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The Origin of Population Diversity: Stochastic Interactions between a Modifier Variant and the Individual Genetic Background

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Abstract

Stochastic epistasis that is one of the characteristics of epistatic gene modules can have an important role in the maintenance of intraspecific population diversity. The effect of an epistatic modifier variant can vary in size and direction among the modifier careers on the basis of stochastic genetic individuality and the entire module effect can be also individually stochastic. This stochastic genetic contribution under a genetic background may be conditional upon the presence of a monomorphic switch locus in the gene module. The genetic background includes multiple modifier variants and the gene module is composed of the switch and the modifiers. The bell-shaped distribution of quantitative traits can be well simulated by the involvement of multiple stochastic epistatic modules. The phenotypic stochasticity makes the presence of switch and modifiers cryptic or missing in the research field and this cryptic gene networks can maintain and innovate in the phenotypic diversity under selection as a process of the evolution of complexity.

Keywords

Population Diversity, Stochastic Epistasis, Human Complex Traits, Autism

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1. Introduction

Stochasticity or randomness is ubiquitous in biological systems and contributes to a variety of phenotypic diversity [1]. Intrinsic molecular stochastic phenomenon ("gene expression noise" and its random fluctuation) can be beneficial to an isogenic bacterial colony which has genetic factors for the wide-range phenotypic noise covering an ability to survive [1]-[4]. In diploid eukaryotic organisms, epigenetically-driven "monoallelic expression" including autosomal random allelic exclusion is closely associated with organ functions and dysfunctions [5]-[7]. The stochasticity originates in circuits of interacting genes and proteins or feedback loops [8] [9] and the need for an enormous assortment of physiological responses in complexity and specificity depends on stochasticity-based phenotypic diversity [9]. Therefore, many complex biological functions in higher eukaryotes may derive from the stochastic interactions [9]. There may be no human trait being outside of complex diversity. Even the degree of phenotypic penetrance of a major variant gene effect, the liability to dichotomous diagnosis, the latent period duration of later-onset diseases, clinical response to treatment, and both resistance and vulnerability to the pathogens, toxins, or mental stress can be illustrated by quantitative complexity [10]. The stochastic epistasis perspective was introduced to explain such human complex conditions [10] [11], and it is characterized by the phenotypic concordance in monozygotic twins in contrast to the discordance of "gene expression noise" and "random monoallelic expression" (**Table 1**). Although involvement of environmental factors and the epigenetic factors is sometimes emphasized to explain the presence of discordant identical twin cases in some complex conditions [12], the stochastic epistasis can have a great role in complex conditions which have a disparity between monozygotic and dizygotic concordances.

The frontiers of research in human complex traits and conditions still survive in the black box between genotype and phenotype. Because co-segregation between phenotypic characteristics and the related genetic variants is a prerequisite for speciation and evolution, dissection of the processes that maintain genetic variation persists as a major challenge in evolutionary biology [13] [14]. The source of replenishment for genetic individual variation is undoubtedly an ongoing load of rare genetic variants [14], and importantly the fitness significance of a variant can be varied among species from beneficial to deleterious [15]. The difficulty in explaining the persistence of genetic variation also manifests itself in a mating arena (lek). Even though the female choice should result in genetic benefits to offspring, the powerful directional selection cannot immediately drive the beneficial alleles to fixation in the population [16]-[18]. In human behavioral and cognitive liability to complex conditions which have sizable heritable component, the prevalence rate of the extreme cases with obvious reproductive demerits strangely seldom decline [19]-[21]. Such conditions including autism and schizophrenia are characterized by a high concordance in monozygotic twins and a low concordance in dizygotic twins [22] [23]. Hundreds of candidate variants associated with complex conditions have recently been found, and most of these variants explain only a modest amount of the observed heritability ("missing heritability") [24]-[26]. The reported gene variants including de novo mutations are detected in a minor part of cases and sometimes show incomplete penetrance in family members and low result reproduction rate in different samples [11]. In addition, the modest genetic overlap among sub-domains in a condition [27] [28] may be indistinguishable from that among multiple other complex conditions [29] [30]. Although the genetic contribution to a quantitative complex trait can theoretically be attributable to the cumulative effect of a set of quantitative trait loci (QTLs) [31], the delay and

Table 1. Stochastic or random influences on human phenotypes.

Main mechanism	Expression in identical twins
Intrinsic	
Gene expression noise	Discordant[a]
Stochastic switching in gene expression noise	Discordant
Germinal mutations/chromosome recombination and shuffling	Concordant
Random monoallelic expression (epigenetically-driven)	Discordant[a]
Stochastic epistasis	Concordant
Ecological	
Non-shared environment	Discordant

[a]The discordance in genetically identical pairs had been exemplified by human fingerprints for the gene expression noise [4] and demonstrated in the mosaic-like coat-coloration pattern of a kitten clone for the random monoallelic expression [5].

difficulty in detecting the causal variant alleles at QTLs is a common problem for complex traits [32]-[34]. The involvement of stochastic epistasis in the genetic architecture of complex traits is an attractive candidate of solution for these outstanding paradoxes in contrast to the insufficient interpretability by traditional perspectives in which the presence of extreme-specific genetic factors is hypothetically underlined [35] [36]. In some of these paradoxes, the stochastic epistasis model provides the sole explanation.

