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Commentary

CANDIDATE MUTATIONS IN *BMPR1B* AFFECTING PIG PROLIFICACY.

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Owing to China having the world's largest pig inventory and being the world's largest consumer of pork, the importance of its pig industry is difficult to overstate. The improvement of reproductive traits such as litter size, would increase industrial competitiveness and give producers an economic boost. For example, if the number of live-born piglets per litter were increased by just one, an average producer could realize an additional 100~150 Yuans (RMB) per year. How to achieve this is the key issue for many of China's pork producers. In general, the reproductive traits of female pigs have low heritability, (i.e. the heritability of litter size is approximately 0.10 (Rothschild, 1996). As we know, there are numerous swine breeds indigenous to China, many with the genetic characteristic of high fecundity. After breeding programs in Europe and North America introduced traits of the Taihu breed into their own domestic stock, those sows realized and average of 1.6 more piglets per litter (Webb, 1998). This commentary is a synopsis for pig producers and researchers about what we currently know about the hyper-prolificacy of the Taihu pig.

Recent Advances in Determining the Molecular Mechanism of Taihu Pig Prolificacy

The Taihu breeds indigenous to China are mainly distributed in Taihu Lake Basin; they include the Erhualian, Fengjing, Jiaxing, Meishan, Shawutou, and the Mi (Figure 1), (China National Commission of Animal Genetic Resources, 2011). These pigs are known for their high fertility, superior meat quality, and high resistance to disease. We have reported that the gene *BMPR1B* (Bone Morphogenetic Protein Receptor Type 1B), is key to the high prolificacy in the Taihu pig (Li et al., 2017). *BMPR1B*, as the growth differentiation factor 5 and the natural ligand of BMP4 in BMPs, has been also reported in humans (Dai et al., 2016; Yang et al., 2017), mice (He et al., 2016), and sheep (Mulsant et al., 2001; Souza et al., 2001; Wilson et al., 2001).

In addition to the *BMPR1B* gene, ESR1 (estrogen receptor 1) (Rothschild et al., 1996), FSHβ (Follicle Stimulating Hormone subunit beta) (Li et al., 2000), RBP4 (Retinol Binding Protein 4) (Rothschild et al., 2000), and PRLR (Prolactin Receptor) (van Rens and van der Lende, 2002) have been reported to be associated high prolificacy in pigs. However, knowledge of the mechanisms of these genes, including *BMPR1B*, is very limited.

The reproductive traits of Taihu pigs, including litter size, are controlled by complicated physiological mechanisms. Many factors, from the preparation of ovulation to the end of delivery affect the litter size. The hyper-prolificacy of Taihu pigs is closely related to their ovary and follicle characteristics and high ovulation rate. Although the onset of puberty of Taihu pigs varies with to great extent, their ovulation rates are relatively consistent, being approximately 16.16. The Taihu multiparous sows have rates of 28.16; this is more than sows of other Chinese indigenous breeds and the European and American commercial pig breeds that have rates of 21.58 and 21.4 respectively. Moreover, the number of follicles in the follicle pool of Taihu pigs is greater than those of other pig breeds until follicular phase (Hunter et al., 1993). Possible reasons for the hyper-prolificacy of the Taihu pig is that their follicles are small compared to those of other commercial pigs, and have a higher concentration of follicle stimulating hormone, which results in a higher expression of aromatase in ovarian granulosa cells and cell membranes, and the production of high concentrations of estrogen. In the development of ovary, estrogen reduces the apoptosis of oocytes, improve the primordial follicle volume of the follicle pool of new-born females, and provide a theoretical basis for high-reproductivity traits.

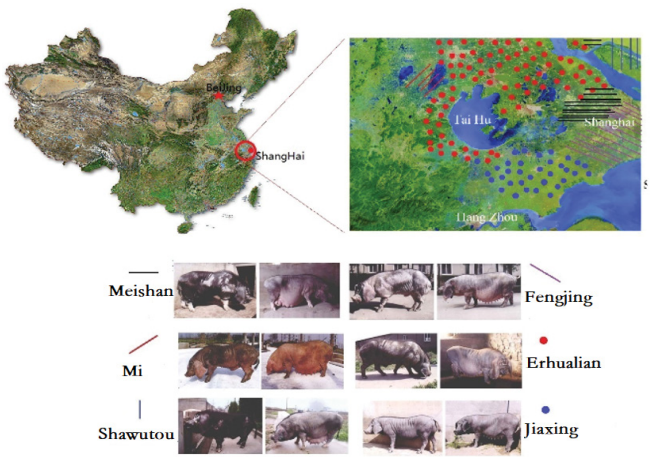

Figure 1: The Taihu pigs and their area of distribution.

