

## Some novel rules of the biological heterozygous effects

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### ABSTRACT

The pure of an individual is relative to the hybrid. No two identical organisms are found on the earth at the level of nucleotide sequence. After two parents mating, the variations of their offspring will occur in the nucleotide sequence compared to their parents, which are called biological heterozygous effect. However, the molecular bases for this phenomenon remain elusive. In our view, biological heterozygous effects at least follow the below rules: Firstly, the contribution of the outcome of traits passed from parents to offspring is not equal. Secondly, progeny variation across the heterozygous individuals is lineage-specific dependent and some difference is found among the individuals within a family. Thirdly, biological variation is absolute, random, non-directional, and is fixed and forms a new species while other variation is getting into the blind branch of the species under some circumstances. In summary, Heterozygous effect is the key reason for the formation of biodiversity on the earth.

**Key words:** Biology, Heterozygous effect, Variations.

### INTRODUCTION

The scientists have discovered and named about 2 million kinds of creatures so far on the earth. But 5 million to 30 million species remain to be named in total on the earth (Wu, 2002). These creatures are not the same with each other and differences are also found between different individuals even within the same species.

The following problems are worthy of further thinking. What is the reason for the biodiversity during the biological evolution on the earth? Will the current species change? How will the new species arise? What is a purebred (true-breeding)? What is a hybrid or crossbred?

With the development of the molecular genetics, scientists have found that biological heredity is mainly determined by a gene. At the molecular level, a gene is a segment of DNA that produces a functional product. From the perspective of nucleotide sequence, no two completely identical organisms can be found on the earth. That is to say, each individual is heterozygous. The purebred or true-breeding is opposed to the hybrid or crossbred (Wang, 2011). Different alterations in nucleotide sequence could be found between the parents and their offspring in the successive generations. That is to say, offspring are similar to their parents in nucleotide sequence rather than the same sequence that their parents possess. Many reasons lead to the alterations in nucleotide sequence. In particular, heterozygous effects aroused by the alterations of nucleotide sequence between two parents are the main reasons for the variations in the offspring. In our view, biological

heterozygous effects follow the below rules.

**The contribution of the outcome of traits passed from parents to offspring is not equal:** The genetic materials for offspring are from two parents, whose nucleotide sequences are different. Thus, heterozygous development is actually based on different genetic inheritance from two parents along with the corresponding cytoplasm interactions. The traditional assumption is that the progeny lineage accounts for 50% of paternal and maternal parent, respectively. Thus, the contribution of parental traits transmitted to offspring is equal. As a matter of fact, both Hardy-Weinberg law of genetic equilibrium (1908) and coefficient of inbreeding calculation are based on this hypothesis (Liu, 1995; Li, 2003). However, biological inheritance is not working in this way. Actually, genes passed from parents to offspring are not same.

A good example is a swine cross experiment. The reciprocal recurrent selection (RSS) was used for Xin Huai pig breeding (1954-1977). A cross (YH) was conducted between Yorkshire (Y) and Huai pig (H). Y served as male parent and H as female parent; whereas HY is the reciprocal cross (Chen et al., 1963). As a result, the four years' data in the reciprocal cross from 1956 to 1959 showed that there was a significant difference in litter size produced by sows in YH and in HY as well as in replacement pig weight in 6 months in YH and in HY, respectively.

In addition, the genetic variability from parents to offspring were also found in the plants such as bringjal (G. Samlind sujin *et al.*, 2017), rice (Pradhan *et al.*, 2017), maize

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(Niharika 2017; Yan *et al.* 2017) and speciality corn (Divya *et al.* 2017) and the performance of some agronomic traits in hybrids were generally found to be different from their parents in crops (Qu *et al.*, 2012; Qi *et al.*, 2013).