2. An Epistatic Switch Locus and Modifier Alleles in a Gene Network Module

Epistasis can be explained as the relationship between a modifier variant and the genetic background in which the variant occurs [37]. The genetic background itself consists of other modifier variants and each modifier is a constituent of a gene network module [38] [39]. In experimental investigations to show the interactions between epistasis-related loci, a remarkable function (an epistatic switch) had been demonstrated at some loci in plant strains [40]-[42]. Although the locus sometimes has little or no effect on trait variation, the phenotypic diversity determined by epistatic modifiers is conditional upon the specific switch allele at the locus (**Figure 1**). Because the presence of epistatic switch is a prerequisite for the manifestation of epistatic interactions, the switch locus may be closely associated with the outcome functions and at least one switch should be involved in each epistatic module [10]. The presence of switch alleles which are necessary for the emergence of environmental fitness effects are also known in association with local adaptation [13].

3. Stochastic Genetic Backgrounds and Stochastic Epistatic Outcomes

Genetic individuality is mainly sustained by an ongoing load of rare genetic variants [14]. Except for pairs of identical twin, the genetic individuality is furthermore warranted by meiotic replacement of the variant assortment in a gamete. These meiotic processes, chromosome recombination and shuffling (independent assortment), provide genetically individual gametes for the following genetically unique zygosis. Because the phenotypic effect size and direction of a modifier allele depend on the individual genetic background, the high individuality of the genetic backgrounds in the modifier carriers allows stochastic epistatic outcomes [39] [42] [43]. The stochastic epistasis components (modules) include stochastic modifiers (C, D, and E in **Figure 2**) and an invisible epistatic switch, and the mean value of the carrier outcomes can be approximately the same as that in the former generation (zero). In traditional (non-stochastic) epistasis model, scattering of the carrier outcomes is limited and the involvement of an epistatic switch may be not necessary.

4. The Epistatic Switch and Its Fixation

The only ground for evolutionary selection of an allele is the fitness value of phenotypic outcomes in the allele

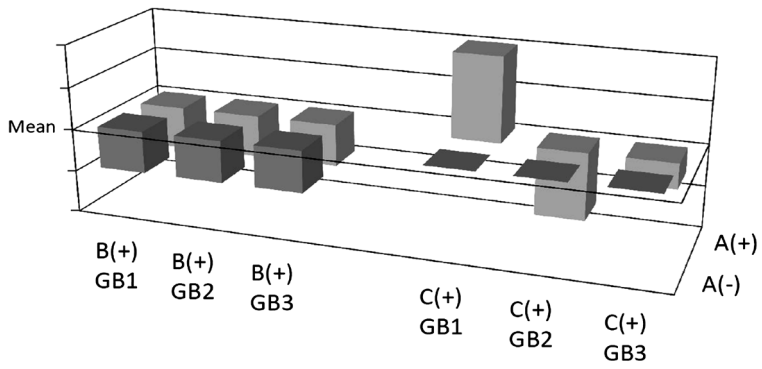

Figure 1. A switch (A) and a modifier (C) in the stochastic epistasis perspective. The presence of A is a prerequisite for the exhibition of interactions between C and individual genetic backgrounds (GB1-3). Variant B is not a modifier and its genetic effect is not influenced by the genetic backgrounds and the effect is not conditional upon the switch A. C itself is a component of the genetic backgrounds, and the absence of C can affect the phenotypic outcome. The y-axis scale is arbitrary and the deviation from the population mean value is assigned to show the genetic effect in the genotype carrier.

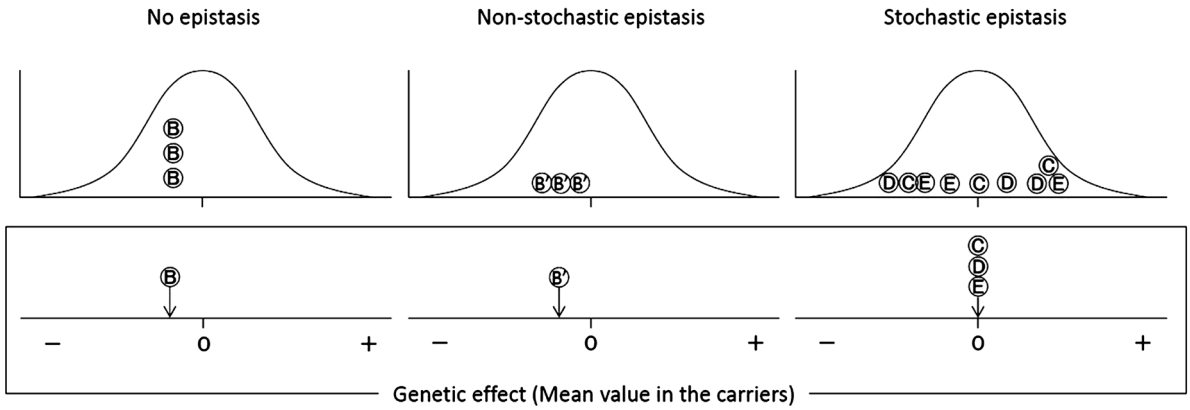

Figure 2. Stochastic epistasis and the mean effect value in the carriers. The phenotypic outcome of a carrier is represented on the x-axis of the bell-shaped population distribution. The scale is arbitrary and the deviation from the population mean is assigned to show the genetic effect in the carrier. In the case of "no epistasis", each phenotypic outcome of a variant (B) carrier and the mean deviation from the population average is all the same. Traditional epistasis (non-stochastic epistasis) causes scattering of the outcomes (B'). A modifier variant (C, D, or E) with stochastic epistasis causes the carrier's stochastic outcome according to the individual genetic background, and the carrier means can be approximately zero. In this stochastic epistasis model, biased or small-sized sampling may induce non-replicable detection of the modifier variants and true association between the complex condition and the modifiers may be more invisible through a bigger population study with enough sample size.

