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Phenotypic plasticity, the missing dimension of phenotypic variation and disease risk

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What if our concept, theory and evidence of phenotypic variation exclude a major determinant? Since Fisher, P= G + E has guided our understanding of the origins of phenotypic variation. But this model fails to account for substantial variation. On average 50% of the variation between twins and among isogenic model organisms is neither genetic nor environmental. Residual variation is usually attributed to undetected genetics, unmeasured environment, measurement error, and irreducible variation. But brief reflection suggests that these are insufficient explanations. Instead, we propose that non-genetic and non-environmental variation results primarily from transiently stochastic epigenetic events that once established are highly stable and deterministic. These mechanisms enable plastic responses to genetic and environmental conditions.

Ongoing work has identified the first epigenetic mediators of plasticity as well as their targets. A survey of isogenic Chromosome Substitution Strains shows that variance QTLs (vQTL's) rival mean-effect QTL's in complexity and effect size. Comparable evidence is also found in many mutant mice and with many treatment-induced conditions, including those of interest to NIDA. In general, examples have been found across every biological system examined and across a broad range of species. These discoveries show that epigenetic triggers and their functional targets are experimentally tractable, especially with unique isogenic mouse genetic resources and novel analytical methods that focus on *both* variance and average effects. A deep understanding of organismal biology and the goals of Precision Medicine depend on discovering the mechanistic origins of this surprisingly pervasive and strong but generally neglected dimension of phenotypic causality.