Rice is the main grain of modern mankind. Some scientists believed that self pollination crops such as rice had no heterosis in the past. However, Jones of American scientist (1926) firstly discovered and put forward the heterosis of rice in the breeding practice. After that, Kadem in India (1937), Broun in Malaysia (1953), Alim in Pakistan (1957), and Okada Kohiro (1958) in Japan all reported the research results of heterosis in rice. But it was very difficult for self pollination of rice to artificial emasculation. Yuan Longping, the famous Chinese scientist in plant breeding, published the paper entitled the "male sterile rice" in 1966 and came up with the idea of cultivation of male sterile line of rice and then rice hybridization had developed rapidly (Adam, 2007). In rice hybridization, the influence of parent on offspring was unequal. Hybridization of different rice strains led to different results. It was reported that the success rate of different parental combination and reciprocal crosses were different when they did distant hybridization between *Indica* and *japonica* rice breeding using cross and backcross and the combination of *indica* hybrid female parent success rate was higher (Li, 2011).

The same results of a difference between reciprocal inheritance in crop genetics were also found in the wheats. For instance, there were significant differences between wheat hybrids and parents when they selected 3 Winter Wheat lines as a group of parents, 3 for another group of parents and made up 18 hybridization combinations of reciprocal cross. These studies suggested that heterosis was caused by some differentially expressed genes and there might be a complex relationship between differential gene expression and heterosis formation during early seed development (Xie *et al.*, 2003).

There were also obvious differences between the offspring of maize hybrids and their parents in protein abundance in metabolism, stress response, glycolysis, transcriptional regulation, protein folding and degradation, three acid cycle, cytoskeleton, development and so on, which might be related to the formation of heterosis in maize leaf size maize. It is also suggested that the influence of parents on offspring was not 50% (Guo *et al.*, 2003).

It is well known that different genetic models for heterosis, including dominance, overdominance, epistasis, and genetic equilibrium hypothesis, have been debated for more than a century (Chen, 2013). Unfortunately, there has been a failure to use these models to maximize heterosis. To our excitement, the recently established techniques called whole-genome haplotype reconstruction using proximity-ligation and shotgun sequencing was able to recognize the

DNA resource that comes from either male parent or female parent (Selvaraj, 2013).

Meat quality was correlated with heterozygous effects in reciprocal crosses. Zhou *et al.* (2010) drew the conclusions in the carcass and meat quality traits in reciprocal cross experiment between Large White (L) and Erhualian pigs (E). They analyzed the differences in the carcass characteristics, meat quality, fatty acid and amino acid contents in reciprocal crosses between 25 heads of 180 day old Large White (L) and Erhualian pigs (E) (Zhou *et al.*, 2010). The results showed that thickness of 6-7 rib and the last lumbar spine of crossbred barrows in LE reduced than that in EL. Furthermore, in LE, eye muscle area increased 4.69 cm<sup>2</sup>, carcass lean meat ratio increased 2.82%, and intramuscular fat content increased 2.56% compared to that in EL. Of note, the content of the myristic acid, palmitic acid, oleic acid in the longissimus muscle was much higher in LE group than that in EL group, whereas the content of suboleic acid and twenty carbon five acid content is on the opposite in LE than that in EL (Zhou, 2010), which was consistent with the previous result that heterosis effects on pig carcass traits (Cassady, 2002).

Small RNAs, including small interfering RNAs (siRNAs), microRNAs (miRNAs) and trans-acting siRNAs (ta-siRNA), mediate gene expression and/or epigenetic regulation. Indeed, siRNA displays expression changes in the reciprocal crosses.

Some epigenetic and epigenomic alterations in crossbreds/hybrids are associated with genomic imprinting effects. Differences in gene expressions of the homologous chromosomes (also called genomic imprinting) further provide powerful evidence at the molecular genetic level, which are significantly reflected in the reciprocal cross between horses and donkeys. In addition, nuclear transplantation experiments also showed that the expressions of gene imprinting were highly correlated with DNA methylation alterations at least in the oocytes (Yang *et al.*, 2002). However, the oocyte methylome was significantly hypomethylated compared to sperm. Strikingly, the paternal DNA methylation pattern was inherited by zebrafish early embryos (Jiang *et al.*, 2013). Furthermore, Zou *et al.* (2015) developed MethBank, a database of DNA methylome programming that integrates the genome-wide single-base nucleotide methylomes of gametes and early embryos. Collectively, differences in siRNA and methylation pattern were observed in the crossbreds. Epigenetic modifications might lead to genomic imprinting effects on gene expression and could exhibit better-parent heterosis in crossbreds.