carrier. If the epistatic switch locus is originally polymorphic, in carriers of the switch-on allele the module-related phenotypic outcome can have any fitness value from the unfavorable extreme to the advantageous extreme according to the individual genetic background. This extensive distribution or the full phenotypic diversity of the switch-on carriers can confer strong evolutionary advantages in socio-ecological changes which affect the fecundity of a part of the population. It can be simply exemplified and simulated in a series of severe environmental changes, by which partial extinction of the population is introduced and the extinct counterpart is different in each case. The presence of an identical-by-descent switch allele causes an intergenerational fluctuation of the fitness outcomes in members of the descent [10] [44], and the fixation of the switch can be facilitated by the intermittent succession of different types of ecological changes and the following rapid restoration of the extinct part through the stochastic epistasis. This restoration process to keep the bell-shape, which is immediately launched after the distributional damage, can be achieved by the survived population and may be one of the switch-specific characteristics. If the epistatic switch locus is originally monomorphic, it ought to have another quite essential function. Although traditional genetic models deal only with segregating genetic variation and thus effects of monomorphic loci are invisible in the research field, both monomorphic and polymorphic loci are involved in the actual gene networks for complex traits [45] [46]. Assuming that the switches are fixed (monomorphic) and the genetic individuality is sufficiently stochastic in the population, the individual stochasticity of the phenotypic outcomes in carriers of a modifier variant also makes it difficult to detect the modifier. The mean genetic effect of a modifier variant in the carriers can be approximately the same as the population mean through generations because of the stochastic individuality (**Figure 2**). This cryptic collaboration between the switch and modifiers can accomplish the maintenance of phenotypic diversity under selection. Non-switch monomorphic involvement is also plausible, but interactions between the non-switch monomorphic loci and polymorphic modifiers are again invisible.

This perspective can explain the situation that mapping epistatic interactions is still challenging, experimentally, statistically, and computationally [47]. However, there are some clues that suggest where the epistatic switch locus is and how the modifier members are. As mentioned above, because the presence of epistatic switch is a prerequisite for the manifestation of epistatic interactions, the function of monomorphic switch may be closely associated with the module phenotypic functions. In stochastic epistasis model, genetic investigations with partial sample sizes may accidentally have valuable information on the candidates of growing modifier variants (**Figure 2**). Therefore, functions and structures derived from the variants which were demonstrated in association with human complex conditions may be informative in spite of the low reproducibility of the association. RNA processing, transcription, cell to cell interaction (including immune reactions), signal transduction,

synaptic infrastructures, and neuronal development may be involved in the modifier functions of human complex conditions [48]-[56]. If there are simple functional links between a switch and modifier variants in a module, the functions of modifier candidates may suggest the function of the switch locus. Because the known stochastic mechanisms originate in circuits of interacting genes and proteins or feedback loops [8] [9], the switch-related network may be associated with multi-subunit molecules, complex feedback loops, cascade structure, hierarchical structure, conformational structure, or the presence of alternative pathways. The reported mutations may not be the causal variants of diseases, but they are mere nonspecific modifiers at the predetermined loci. The evolutionary significance of the epistatic switch implies that some of the modifier variants may hitchhike alongside the monomorphic switch locus [57]. Hot spots for de novo germinal mutation in relation to complex conditions [58] may be derived from such hitchhiking. Because genes that act as genetic hubs are also important for buffering stochastic genetic variation [59], genes that interact with many different loci with different functions might have the epistatic switch. Epistasis that involves essential reactions often occurs between reactions without overlapping functions [60]. A long string of complex links or biological endo-phenotypes may intermediate between a switch and modifiers. If the functional link between the switch and modifiers is unintelligible, it may be difficult to detect the monomorphic switch locus.

5. Modules and Environmental Factors

The bell-shaped distribution of quantitative traits can be well simulated by the involvement of multiple stochastic components [10], and stochastic genetic individuality is reflected in the stochastic phenotypic outcomes. The stochastic constituent is a modifier in a module, and phenotypic outcomes sometimes need multiple gene modules as stochastic components. If there was no interaction with the environment, the stochastic outcome through stochastic epistasis was never accidental. As described above, both germinal genetic alterations and stochastic epistasis are concordant in identical twins (**Table 1**). In the real natural world, however, the environment influences every level of genotype-phenotype relationships (**Figure 3**). Especially, the behavioral and cognitive world provides complex gene-environment interactions. Even if a pair of identical twins in the same ecological niche has extrinsically the same behavioral experiences, they each intrinsically experience the individually original non-shared environment, and the non-shared environment can be accidentally variable. Individual phenotypes themselves can influence the accidentally variable non-shared environments. The developmental trajectory is one of the complex phenotypes interacting with the environment and can also be highly individualized by the non-shared environments. The network module structure plays a key role at each level of genotype-phenotype relationships [38] [61] [62] (**Figure 3**), and stochastic epistatic gene modules affect individual responses to environmental cues through the hierarchical cascades of the overlapped modules. In multi-dimensions of trait vectors, a change in modifier members or an ecological cue may nonlinearly move the position of phenotypic distribution [63].

