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Commentary: Why are there difficulties in controlling genetic variability?

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More than 20 years ago, K. Gärtner published a paper in the journal *Laboratory Animals*.[1] According to the author: 'Reduction of genetic variability by using inbred strains and reduction of environmental variability by highly standardized husbandry in laboratory animals did not remarkably reduce the range of random variability in quantitative biological traits.' As far as I can see, this statement is correct and has certainly survived the test of time. Similar conclusions, although in a different form, were drawn by other researchers. For instance, Fitch and Atchley[2] wrote: 'Genetic variation at 97 loci in ten commonly used inbred strains of mice is greatly in excess of that expected under current assumptions.' Ruvinsky *et al*.[3] found that even those traits which are the closest to genes, like electrophoretic mobility of enzyme glucose 6-phosphate dehydrogenase, varied within parthenogenetic *Daphnia pulex* clones. There is plenty of other evidence supporting the conclusion expressed in the Gärtner paper and only the brief nature of these commentaries prevent me from going into details.

Gärtner rightly deduced that environmental variation could not be significant enough to explain the results. He also believed that 'Due to the lack of genetic variability in inbred strains all the phenotypic variability should be environmentally induced.' At the time, such statements were quite common but nevertheless incorrect. Now it is clear that even identical monozygotic twins do have some genetic differences and all inbred strains also have residual heterozygosity. One way or another, Gärtner suggested there was a so-called 'third component' that was particularly influential in the situation he investigated and 'may originate from ooplasmic differences'. While such a difference might exist and could contribute to the phenomenon, our current knowledge about numerous factors causing variability is much greater and briefly mentioned below. Gärtner also thought that the lack of uniformity even in inbred animals 'seems to be an arrangement supporting natural selection'. No doubt genetic variation is essential for effective selection, but one should hardly entertain a view that random variation was arranged especially for this purpose alone. This is rather an integral feature of any biological unit. My recently published book 'Genetics and Randomness'[4] provides broad characterization of various factors causing randomness in the biological world. Here we just refer to the processes that commonly generate phenotypic variability in inbred strains of laboratory animals or individuals with identical zygotic genotype. Among them are novel mutations acquired during development of multicellular individuals, random somatic recombination, alternative splicing, stochastic variation in gene activity, random gene inactivation events and several less understood phenomena. Some level of heterozygosity, which cannot be brought to zero even in highly inbred strains, will also enhance phenotypic variation.

Importantly, a sense of limits existing in nature is not always highlighted in biological publications. Why would one expect that certain experimental procedures might lead to complete disappearance of phenotypic variation? An alternative question could be asked whether it is possible at all to remove phenotypic variation from populations. The answer to this question, as discussed in the above-mentioned book, is a resounding 'NO'. Hopefully in the future, biological thinking will embrace the idea of randomness much more. No matter how far science advances, the proportion of what is knowable to what is random will remain unchanged, and attempts to ignore this critical threshold are futile at best. With the revolutionary explosion in genetic information discovery, it is crucially important to recognize the underlying limitations of scientific prediction in genetics.

Conflict of interest: None declared.

References

[1] Gärtner K. A third component causing random variability beside environment and genotype. A reason for the limited success of a 30 year long effort to standardize

laboratory animals? *Lab Animals* 1990;**24:**71–77. Reprinted *Int J Epidemiol* 2012;**41:**335–41.
[2] Fitch WM, Atchley WR. Evolution in inbred strains of mice appears rapid. *Science* 1985;**228:**1169–75.
[3] Ruvinsky AO, Lobkov YuI, Belyaev DK. Spontaneous and induced activation of genes affecting the phenotypic expression of glucose 6-phosphate dehydrogenase in Daphnia pulex. I. Intraclonal variations in the electrophoretic mobility of G6PD. *Mol General Genet* 1983;**189:**485–89.
[4] Ruvinsky A. *Genetics and Randomness*. Boca Raton, FL, USA: CRC Press, Taylor and Francis Group, 2009, p. 169.

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Commentary: A gerontological perspective on Klaus Gärtner's discovery that phenotypic variability of mammals is driven by stochastic events

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About 40 years ago, an exceptionally dedicated investigator began a 20-year series of remarkable studies in an effort to understand why, despite every effort to control the genotypes and the environments of his rodent colonies, there was a frustrating degree of phenotypic variability. Many of his papers were published in German and therefore perhaps not widely available to the international community. This situation began to change when Klaus Gärtner published his seminal review of that 20-year odyssey in 1990.[1] I say 'began' because there was a lag period before one began to see a crescendo of growth of citations to this paper; of the 71 citations to that review listed in PubMed as I write this review, some 19 were published in 2010 and the still incomplete record for 2011. Possibly because I am a gerontologist recently interested in stochastic variation underlying intra-specific variations in health span and life span, I must admit that I too have come very late to the party celebrating Gärtner's contributions. I am grateful to George Davey Smith, co-editor of this journal, for having introduced me to this classic paper and to his splendid summary of the previous history of publications of relevance to this field of scholarship.[2]

Gärtner's review cited research comparing parameters of phenotypic variability of rats at two age groups: 81 and 181 days. A typical gerontological experiment with rats or mice would choose the latter cohort as the baseline of young mature animals and compare them with middle-aged animals about twice that age and old animals at about four times that age. If Professor Gärtner had embraced that experimental design, he would have found a much greater degree of phenotypic variability, even for body and organ weights, especially given the impacts of the many diseases of ageing that are driven by intrinsic mechanisms of biological ageing. (He also would have annihilated his research budget and the patience of his co-workers!) But what is the evidence for the statement that variability increases during the course of ageing, and why do I believe that this phenomenon is driven by stochastic events? Moreover, what categories of stochastic events may be primarily responsible for such variegation?

The best model system to address the variability of the penultimate gerontological phenotype, life span, is the humble roundworm, *Caenorhabditis elegans*. As these nematodes are hermaphrodites, every diploid