch₈ flies heterozygous for abnormal abdomen, even if the culture conditions were not favorable for a general manifestation of the character. This was found, however, not to be the case. Several crosses were made up by mating notch₈ females to abnormal-abdomen males in which cultures the latter character failed to show in F₁ either in the notch or in the not-notch females. In later experiments, however, where the attempts to create the special conditions necessary for the development of abnormal abdomen were successful, it was found that notch females generally had a more marked abnormal abdomen than their heterozygous, not-notch sisters.

Summing up, we find that the deficiency notch₈ resembles the earlier described bar-deficiency in the fact that, when it is present, recessive genes in that region which is homologous to the deficient region manifest themselves when present in heterozygous condition. Like the bar-deficiency, too, this new deficiency also acts as a lethal in the males.

But in addition to allowing them to show, this new deficiency exaggerates the effect of all known mutant genes located in the corresponding region of the opposite X chromosome. This effect was not observed in the case of bar-deficiency.

The analysis of bar-deficiency led to the conclusion that deficiency was due to a physical loss or a total inactivation of an entire region of a chromosome. These alternatives, loss or inactivation, can hardly be maintained as an explanation of the case of deficiency here described. This deficiency is shown to have a striking general effect on all mutant genes in the corresponding region of the other X chromosome. It would be very difficult to conceive that this effect could be caused by a total loss or a complete inactivation, for it has been demonstrated that the total absence of one sex chromosome in a non-disjunctional XO male (which contains not even a Y chromosome) had not the slightest effect upon a mutant character (cherry) which was markedly changed by the deficiency notch₈.

Moreover, ordinary males (XY) carrying one of the allelomorphs of white are all, except eosin, of just the same eye color as females homozygous for the same allelomorph.

Thus, if the deficiency were regarded as a total loss or a complete inactivation we should be confronted with the situation that, whereas a single gene in the female gives the lighter eye color seen in the heterozygous notch₈ flies, two genes together in the female give an eye color exactly like that of the male carrying one gene. This would be a too strange coincidence when we remember that it applies to six genes of very different grades of eye color.

It has been shown that deficiency notch₈ exaggerates the effect of all the known mutant genes located in the corresponding region of the other X chromosome. The visible result is that flies carrying the deficiency in one chromosome and one of these genes in the other are further removed from normal, than is the case in homozygous females or males carrying the same gene.

The question arises accordingly if normal genes in the region opposite to the deficient piece are not also influenced in a similar way.

To some extent this seems to be the case. The series of somatic abnormalities found in the notch₈ flies points in this direction. The notch₈ flies are different from wild-type flies in the following respects: The wings are irregularly nicked at the ends, and often somewhat extended forming an angle with each other; certain veins are thickened; the eyes

are generally small and show a slight tendency to roughening; the acrostical hairs are irregular in their distribution, not arranged in definite rows as is the case in the wild-type fly; extra scutellar bristles are apt to appear.

It is natural to suppose that these somatic peculiarities are a result of the modification of the effects of one or more of the normal genes in the region opposite to the deficient piece, similar to that which has been demonstrated in the case of the mutant genes. It is superfluous to regard the character notch as due to an independent specific mutant gene contained in or linked to the deficient region.

It would seem probable that many normal genes are contained in such a piece of the X chromosome as that opposite to the deficient region. The fact that more extensive alterations are not caused when the deficient chromosome is present could perhaps be said to point in the direction that the normal genes must have different potencies. The mentioned mutant genes and some of the normal ones in the region opposite are affected, while other normal genes, supposedly present in the same region, are not visibly influenced.

In connection with the description of this case of deficiency the remarkable fact might be recalled that a majority of the known dominant genes in *Drosophila* are lethal when homozygous, like yellow body color in mice. Notch itself was in fact previously placed in this group (MULLER 1917). The notch₈ case is the first in which an explanation of this peculiar relation has been possible. It might very well be that some of the not-sex-linked cases of this type are also due to deficiency. The lethal effect of the genes in homozygous condition is just what was to be expected if this were true. Deficiency may be a more common phenomenon than so far regarded probable. If the region opposite to the deficient piece did not contain mutant genes or normal ones which are modified in their effect in the presence of the deficiency, the deficiencies would not be recorded as such, but only as lethals. Some of the numerous lethals in *Drosophila* may be due to such deficiencies.

The data obtained concerning the effect of deficiency notch₈ on the process of crossing over will not be presented here. It should only be said that no crossing over takes place within the deficient region. The presence of deficiency seems also to influence in a special way the amount of crossing over in the neighborhood of the deficient region. Preliminary linkage tests indicate that the deficient region extends somewhat to the left of eosin and considerably to the right of facet, in fact to within

0.7 unit of echinus, making at total length of about 4.8 units. This indicates that the extent of the notch₈ deficiency is so considerable that a cytological examination might throw light on the physical nature of deficiency.

It should be mentioned that of the previously recorded notch mutations two were tested in crosses to facet and proved to be deficiencies for this locus (see above). Five were used in experiments in which they were crossed to white or its allelomorphs, but these genes did not manifest themselves when heterozygous in the notch flies. Deficiencies in this region of the X chromosome may accordingly differ in length and still give the notch character.

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