October 4, 1948

Dr. Barbara McClintock
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Dear Dr. McClintock:

Thanks very much for the set of your reprints. They will be very useful.

In about a month, I shall be in New Haven to give some lectures on bacterial genetics. I'll try to make it to Cold Spring Harbor, but it's rather doubtful that I can make it. Could I see you in N. Y.?

Lately, I've been puzzling over a segregation phenomenon in E. coli K-12 that is still far from solution. You may be interested to read this precis of it, which I'm putting to you in hopes you may have some suggestions.

Work on standard stocks suggests one linkage group, with factors arranged:

B_1 M B Mal_1 Lac_1 V_1 T L . Mal_1 and Lac_1

relate to the fermentation of maltose and lactose; V_1 to phage-resistance and the others to nutritional requirements. In a cross using parents different in these factors, one can recover haploid prototrophs as previously published. These recombinants are regularly either Lac- or Lac+, V_1^r or V_1^s, i.e. they have presumably already segregated from the diploid zygote. By chance, however, I noticed a single prototroph whose behavior is quite aberrant, being heterozygous for some of these factors. The heterozygote is maintained on synthetic medium, on which the (for the most part) nutritionally exacting segregants are unable to compete with it; when plated on a complete medium, the segregants are produced at a large proportion of cell divisions, and can be purified by subsequent plating. To summarize very briefly:

1) Segregation is accompanied by crossing over, and all classes of recombinants (including the hitherto elusive multiple mutants) are found with varying frequencies. The segregants are apparently pure-line, and do not segregate further.

2) When crossed with appropriate standard stocks, segregants may yield prototrophs 1-10% of which are heterozygous for Lac. One heterozygote gave three segregants, which were tested. (I call these "H".) Two gave F2 heterozygotes beyond question; I am not as sure as I'd like to be yet of the third, but it seems to give heterozygotes in crosses with standard and definitely does on crossing with one of the other "H" stocks.

3) The heterozygotes may be heteroploid. In a cross involving all the factors listed above, where one of the parents is a "heterozygote producer" derived from the F1, heterozygotes were found digenic for all those loci except Mal, which was typically Mal- (as it happened, the allele contributed by the "H" parent in one series, by the standard in another). This might be interpreted as homozygosity, but from several such stocks, Mal+ reversions were obtained, which would be expected to be Mal+/Mal- (from Mal-/Mal-) and therefore to segregate. This was not observed, the reversions behaving like pure Mal+, although still heterozygous for Lac+-. From this, it is tentatively concluded that the aberrant heterozygote is hemizygous for Mal, and therefore heteroploid. By successive mutations, we have just made up stocks so that four additional fermentation characters can be introduced in such crosses. Unfortunately, these are all more or less close to Mal, and so far have shown comparable behavior. I do not know whether some loci can be homozygous in these heterozygotes, but am trying to check.

4) As one might expect from (3) (although this came first), segregation from the heterozygote is not random, but biased to different extents for different factors. M shows this especially. There seems to be, for a given heterozygote, a predominant class of segregant, with a minority of other types. Different heterozygotes have a different predominant segregant. This is consistent with the notion that the presumed deficiency in the Mal region acts as a recessive lethal, and that crossing over occurs to form those less frequent segregations which are originally coupled with it.

I badly need some testable hypotheses which will explain how a heterozygote can split off segregants apparently capable of effecting (a) a deficiency for the Mal region in many of the F2 zygotes which it forms with normal stocks, and (b) prolongation of the diploid phase. Of course, with more detailed study, the difficulties may be resolved by correction of the data, but as they stand they are rather puzzling.

In the back of my head is the notion that the answer to these perplexities may be found in your corn work, but I haven't yet found it. However, although the problem has not been solved, it has already been a useful tool in my other work on the gene enzyme relationship which you may have noticed in the Genetics Records. Judging by their recombination to give Lac+ phenotypes, quite a few loci are connected with lactase (Betagalactosidase), which by the way, I have gotten out cell-free, somewhat purified and have reasonably good evidence for its "single enzyme" nature. Some of these loci (e.g. Lac_1 and Lac_4) are linked so closely that the Lac+ recombinants are exceedingly rare. Crossing an H Lac_1- with a standard Lac_4-, however, Lac+ heterozygotes were obtained which clearly segregated into the Lac- components, confirming their non-allelism and the dominance of Lac+. Phage sensitivity is also dominant.

With best wishes,

Yours sincerely,

Joshua Lederberg

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