6. Stochastic Epistasis and Evolution

The stochastic epistasis model never dismiss the comprehensive view of the known genetic contribution, including major variant effects, additive networks, and non-stochastic epistasis [10] [11] [44]. This model was originally described as fitness uncertainty of the phenotypic consequences whose underpinnings involve additive genetic factors, gene-environment interactions, and epistasis [44]. To simulate the significance of stochastic epistatic gene components, the stochasticity was substituted by the random contribution from a module with a switch locus [10]. Random effects of associated modifiers additively constitute the module stochastic contribution and the sum total of each module contribution in an individual can be regarded as the overall phenotypic outcome. For evolutional considerations, the dimensional phenotypic distribution is viewed in a fitness vector. From a comprehensive view, the effect value of a variant can be evaluated as the mean of the individual phenotypic outcomes in variant carriers in the population, and the difference between the variant mean and the population mean value is assigned to show the genetic effect (**Figure 2** and **Figure 4**). In this article, the involvement of non-stochastic epistasis is taken for granted and the non-stochastic participants are included in variants with certain level of mean effects. Variants with major genetic effects have big mean effects, but are exposed to big selection pressures, resulting in low contribution to the maintenance of phenotypic diversity under selection (**Figure 4**). The mean genetic effect of a modifier variant that is a component of the stochastic epistatic module can be approximately the same as the population mean through generations, and the modifier can contribute to

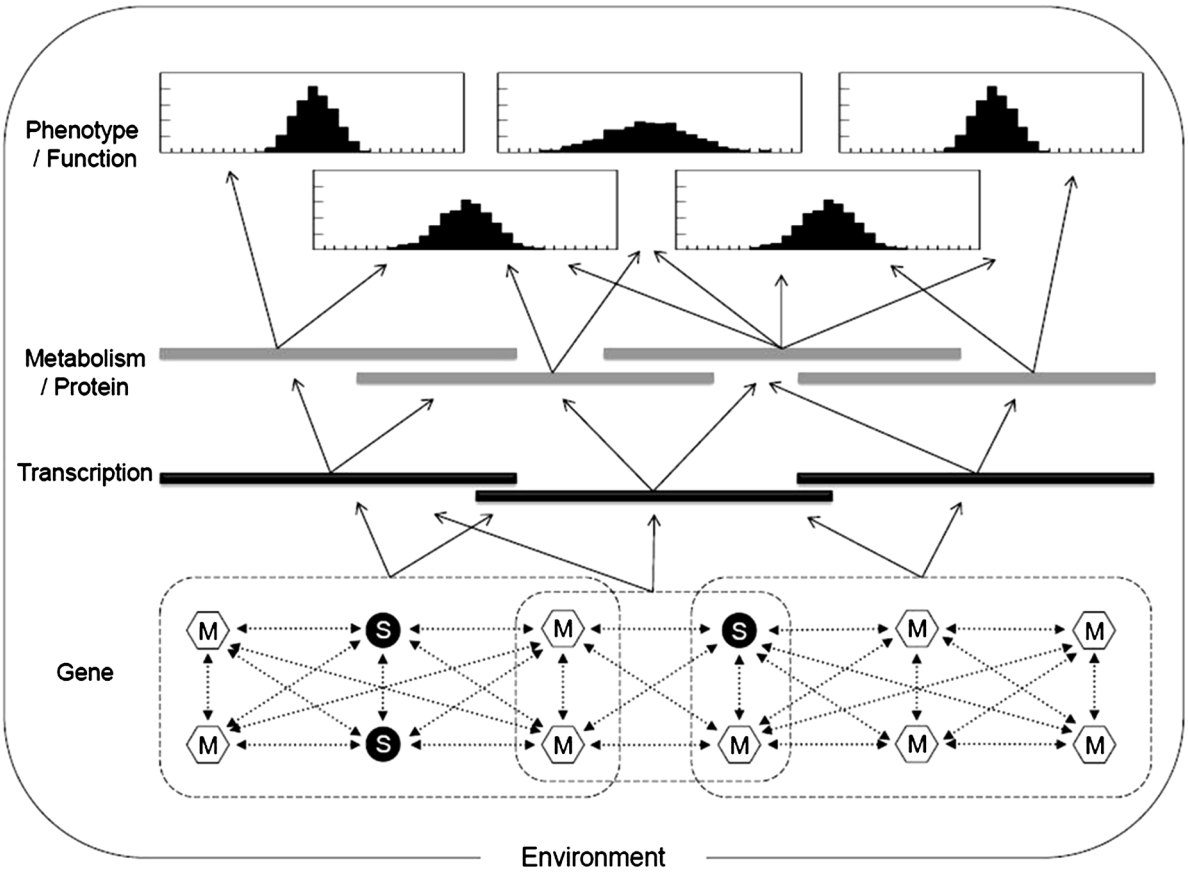

Figure 3. Schematic drawing of genotype-phenotype relationships from the view point of stochastic epistasis. At each level, environment has interactions with the components. The expression of relationships depends on the individual developmental timetable, which is also one of the complex phenotypes interacting with the environment. Stochastic epistatic gene modules (broken line boxes) are composed of at least one monomorphic epistatic switch (closed circles with letter S) and multiple modifier variants (open hexagons with letter M). The number of modifiers in a module may be from several to dozens. Complex interactions between the loci (dotted arrows) and the overlap of gene modules may be critical for the stochastic phenotypic outcomes. At transcription, protein, and metabolism levels (endo-phenotype levels), network modules are depicted as bars. Functional and/or positional links between the components of a module may be sometimes subtle. The overlap of gene modules is the basis of pleiotropy and the pleiotropic structure includes interactions between the endo-phenotypes at each level and the complex effects from the lower-level endo-phenotypes (upward arrows). The overlap of phenotypic dimensions denotes hierarchical complexity of each phenotype. The bell-shape of quantitative traits can be well simulated by the involvement of multiple stochastic components and a phenotype can be ultimately underpinned by multiple gene modules including hundreds of modifiers.

the maintenance of phenotypic diversity under selection. Major variants can take one variant-one condition manner and stochastic epistatic modules underpin complex conditions.

