

## **Intra-strand DNA symmetry provides insight into evolution of complex life form**

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A major challenge of modern biology is to understand how random genetic variations cause phenotypic variation in a quantitative trait. Francis Crick's central dogma provides residue-by-residue mechanistic explanation of the flow of genetic information in living systems. However, this principle may not be sufficient to address the above problem. Chargaff's Second Parity Rule (CSPR), also referred to as intra-strand DNA symmetry, and defined, as near exact equalities  $G \approx C$  and  $A \approx T$  within single DNA strand, is a statistical property of cellular genomes. Analysis of mutation spectra inferred from single nucleotide polymorphisms observed in human and mice populations revealed near exact equalities of the reverse complementary mutations, indicating that random genetic variations are in compliance with CSPR. Furthermore, the nucleotide compositions of coding sequences are statistically interwoven via CSPR, since pyrimidine bias at 3rd codon position compensates purine bias at 1st and 2nd positions. Based on Fisher's infinitesimal model, we propose that accumulation of reverse complementary mutations results in the continuous phenotypic variation due to small additive effects of statistically interwoven genetic variations. Therefore, additive genetic interactions can be inferred as a statistical entanglement of the nucleotide compositions of separate genetic loci. CSPR challenges neutral theory of molecular evolution, since all random mutations participate in variation of a trait and provides alternative solution to Haldane's dilemma by making a gene function diffuse. We propose that CSPR is a symmetry of Fisher's infinitesimal model and that genetic information can be transferred in implicit, contactless manner. Natural selection acts on many traits at once, consequently, evolution proceeds via accumulation of small effect-size mutations distributed over entire genome. Statistical entanglement of random genetic variations is the way to store information despite genetic drift.