#### **Variations in hybrids among the individuals exhibit conservative and variable over the course of generations:**

Some genomes or nucleotide sequences are very conservative in the continuity generation in generation. The similarly

varied genome is found in the offspring derived from a paternal parent. In another word, some genome including nucleotide sequences or fragments is very conservative in the successive generations within a family. We define it as varied conservative property or lineage-specific phenomenon, which function is conservative during the biological evolution.

An example is about cytochrome C in an organism. It is well known that cytochrome C in the electron transfer has 27 amino acids, which is highly conservative. In particular, these 27 amino acids are identical in all organisms including the original yeast and the advanced humans. In contrast, the amino acid in other parts of the cytochrome C changed much or a little bit (Wu, 2002b). Interestingly, only 1.5% difference in genomic DNA sequences was found between humans and chimpanzees and many gene sequences are exactly the same. Meanwhile, even in the non coding region, differences in sequence rarely exceed 3% (Zhao *et al.*, 2001).

MicroRNA (miRNA) is one of the most important regulatory factors in a gene family of eukaryotic cells discovered by scientists over the last decade. These small RNA about 22 nucleotides induce mRNA degradation or (and) inhibit its translation (Bartel *et al.*, 2004). Almost all the miRNAs are conservative across the close species while many miRNAs have homology across the distant species. For example, at least one third of the *Caenorhabditis elegans* has the homology with humans in miRNA (Lin *et al.*, 2003). Taken together, some differences in nucleotide sequence were found in individuals within the same family, including taxa, lines, varieties, genus, family, order, class and phylum, among the offspring, which may vary for different genus, family, order, class and phylum. This is the common phenomenon that one parent born nine children, but nine are not identical.

**Biological variation is absolute, random, non-directional, but some variation is fixed and forms a new species while other variation is getting into the blind branch of the species under some circumstances:** Biological evolution is from lower to higher and from simple to complex, which displays the complexities of the morphological structures and improvements in physiological functions of an organism. These mutations are divided into favorable and unfavorable alterations, which are relative to each other. For example, is it good or bad for snakes to evolve from lizards losing limbs and legs and humans to evolve from chimpanzees losing tails? In mammals, horses and rabbits have powerful cecum to digest roughage while human cecum is very small and loses its function. It is difficult to answer these questions.

Here is an interesting example of whale's move from land to sea for natural selection. The original whales, who grew on land, lived by hunting other animals and fish,

and had four legs like any other land animal. Later, they gradually moved into the sea due to the lure of a large number of fish. About 50 million years ago, the whales began to enter the water due to the water food and the proportion of predators relative to the terrestrial environment for ancient whales to survive. In the long-term evolution process, the forelegs gradually degenerated into flippers, hind legs and hips disappeared but modern whales still have traces of the pelvis. About 10 million years ago, the offspring of ancient whales were very similar to modern whales and metapedes were degenerated into finlike appendages. From then on they stopped coming ashore.

It has been thousands of years of history for human to domesticate animals such as pigs, cattle, horses, sheep, dogs, birds and so forth. These domesticated animals have originated from wild animals through the process of long-term and gradual change of hybridization, variation, breeding (selection) and re-hybridization, variation, re-selection. In this way, the variation in the offspring is random, non-directional while both selection in the mating combinations of parents and selection in progeny are directional due to the artificial selection. In different times, there are different breeding objectives and directions. Therefore, the combination of random variation and artificial selection results in a big difference in body size, head type, ear type, reproductive performance, growth performance, carcass composition and so on between modern pigs and the original wild boars.

Taken together, it demonstrates that biological variation is absolute, random, non-directional in the continuity generation in generation.