Physiological and cognitive functions need an enormous assortment of responses that are available as necessary to deal with a variety of targets and stimulations [9]. Both complexity and specificity is required for the stock or supplies, and stochasticity-based phenotypic diversity is an efficient strategy for the complexity. Furthermore, the stochasticity eventually plays a role in building up the repertoire of specificity [9] and inter-module complexness. This diversification strategy is, no doubt, the only way to win the chance at survival [64] [65]. Interactions between polymorphic loci can make the organisms insensitive to the impact of novel mutations or environmental perturbation [59] [66] [67], and stochastic epistatic modules may have critical roles in this buffer system. A variant which was buffered and harbored in the stochastic genetic network is one of the modifiers of the module and can participate in an active evolutionary phenotypic change through a nonlinear alteration of the mean value or the position of the distribution in multi-dimensions of trait vectors [63] [68]. Like uncovering cryptic genetic variation [69] [70], a genetic or ecological change may unveil the phenotypic or evolutionary

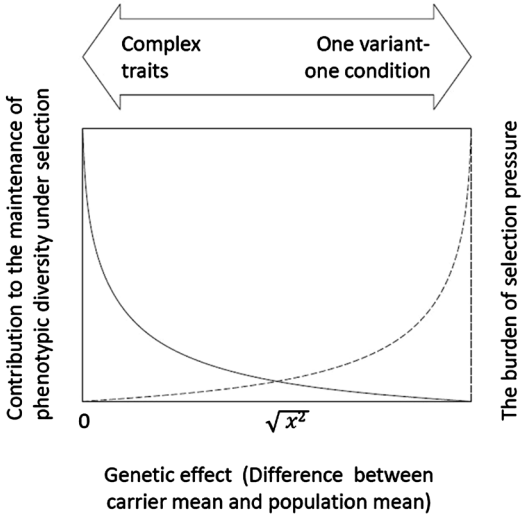

Figure 4. Implications of a variant and human conditions. The difference (x) between the mean of the carrier distribution and the population mean has a contribution to the maintenance of phenotypic diversity (solid line) and the burden of selection pressure (broken line). Complex traits are underpinned by stochastic epistasis whose components include modifiers with tiny or zero mean effect. Such a modifier has an important role to keep phenotypic diversity under selection. The causal variant of a one variant-one condition trait has a considerable genetic effect under high selection pressure. Nonlinear alteration of the genetic effect is available through a change in modifier members in the module or an ecological cue.

significance of an old member in the module. The accumulation of transiently concealed genetic alterations may be associated with the evolution of complexity. Moreover, the phenotypic complexation increases the complexity of the social-ecological niche (social structure) and individual non-shared environments. The evolution of social complexity needs a more enormous assortment of individual responses to the local ecological conditions [13] and changing human activities [71], resulting in an evolutionary cycle or spiral. “Genes do not exist to cause diseases” [72], but perhaps one of the purposes of the genetic architecture is to cope with complexity.

7. Conclusion

The stochastic epistasis mechanism warrants evolutionary robustness of bell-shaped distribution of a complex trait. In other words, it reproduces the bilateral extreme tails of the population distribution in each generation as well as the major part around the mean value. On the other hand, the stochastic epistasis may also explain the phenotype changes. In the fitness-related dimension including fecundity, selection pressures can rapidly purge the unfavorable tail. Therefore, one extreme tail may include the non-fittest who cannot leave offspring and the other tail or the border flanking to the non-fittest tail may provide the founder or pioneer who is the key person for human terrestrial migration and local adaptation. In spite of the stochastic manner of the stochastic epistasis, the repeated purge of the same non-fittest extremes may be another process of evolutionary trends in which the phenotypic mean value can be passively changed [67]. In a liability-probability model, the non-fittest extreme tail possesses extremely low fecundity and the fecundity is continuously and sharply recovered at the majority of the bell-shaped population [73]. Both the active directional trend by de novo epistatic modifiers and the passive directional trend by repeated purge of the non-fittest tail may affect the position of the distribution in the nonlinear relation to fecundity probability, especially through a population bottleneck or reproductive isolation of a smaller population. To predict the ongoing trends or future directional changes of the complex trait distributions, the presence of fitness benefits of border cases who is located in the transitional zone flanking to the non-fittest tail [11], a trade-off between the non-fittest outcomes and fitness benefits by expanding the range of complexity [74], and the role of female carriers of modifiers to maintain the non-fittest tail in the population distribution [75] should be involved in the consideration.

References

[1] Ozbudak, E.M., Thattai, M., Kurtser, I., Grossman, A.D. and van Oudenaarden, A. (2002) Regulation of Noise in the Expression of a Single Gene. *Nature Genetics*, **31**, 69-73. http://dx.doi.org/10.1038/ng869

[2] Elowitz, M.B., Levine, A.J., Siggia, E.D. and Swain, P.S. (2002) Stochastic Gene Expression in a Single Cell. *Science*, **297**, 1183-1186. http://dx.doi.org/10.1126/science.1070919

[3] Balaban, N.Q., Merrin, J., Chait, R., Kowalik, L. and Leibler S. (2004) Bacterial Persistence as a Phenotypic Switch. *Science*, **305**, 1622-1625.

[4] Raser, J.M. and O'Shea, E.K. (2005) Noise in Gene Expression: Origins, Consequences, and Control. *Sicence*, **309**, 2010-2013.

