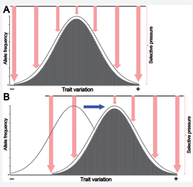
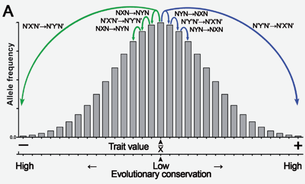
Chargaff's second parity rule lies at the origin of additive genetic interactions in quantitative traits to make omnigenic selection possible

INTRODUCTION

Francis Crick's central dogma provides a residue-by-residue mechanistic explanation of the flow of genetic information in living systems. However, this principle may not be sufficient for explaining how random mutations cause continuous variation of quantitative, highly-polygenic complex traits. Chargaff's second parity rule (CSPR), also referred to as intrastrand DNA symmetry and defined as near exact equalities of nucleotides A and T and of C and G (G ≈ C and A ≈ T) within a single DNA strand, is a statistical property of cellular genomes.

The phenomenon of intrastrand DNA symmetry was discovered more than 50 years ago; at present, it remains unclear what its biological role is, what the mechanisms are that force cellular genomes to comply strictly with CSPR, and why genomes of certain noncellular organisms have broken intrastrand DNA symmetry. The present work is aimed at studying a possible link between intrastrand DNA symmetry and the origin of genetic interactions in quantitative traits.



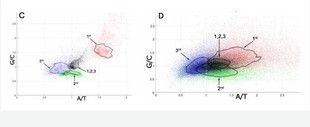


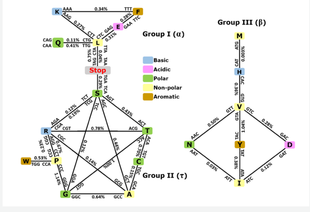
METHODS

Computational analysis of single-nucleotide polymorphisms in human and mouse populations and of nucleotide composition biases at different codon positions in bacterial and human proteomes.

Table 1. Mutation spectra inferred from single nucleotide polymorphisms in human and mouse populations.

N°	N X N	N Y N	X	Y	Total number of SNPs	Fraction	N'X'N'	N'Y'N'	X'	Y'	Total number of SNPs	Fraction	Difference (%)
Human SNPs													
1	AGC	ATC	G	T	312720	0.37	GAT	GCT	A	C	310244	0.36	0.79
2	CAA	CTA	A	T	227826	0.27	TAG	TTG	A	T	229630	0.27	0.79
3	ACT	ATT	C	T	2367625	2.77	AAT	AGT	A	G	2375298	2.78	0.32
4	AAA	AGA	A	G	1729945	2.02	TCT	TTT	C	T	1734336	2.03	0.25
5	TAT	TTT	A	T	544308	0.64	AAA	ATA	A	T	543030	0.64	0.23
6	GAG	GTG	A	T	287742	0.34	CAC	CTC	A	T	288408	0.34	0.23
7	GCG	GTG	C	T	2008008	2.35	CAC	CGC	A	G	2008195	2.35	0.01
8	TAA	TGA	A	G	1448254	1.69	TCA	TTA	C	T	1448196	1.69	0.00



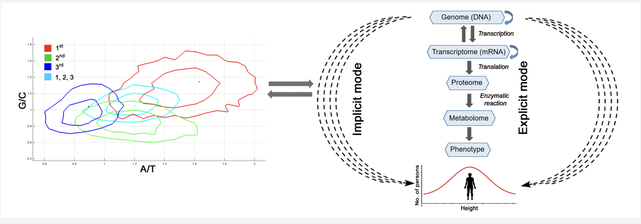


RESULTS

The analysis of mutation spectra inferred from single-nucleotide polymorphisms observed in murine and human populations revealed near-exact equalities of numbers of reverse complementary mutations, indicating that random genetic variations obey CSPR. Furthermore, nucleotide compositions of coding sequences proved to be statistically interwoven via CSPR because pyrimidine bias at the 3rd codon position compensates purine bias at the 1st and 2nd positions.

CONCLUSION

According to Fisher's infinitesimal model, we propose that accumulation of reverse complementary mutations results in a continuous, phenotypic variation due to the small, additive effects of statistically-interwoven genetic variations. Therefore, additive genetic interactions can be inferred as a statistical entanglement of nucleotide compositions of separate genetic loci. CSPR challenges the neutral theory of molecular evolution—because all random mutations participate in variation of a trait—and provides an alternative solution to Haldane's dilemma by making the gene's function diffuse. We propose that CSPR is a symmetry of the Fisher's infinitesimal model and that genetic information can be transferred in an implicit contactless manner.



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