Submitter name: Joe Nadeau
Submitted Email: jnadeau3@mmc.org

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

Joe Nadeau[1], David Buchner[2], David Carey[3], Peter Gluckman[4], Neerja Karnani[5], Christine Lary[1], Ruth Loos[6], Jesse Riordan[7], Tim Triche[8], J. Andrew Pospisilik[7].

[1]Maine Medical Center Research Institute, [2]Dept. of Genetics and Genome Sciences, Case Western Reserve University School of Medicine, [3]Geisinger Clinic, [4]Singapore Institute of Clinical Sciences, [5]Icahn School of Medicine at Mount Sinai, [6]Dept. of Anatomy and Cell biology, University of Iowa, [7]Van Andel Research Institute

Phenotypes are often noisy, sometimes varying dramatically, even among genetically identical individuals in standardized conditions. Dogma argues that genetics (G) and environment (E), acting in a deterministic and linear manner, are the primary determinants of phenotypes (P). Unaccounted phenotypic variation is considered to be residual (R), where R usually includes only undetected G, unmeasured E, measurement error, and irreducible variation. Largely ignored is the increasing evidence that a third factor – '*Noise*' (N) – contributes significantly through as-yet ill-defined regulatory mechanisms. Various considerations suggest that R results largely from N and that P = G + E + N.

We propose that the input for *Noise* - epigenetic change - is transient, stochastic and therefore probabilistic during development, while its often non-linear output - alternative phenotypic states – endures, impacting health and disease across a lifetime. After the window of epigenetic vulnerability has passed, each decision is fixed, thus generating a stable but distinct phenotypic trajectory. These epigenetic triggers and functional targets are experimentally tractable, especially with our unique mouse mutants, pioneering Chromosome Substitution Strains, and novel analytical methods that focus on *both* variation and mean effects. Indeed, ongoing work has identified the first epigenetic mediators as well as candidate targets.

Strong evidence for humans and mouse models suggests that *Noise* accounts for as much as 50% of phenotypic variation across all traits examined. An understanding of the mechanistic origins of this surprisingly large and neglected dimension is essential to achieve the goals of precision medicine.