It is well known that heterozygous individuals cross with each other and produce various mutations. This kind of mutation is heterozygous effects. At the molecular level, heterozygous effects consist of DNA nucleotide sequence variations, mRNA expression differentials including gene expression rate and enrichment, protein structure alterations, DNA methylation at some regions, and gene duplication in nucleotide sequence, chromosome as well as whole genome. Heterosis (heterozygous effects) facilitates plant stress tolerance, yield and yield components (Stuber *et al.*, 1992; Yu *et al.* 1997; Huang *et al.*, 2017), cell growth (Herbst *et al.*, 2017), animal longevity (Clasen *et al.*, 2017) and so on. For instance, the recent study showed that the 32 significant loci and 36 stress tolerance-related candidate genes were identified in maize by GWAS across the testcrossing association mapping population produced by crossing a cytoplasmic male sterility S line (S-MO17) rather than in maize inbred lines. Of note, expression of ten of the candidate genes was induced by chilling stress in a maize hybrid and only a few of these genes were upregulated in its tolerant parent. So, heterosis might be involved in maize chilling tolerance (Yan *et al.* 2017).

In addition, Tian *et al.* (2008) had found the DNA insertion/deletion (Indel) could lead to a series of variation in the nearby region when compared with gene sequences across the different species of humans, chimpanzees, mice, drosophila, Ganges River monkey, rice and yeast using biological information technology since 2005 (Tian *et al.*, 2008). Based on this, the hypothesis of Indel was put forward to induces spontaneous mutation mechanism. Of note, the hypothesis suggests that biological variation is absolute, random, non-directional and even no so-called evolution and degradation. In particular, some variation is fixed and produces a new species while some variation is getting into the blind branch within a species under some circumstances. The evolution and differentiation of *Microtus fortis* is an example of a new species that has been formed. *Microtus fortis*, which belongs to *Microtus*, *Microtinae*, *Cricetidae* and *Rodentia*, is currently the unique rodent animals to resist to Japanese schistosomiasis. China is the main distribution area for *Microtus fortis*, which is widely distributed in the infected and non-infected Japanese schistosomiasis areas. Those *Microtus fortis* who were resistant to the Japanese schistosomiasis in the infected schistosomiasis areas survived and produced the significant differences when compared to those who grew up in the non-infected areas, whereas those who were not resistant to the schistosomiasis were eliminated (Ni, 2004). The people in Shanghai Laboratory Animal Research Center caught *Microtus fortis* from three different places including Dongting Lake in Hunan (named *M.f. calamorum*), Qingtongxia in Ningxia (*M.f. fortis*) and Yichun City in Heilongjiang and bred them. As a result, they found that Hunan rat (*M.f. calamorum*) cross Ningxia mice (*M.f. fortis*) could produce offspring, whereas Heilongjiang mice segregated to Hunan mice and Ningxia rat, respectively (Ni, 2004).

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In addition, they also found that 20-50g of the smaller mice and 50-90g of the bigger one could not produce offspring when they interbred. So, these two populations were separately raised and formed two independent populations, which were named after the smaller Heilongjiang mice and the bigger one, respectively. This indicated that Heilongjiang mice had already separated from Hunan mice and Ningxia mice and formed a new species (Ni, 2004).

Let's take a look at another example of the evolution of giant panda. The modern giant panda is evolved from the *Ailuropoda lufengensis* lived in Miocene Epoch, who was originally a little kind of omnivorous animal. Then it turned to *Ailuropoda microta*, *Ailuropoda melanoleuca baconi*, and finally changed to modern giant panda species. Giant panda was evolved from original omnivorous animal to the animal only to eat a plant named cold bamboo with low nutrition and withered flowers (Li, 2004). Finally, it became an extinguished species with late sexual maturity and difficulty in estrus, breeding and gestation. The population of giant panda was smaller and smaller. The total population of wild giant panda was only 1,596 by 2003 in China. Furthermore, their lineage was very close to each other and it was difficult to adapt to its surrounding environment (Yan, 2005). Therefore, panda was likely to have evolved into the blind branches.

## CONCLUSION

In conclusion, we have proposed some novel rules for biological heterozygous effect in the current paper. Heterozygous effect can happen not only in different maternal and paternal traits but also in different breeding, species and populations. Importantly, heterozygous effect will occur in the future biological evolution. In a word, heterozygous effect is the key reason for the formation of the biodiversity on the earth.

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