Comment

Dissecting genomic imprinting and genetic conflict from a game theory prospective: Comment on: “Epigenetic game theory: How to compute the epigenetic control of maternal-to-zygotic transition” by Qian Wang et al.

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Game theory as a tool to model genomic imprinting

Epigenetics typically refers to changes in the structure of a chromosome that affect gene activity and expression. Genomic imprinting is a special type of epigenetic phenomenon in which the expression of an allele depends on its parental origin. When an allele inherited from the mother (or father) is imprinted (i.e., silent), it is termed as maternal (or paternal) imprinting. Imprinting is often resulted from DNA methylation and tends to cluster together in the genome [1]. It has been shown to play a key role in many genetic disorders in humans [2]. Imprinting is heritable and undergoes a reprogramming process in gametes before and after fertilization [1]. Sometimes the reprogramming process is not reversible, leading to the loss of imprinting [3]. Although efforts have been made to experimentally or computationally infer imprinting genes, the underlying molecular mechanism that leads to unbalanced allelic expression is still largely unknown.

The game theory proposed by Wang et al. [4] provides a promising tool to understand the epigenetic control of maternal-to-zygotic transition that leads to genomic imprinting. Game theory was originally proposed to solve economic and financial problems, but it has been extended to biological fields with applications such as for gene mapping [5] and for understanding the evolution of ATP-producing pathways [6]. As the major contributing factor for genomic imprinting, DNA methylation is a dynamic reprogramming process where methylation signals are removed during the gamete stage and are subsequently reprogrammed after fertilization [7]. Recent studies show that many epigenetic events are spontaneous, and meiotically stable epialleles can be produced due to changes in DNA methylation [8]. Such transgenerational epigenetic variation in DNA methylation can lead to new epialleles that alter gene expression and morphology, providing new insights for phenotypic diversity [9]. At the molecular level, the degree of epigenetic changes largely relies on the cooperation and competition between the two sets of gametes, the so called epiallelic interactions. Such interactions have consequences on individual fitness. As pointed out in the paper, “each sex tends to maximize the expression of its genes in the zygote toward the maximum fitness of the

progeny” [4]. Thus, the maternally and paternally derived alleles tend to compete with each other to gain the advantage of natural selection [4]. In the meanwhile, they both cooperate to maintain a coherent development of the embryo. This brings *a tug of war* between the two sets of gametes. In general, an equilibrium stage can be properly maintained. When it breaks, there will be consequences. In extreme cases, diseases may occur [10].

The parent-specific epigenetic reprogramming is a dynamic process during embryo development. Thus, the competition between the two sets of gametes is a dynamic process. Using differential equations to model the dynamic process between the two sets of gametes provides a new means to understanding this complicated process. By embedding the mathematical ordinary differential equations (ODEs) into the game theory framework, one can mathematically quantify the imprinting process and further make statistical inference [4]. In addition, Wang et al. [4] proposed an estimation method under the functional mapping framework [11] and further derived an interaction test to statistically assess the competition (or interaction) between different epigenomes. Under the new framework, one is able to model and test the effects of epialleles associated with phenotypic variation. Combined with the imprinting quantitative trait loci mapping framework [12], the game theory strategy can be a powerful tool to understand the dynamic imprinting effect associated with a disease trait and gain novel insights into the transgenerational epigenetic variation.

Game theory as a tool to dissect genetic conflict

When a baby resides inside of its mother’s womb, a proper development of an embryo relies on the underlying harmony of interest between a mother and a fetus. A fetus carries one copy of the genome from its mother and one copy from its father. The maternal copy is crucial to avoid conflict (at molecular level) between the two generations. However, the underlying harmony can be broken when the maternal and paternal copies inherited by a fetus invest differently on fetal fitness. Haig [10] pointed out that when the balance of the mutual benefits is broken, disease may occur.

In general, genetic conflict happens among three sets of alleles: 1) non-inherited maternal allele (NIMA) in the mother genome; 2) maternally derived fetal alleles (MDFA) in the fetal genome; and 3) paternally derived fetal alleles (PDFA) in the fetal genome [10]. Based on the three sets of alleles, two types of genetic conflict can be defined: one is between MDFA and PDFA in the fetus genome; another is between NIMA and PDFA between the maternal and the fetal genome. The cooperation between MDFA and PDFA is important to maintain proper development and function of an individual. In the meantime, conflict between MDFA and PDFA also exists based on the natural selection theory [13]. As a fetus resides inside of a mother’s womb, genetic conflict can arise between PDFA and NIMA during early stage of fetal development, which is

also coined as maternal-fetal genotype incompatibility (MFGI) [14]. Example includes the RhD MFGI which increases susceptibility to schizophrenia [15].

Statistical methods for testing MGFI have been studied [14, 16-18]. These methods were developed for assessing genetic conflict associated with a disease between the maternal and fetal genome, i.e., between NIMA and PDFA. In an epigenetic level, conflict between PDFA and MDFA is associated with different degrees of epigenetic state, such as different degrees of DNA methylation. Li et al. [19] recently proposed a unified method to model and test the effect of the two types of conflicts associated with a disease. However, modeling the dynamic conflict process underlying a disease state has not been studied. Given the dynamic nature of conflict, the game theory coupling with the ordinary differential equations proposed by Wang et al. [4] offers a promising tool to model the underlying mechanism. Properly developed statistical inference procedures can be applied to dissect the role of epialleles derived from different genomes.

Prospect and conclusion

Driven by the advancement of modern sequencing technologies, there is almost no limit to generate genomic data such as gene expressions, genetic variants, DNA methylation and histone modification data. Especially, the bisulfite sequencing (BS-seq) and ChIP-seq technology can generate epigenetic data in digital resolution with no limit. These data offer unprecedented opportunities to understand the epigenetic control process and the underlying machinery associated with complex diseases. The availability of these sequencing data provides rich resources to test epigenetic control of phenotypic variation based on the proposed game theory [4].

To conclude, the game theory framework proposed by Wang et al. [4] provides a highly promising and powerful tool towards modelling epigenetic control of maternal-to-zygotic transition (i.e. to model the dynamics of epigenetic changes and to understand how such changes affect phenotypic variation). The ever-increasing amount of sequencing data makes it possible to test the game theory at the molecular level, which can lead to novel insights or even major breakthrough in epigenetics.

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