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Non-Genetic Non-Environmental Phenotypic Variation in Health and Disease

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What if our ideas about phenotypic variation overlook a primary determinant? Fisher's century-old variance model, Phenotype VP = genetics VG + environment VE + error Ve, guides many areas of biological research. But substantial phenotypic variation is not represented in this model. On average 50% of variability is neither genetic nor environmental. We propose that considerable non-G and non-E variation emerges during development, arising from stochastic noise that triggers probabilistic epigenetic changes that once established are stable and deterministically propagated throughout life. These epigenetic changes lead to wide variation in phenotypic outcomes across many traits, in many species, and in health and disease. Individuality emerges from this interplay between genes, environment and chance. A deep understanding of organismal biology and the goals of Precision Medicine depend on discovering the mechanistic origins and systems properties of this surprisingly pervasive and strong but generally neglected dimension of phenotypic variation. I will share evidence and arguments about chance as a primary driver of non-G non-E phenotypic variation, propose an 'accidental individuality' model, and suggest a phenotype-driven strategy to improve diagnosis and treatments for disease involving a virtuous cycle of discovery, experiments and translation between model organisms and humans.

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