[5] Shin, T., *et al*. (2002) Cell Biology: A Cat Cloned by Nuclear Transplantation. *Nature*, **415**, 859. http://dx.doi.org/10.1038/nature723

[6] Gimelbrant, A., Hutchinson, J.N., Thompson, B. and Chess, A. (2007) Wide Spread Monoallelic Expression on Human Autosomes. *Science*, **318**, 1136-1140. http://dx.doi.org/10.1126/science.1148910

[7] Chess, A. (2013) Random and Non-Random Monoallelic Expression. *Neuropsychopharmacology*, **38**, 55-61. http://dx.doi.org/10.1038/npp.2012.85

[8] Eldar, A. and Elowitz, M.B. (2010) Functional Roles for Noise in Genetic Circuits. *Nature*, **467**, 167-173. http://dx.doi.org/10.1038/nature09326

[9] Magklara, A. and Lomvardas, S. (2013) Stochastic Gene Expression in Mammals: Lessons from Olfaction. *Trends in Cell Biology*, **23**, 449-456. http://dx.doi.org/10.1016/j.tcb.2013.04.005

[10] Ijichi, S., *et al*. (2011) Non-Additive Interactions between Monomorphic and Polymorphic Loci: A Theoretical Explanation of the Genetic Underpinning for Complex traits. In: Berhardt, L.V., Ed., *Advances in Medicine and Biology, Vol.* 13, Nova Science Publishers Inc., Hauppauge, 133-147. https://www.novapublishers.com/

[11] Ijichi, S., Ijichi, N., Ijichi, Y., Sameshima, H. and Morioka, H. (2011) The Genetic Basis of Phenotypic Diversity: Autism as an Extreme Tail of a Complex Dimensional Trait. In: Deutsch, S., Ed., *Autism Spectrum Disorders*: *The Role of Genetics in Diagnosis and Treatment*, InTech, Rijeka, 83-102. http://dx.doi.org/10.5772/19032 http://www.intechopen.com/download/pdf/17279

[12] Bell, J.T. and Spector, T.D. (2011) A Twin Approach to Unraveling Epigenetics. *Trends in Genetics*, **27**, 116-125. http://dx.doi.org/10.1016/j.tig.2010.12.005

[13] Mitchell-Olds, T., Willis, J.H. and Goldstein, D.B. (2007) Which Evolutionary Processes Influence Natural Genetic Variation for Phenotypic Traits? *Nature Reviews Genetics*, **8**, 845-856. http://dx.doi.org/10.1038/nrg2207

[14] Olson, M.V. (2012) Human Genetic Individuality. *Annual Review of Genomics and Human Genetics*, **13**, 1-27. http://dx.doi.org/10.1146/annurev-genom-090711-163825

[15] Breen, M.S., Kemena, C., Vlasov, P.K., Notredame, C. and Kondrashov, F.A. (2012) Epistasis as the Primary Factor in Molecular Evolution. *Nature*, **490**, 535-538. http://dx.doi.org/10.1038/nature11510

[16] Brooks, R. (2000) Negative Genetic Correlation between Male Sexual Attractiveness and Survival. *Nature*, **406**, 67-70. http://dx.doi.org/10.1038/35017552

[17] Kotiaho, J.S., Simmons, L.W. and Tomkins, J.L. (2001) Towards a Resolution of the Lek Paradox. *Nature*, **410**, 684-686. http://dx.doi.org/10.1038/35070557

[18] Hughes, K.A., Houde, A.E., Price, A.C. and Rodd, F.H. (2013) Mating Advantage for Rare Males in Wild Guppy Populations. *Nature*, **503**, 108-110. http://dx.doi.org/10.1038/nature12717

[19] Vogel, H.P. (1979) Fertility and Sibship Size in a Psychiatric Patient Population. A Comparison with National Census Data. *Acta Psychiatrica Scandinavica*, **60**, 483-503. http://dx.doi.org/10.1111/j.1600-0447.1979.tb00558.x

[20] Stefansson, H., *et al*. (2008) Large Recurrent Microdeletions Associated with Schizophrenia. *Nature*, **455**, 232-236. http://dx.doi.org/10.1038/nature07229

[21] Power, R.A., *et al*. (2013) Fecundity of Patients with Schizophrenia, Autism, Bipolar Disorder, Depression, Anorexia Nervosa, or Substance Abuse vs Their Unaffected Siblings. *JAMA Psychiatry*, **70**, 22-30. http://dx.doi.org/10.1001/jamapsychiatry.2013.268

[22] Kendler, K.S. and Diehl, S.R. (1993) The Genetics of Schizophrenia: A Current, Genetic-Epidemiologic Perspective. *Schizophrenia Bulletin*, **19**, 261-285. http://dx.doi.org/10.1093/schbul/19.2.261

[23] Rapin, I. and Katzman, R. (1998) Neurobiology of Autism. *Annals of Neurology*, **43**, 7-14. http://dx.doi.org/10.1002/ana.410430106

[24] Beaudet, A.L. (2007) Autism: Highly Heritable but Not Inherited. *Nature Medicine*, **13**, 534-536.

http://dx.doi.org/10.1038/nm0507-534

[25] Lander, E.S. (2011) Initial Impact of the Sequencing of the Human Genome. *Nature*, **470**, 187-197. http://dx.doi.org/10.1038/nature09792

[26] van Dongen, J. and Boomsma, D.I. (2013) The Evolutionary Paradox and the Missing Heritability of Schizophrenia. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **162**, 122-136. http://dx.doi.org/10.1002/ajmg.b.32135

[27] Ronald, A., Happé, F. and Plomin, R. (2005) The Genetic Relationship between Individual Differences in Social and Nonsocial Behaviours Characteristic of Autism. *Developmental Science*, **8**, 444-458. http://dx.doi.org/10.1111/j.1467-7687.2005.00433.x

[28] Ronald, A., *et al*. (2006) Genetic Heterogeneity between the Three Components of the Autism Spectrum: A Twin Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, **45**, 691-699. http://dx.doi.org/10.1097/01.chi.0000215325.13058.9d

[29] Kendler, K.S., Prescott, C.A., Myers, J. and Neale, M.C. (2003) The Structure of Genetic and Environmental Risk Factors for Common Psychiatric and Substance Use Disorders in Men and Women. *Archives of General Psychiatry*, **60**, 929-937. http://dx.doi.org/10.1001/archpsyc.60.9.929

