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Molecular Characterization of Hypothalamo–Pituitary-Thyroid Genes in Pig (Sus Scrofa)

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1. Introduction

Almost all the body functions of vertebrate animals including swine are regulated by the nervous system and endocrine system. Especially the hormones released from the endocrine system have effective biological amplifying effects. Minor changes in the hormone level could cause huge alternations in physiology.

Hypothalamus, extensively connected with other brain regions, is the vital bridge between nervous system and endocrine system. It exerts its regulating function on endocrine system mainly via the pituitary, which is the central endocrine organ in vertebrate animals. Except the growth hormone, most of the hormones secreted by pituitary have their specific target organs. For example, thyrotropin target thyroid. The hypothalamus, pituitary and target organs are always described together as "axis", e.g. hypothalamo-pituitary-gonadal axis, hypothalamo-pituitary-adrenal gland axis, and hypothalamo-pituitary-thyroid (HPT) axis.

2. The axis of hypothalamo-pituitary-thyroid

Hypothalamus synthesizes and secrets thyrotropin-releasing-hormone (TRH) to send regulating information to pituitary (see Figure 1). TRH binds to the thyrotropin-releasing-hormone receptors (TRHR) on the thyrotroph cells of pituitary to activate the intracellular signal pathways and induce the secretion and synthesis of thyrotropin (TSH). Circulating TSH in blood then binds to the thyrotropin receptors (TSHR) on the follicular cells of thyroid to activate the synthesis and secretion of thyroid hormone (TH).

TH secreted by thyroid is important to growth, development, and protein, fat, and carbohydrate metabolisms (Porterfield and White, 2007). It acts on almost all the organs and tissues. Each individual has a unique thyroid function set-point, and this set-point was suggested to be genetically determined (Hansen et al., 2004). Genetic variations of the hormones of HPT axis and their respective receptors could be the excellent candidates as the causing of related phenotype variations.

2.1 Thyrotropin releasing hormone gene (*TRH*)

Thyrotropin releasing hormone, produced in the paraventricular nucleus of the hypothalamus, is fully conserved in all species from human to bony fish that have been

investigated so far (Harder, 2001). It is the tripeptide pyro-Glu-His-Pro-NH_2 derived from the preprohormone gene *TRH*, which also produces other non-TRH active peptides e.g. $ppTRH_{160-169}(pST_{10})$ and $ppTRH_{178-199}$ (pFE_{22}).