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Our Principal Results

Our research team has applied the whole-genome re-sequencing technique to reveal candidate mutations in *BMPR1B* that affect pig prolificacy. Our findings demonstrated that an integrated approach (population genetics, comparative genomics, and molecular experiments), can efficiently identify functional elements underlying important phenotypes in domesticated pigs, and provide a pathway for subsequent investigations.

In the Taihu-specific haplotype of *BMPR1B* (approximately 1.2 kb), 18 of 19 SNPs showed a marked difference in allele frequency between the Taihu and other breeds; these SNPs were confirmed to be candidate mutations for pig prolificacy. Using comparative genomic analysis we found a conserved Estrogen Response Element (ERE) in the haplotype region. Evidence from luciferase assays showed that binding activity with estrogen receptor I is stronger in the Taihu-specific haplotype than in the Duroc-specific haplotype. Higher *BMPR1B* levels were found in the endometria of pregnant Meishan sows relative to Duroc. Meishan pigs also have more endometrial glands than Duroc pigs, as shown by assays of histological sections. Thus, the Taihu-specific haplotype promotes ESR1 binding activity, cis-regulate *BMPR1B* expression, and enhance the endometrial gland development.

In summary, the Taihu-specific haplotype can affect the expression of mRNA and protein of the endometria to increase the number of endometrial glands and ultimately increase the number of Pigs Born Alive (PBA) (Figure 2). What's more, from association studies of reproductive traits and the Taihu-ERE haplotype, the effect of the *BMPR1B* gene is estimated to increase litter size by 0.4~1 pigs. These results demonstrate that *BMPR1B*, as the candidate gene responsible for pig prolificacy, can be used in animal breeding programs to improve pig fecundity.

Future Research

Some segments of the genetic control pathway remain unclear, and further research is required to fill the gaps in our knowledge. For example, the Taihu-specific haplotype contains 19 SNPs and the group verification tests have not been done, and the causative SNP locus has not been identified. Also, HeLa cells, not pig endometrial cells, were used in the luciferase assays to compare the binding activity of the Taihu-ERE with the Duroc-ERE. Although

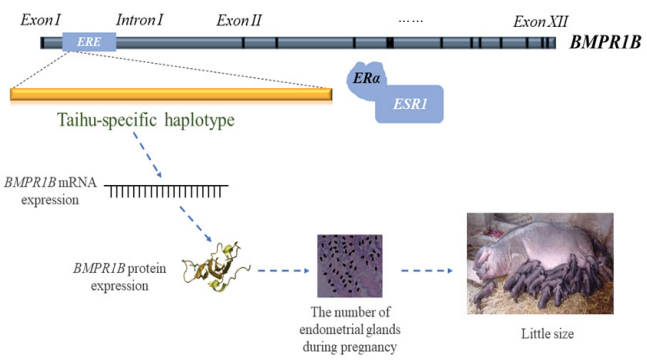

Figure 2: The genetic mechanism of the *BMPR1B* gene.

useful, a HeLa cell does not completely simulate the internal environment of a pig endometrial cell (Lucey et al., 2009).

The differences in the expression of *BMPR1B* (RNA and protein) in the endometrium of Taihu and Duroc pigs at 72 days post-pregnancy is well documented, but these data do not directly address the specific expression of the *BMPR1B* gene in the endometrium; thus immunohistochemistry is needed (Duraiyan et al., 2012). In our previous study (Li et al., 2017) we found that the Taihu-specific haplotype in the first intron of the *BMPR1B* gene was related to the breed's high prolificacy, but the effect of the Taihu-specific haplotype on neither the regulation of *BMPR1B* expression nor its mode of action were clarified. Thus, the genetic characteristics of the *BMPR1B* gene in pigs needs to be further investigated.

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