[30] Rzhetsky, A., Wajngurt, D., Park, N. and Zheng, T. (2007) Probing Genetic Overlap among Complex Human Phenotypes. *Proceedings of the National Academy of Sciences of the United States of America*, **104**, 11694-11699. http://dx.doi.org/10.1073/pnas.0704820104

[31] Plomin, R., Haworth, C.M.A. and Davis, O.S.P. (2009) Common Disorders Are Quantitative Traits. *Nature Reviews Genetics*, **10**, 872-878. http://dx.doi.org/10.1038/nrg2670

[32] Hill, W.G. (2012) Quantitative Genetics in the Genomics Era. *Current Genomics*, **13**, 196-206. http://dx.doi.org/10.2174/138920212800543110

[33] Feltus, F.A. (2014) Systems Genetics: A Paradigm to Improve Discovery of Candidate Genes and Mechanisms Underlying Complex Traits. *Plant Science*, **223**, 45-48. http://dx.doi.org/10.1016/j.plantsci.2014.03.003

[34] Flint, J. and Mackay, T.F.C. (2009) Genetic Architecture of Quantitative Traits in Mice, Flies, and Humans. *Genome Research*, **19**, 723-733. http://dx.doi.org/10.1101/gr.086660.108

[35] Mitchison, N.A. (2000) Polymorphism in Regulatory Gene Sequences. *Genome Biology*, **2**, Comment 2001.

[36] Kristiansson, K., Naukkarinen, J. and Peltonen, L. (2008) Isolated Populations and Complex Disease Gene Identification. *Genome Biology*, **9**, 109. http://dx.doi.org/10.1186/gb-2008-9-8-109

[37] Poelwijk, F.J., Kiviet, D.J., Weinreich, D.M. and Tans, S.J. (2007) Empirical Fitness Landscapes Reveal Accessible Evolutionary Paths. *Nature*, **445**, 383-386. http://dx.doi.org/10.1038/nature05451

[38] Segrè, D., Deluna, A., Church, G.M. and Kishony, R. (2005) Modular Epistasis in Yeast Metabolism. *Nature Genetics*, **37**, 77-83.

[39] Wang, Y.H., Arenas, C.D., Stoebel, D.M. and Cooper, T.F. (2012) Genetic Background Affects Epistatic Interactions between Two Beneficial Mutations. *Biology Letters*, **9**, Article ID: 20120328. http://dx.doi.org/10.1098/rsbl.2012.0328

[40] Lark, K.G., Chase, K., Alder, F., Mansur, L.M. and Orf, J.H. (1995) Interactions between Quantitative Trait Loci in Soybean in Which Trait Variation at One Locus Is Conditional upon a Specific Allele at Another. *Proceedings of the National Academy of Sciences of the United States of America*, **92**, 4656-4660. http://dx.doi.org/10.1073/pnas.92.10.4656

[41] Weinig, C., *et al*. (2003) Heterogeneous Selection at Specific Loci in Natural Environments in *Arabidopsis thaliana*. *Genetics*, **165**, 321-329. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1462755/pdf/14504239.pdf

[42] Kroymann, J. and Mitchell-Olds, T. (2005) Epistasis and Balanced Polymorphism Influencing Complex Trait Variation. *Nature*, **435**, 95-98. http://dx.doi.org/10.1038/nature03480

[43] Pettersson, M., Besnier, F., Siegel, P.B. and Carlborg, Ö. (2011) Replication and Explorations of High-Order Epistasis Using a Large Advanced Intercross Line Pedigree. *PLoS Genetics*, **7**, e1002180. http://dx.doi.org/10.1371/journal.pgen.1002180

[44] Ijichi, S., *et al*. (2008) For Others: Epistasis and the Evolutionary Survival of an Extreme Tail of the Quantitative Distribution of Autistic Assets. *Medical Hypotheses*, **70**, 515-521. http://dx.doi.org/10.1016/j.mehy.2007.07.016

[45] Gjuvsland, A.B., Hayes, B.J., Omholt, S.W. and Carlborg, Ö. (2007) Statistical Epistasis Is a Generic Feature of Gene Regulatory Networks. *Genetics*, **175**, 411-420. http://dx.doi.org/10.1534/genetics.106.058859

[46] Benfey, P.N. and Mitchell-Olds, T. (2008) From Genotype to Phenotype: Systems Biology Meets Natural Variation. *Science*, **320**, 495-497. http://dx.doi.org/10.1126/science.1153716

[47] Mackay, T.F.C. (2014) Epistasis and Quantitative Traits: Using Model Organisms to Study Gene-Gene Interactions.

Nature Reviews Genetics, **15**, 22-33. http://dx.doi.org/10.1038/nrg3627

[48] Voineagu, I., *et al*. (2011) Transcriptomic Analysis of Autistic Brain Reveals Convergent Molecular Pathology. *Nature*, **474**, 380-384. http://dx.doi.org/10.1038/nature10110

[49] Sanders, S.J., *et al*. (2012) *De Novo* Mutations Revealed by Whole-Exome Sequencing Are Strongly Associated with Autism. *Nature*, **485**, 237-241. http://dx.doi.org/10.1038/nature10945

[50] Neale, B.M., *et al*. (2012) Patterns and Rates of Exomic *de Novo* Mutations in Autism Spectrum Disorders. *Nature*, **485**, 242-245. http://dx.doi.org/10.1038/nature11011

[51] O'Roak, B.J., *et al*. (2012) Sporadic Autism Exomes Reveal a Highly Interconnected Protein Network of *de Novo* Mutations. *Nature*, **485**, 246-250. http://dx.doi.org/10.1038/nature10989

[52] King, I.F., *et al*. (2013) Topoisomerases Facilitate Transcription of Long Genes Linked to Autism. *Nature*, **501**, 58-62. http://dx.doi.org/10.1038/nature12504

[53] Oksenberg, N. and Ahituv, N. (2013) The Role of *AUTS2* in Neurodevelopment and Human Evolution. *Trends in Genetics*, **29**, 600-608. http://dx.doi.org/10.1016/j.tig.2013.08.001

[54] Fromer, M., *et al*. (2014) *De Novo* Mutations in Schizophrenia Implicate Synaptic Networks. *Nature*, **506**, 179-184. http://dx.doi.org/10.1038/nature12929

[55] Purcell, S.M., *et al*. (2014) A Polygenic Burden of Rare Disruptive Mutations in Schizophrenia. *Nature*, **506**, 185-190. http://dx.doi.org/10.1038/nature12975

[56] Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological Insights from 108 Schizophrenia-Associated Genetic Loci. *Nature*, **511**, 421-427. http://dx.doi.org/10.1038/nature13595

[57] Chun, S. and Fay, J.C. (2011) Evidence for Hitchhiking of Deleterious Mutations within the Human Genome. *PLoS Genetics*, **7**, e10002240. http://dx.doi.org/10.1371/journal.pgen.1002240

[58] Michaelson, J.J., *et al*. (2012) Whole-Genome Sequencing in Autism Identifies Hot Spots for *de Novo* Germline Mutation. *Cell*, **151**, 1431-1442. http://dx.doi.org/10.1016/j.cell.2012.11.019

[59] Lehner, B. (2011) Molecular Mechanisms of Epistasis within and between Genes. *Trends in Genetics*, **27**, 323-331. http://dx.doi.org/10.1016/j.tig.2011.05.007

[60] He, X.L., Qian, W.F., Wang, Z., Li, Y. and Zhang, J.Z. (2010) Prevalent Positive Epistasis in *Escherichia coli* and *Saccharomyces cerevisiae* Metabolic Networks. *Nature Genetics*, **42**, 272-276. http://dx.doi.org/10.1038/ng.524

[61] Konopka, G., *et al*. (2012) Human-Specific Transcriptional Networks in the Brain. *Neuron*, **75**, 601-617. http://dx.doi.org/10.1016/j.neuron.2012.05.034

[62] Bolhuis, J.J., Brown, G.R., Richardson, R.C. and Laland, K.N. (2011) Darwin in Mind: New Opportunities for Evolutionary Psychology. *PLoS Biology*, **9**, e1001109. http://dx.doi.org/10.1371/journal.pbio.1001109

[63] Gibson, G. (2009) Decanalization and the Origin of Complex Disease. *Nature Reviews Genetics*, **10**, 134-140. http://dx.doi.org/10.1038/nrg2502

[64] Aertsen, A. and Michiels, C.W. (2005) Diversity or Die: Generation of Diversity in Response to Stress. *Critical Reviews in Microbiology*, **31**, 69-78. http://dx.doi.org/10.1080/10408410590921718

[65] Fraser, D. and Kærn, M. (2009) A Chance at Survival: Gene Expression Noise and Phenotypic Diversification Strategies. *Molecular Microbiology*, **71**, 1333-1340. http://dx.doi.org/10.1111/j.1365-2958.2009.06605.x

[66] Rice, S.H. (2008) Theoretical Approaches to the Evolution of Development and Genetic Architecture. *Annals of the New York Academy of Sciences*, **1133**, 67-86. http://dx.doi.org/10.1196/annals.1438.002

[67] de Visser, J.A.G.M., Cooper, T.F. and Elena, S.F. (2011) The Causes of Epistasis. *Proceedings of the Royal Society B*: *Biological Sciences*, **278**, 3617-3624. http://dx.doi.org/10.1098/rspb.2011.1537

[68] Carroll, S.B. (2001) Chance and Necessity: The Evolution of Morphological Complexity and Diversity. *Nature*, **409**, 1102-1109. http://dx.doi.org/10.1038/35059227

[69] Gibson, G. and Dworkin, I. (2004) Uncovering Cryptic Genetic Variation. *Nature Reviews Genetics*, **5**, 681-690. http://dx.doi.org/10.1038/nrg1426

[70] Le Rouzic, A. and Carlborg, Ö. (2008) Evolutionary Potential of Hidden Genetic Variation. *Trends in Ecology Evolution*, **23**, 33-37. http://dx.doi.org/10.1016/j.tree.2007.09.014

[71] Laland, K.N., Odling-Smee, J. and Myles, S. (2010) How Culture Shaped the Human Genome: Bringing Genetics and the Human Sciences Together. *Nature Reviews Genetics*, **11**, 137-148. http://dx.doi.org/10.1038/nrg2734

[72] Gee, H. (2000) Eyes left. *Nature*, Published Online 15 February. http://www.nature.com/news/2000/000215/full/news000217-6.html

[73] Ijichi, S., *et al*. (2013) Quantitative Nature of Social Vulnerability and Autism: An Important Paradigm Shift in the DSM-5 for Autism Spectrum Disorder. *ISRN Neurology*, **2013**, Article ID: 201719. http://dx.doi.org/10.1155/2013/201719 http://downloads.hindawi.com/journals/isrn/2013/201719.pdf

[74] Hayden, E.C. (2009) The Other Strand. *Nature*, **457**, 776-779. http://dx.doi.org/10.1038/457776a

[75] Robinson, E.B., Lichtenstein, P., Anckarsäter, H., Happé, F. and Ronald, A. (2013) Examining and Interpreting the Female Protective Effect against Autistic Behavior. *Proceedings of the National Academy of Sciences of the United States of America*, **110**, 5258-5262. http://dx.doi.org/10.1073/pnas.1211070110