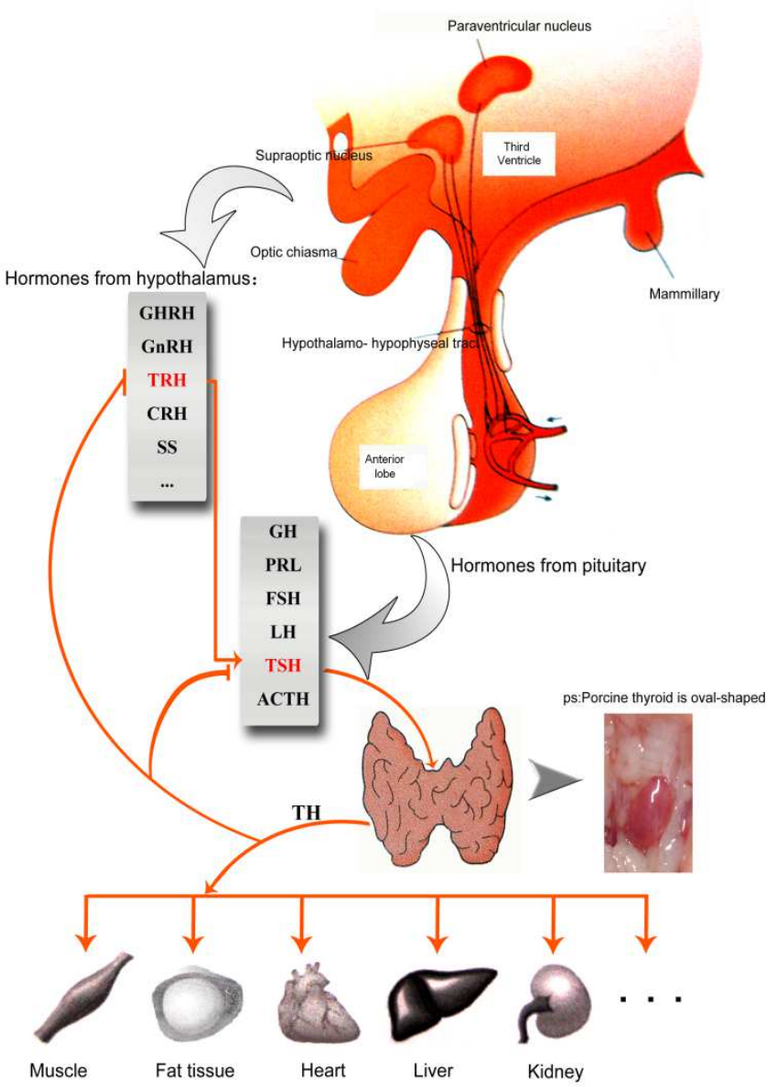

Fig. 1. Schematic map of hypothalamo-pituitary-thyroid axis regulatory network, according to Porterfield and White (2007).

No experiments on the porcine *TRH* gene have been done previously. However genomic information of this gene has became available as a result of the porcine whole genome sequencing, and comprehensive sequence analysis on it with bioinformatics method has been done (Wallis, 2010). Porcine *TRH* gene was found to be 3, 136 bp with 3 exons and two introns. A conserved signal peptide of 24 amino acids was predicted to be present, and there existed six copies of TRH sequences in the preprohormone peptide.

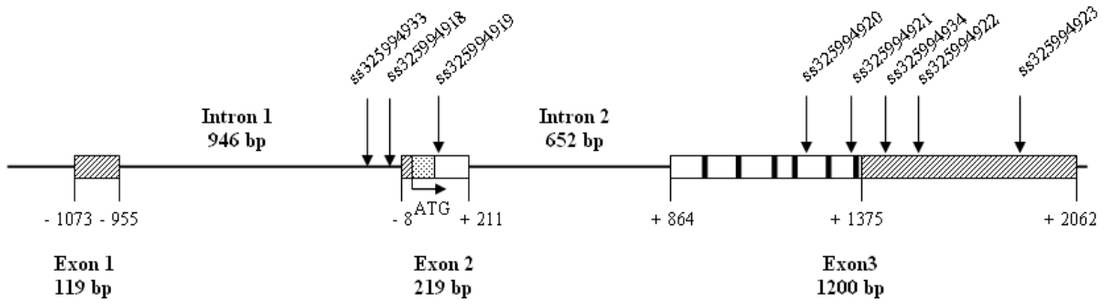

Fig. 2. The schematic map of the porcine *TRH* gene. Boxes represented the exons (according to Wallis), of which the regions filled with diagonal lines were un-translated regions (UTR), the region filled with dots represented the signal peptide, and the regions full filled with black color represented the six copies of TRH precursor peptides.

2.2 Thyrotropin Releasing Hormone Receptor gene (*TRHR*)

TRH initiates its effects by interacting with its receptor TRHR in the anterior pituitary. TRHR is a seven transmembrane spanning receptor and belongs to the G protein-coupled receptor superfamily. Actually, to date in total of three TRH receptors have been reported, each encoded by their specific genes. The first subtype of TRHR found in 1990 have been described in many species, e.g. mouse, rat, human, cow, chicken, frog and fish (Sun et al., 2003). However, the second subtype of TRHR identified in 1998 has only been reported in rodents, frog and fish. Further information of human genome sequence does not support the existence of the second TRHR subtype (Pfleger et al., 2004). The third TRHR subtype has only been reported in frog and fish (Mekuhi et al., 2010) so far. Figure 3 shows the evolution tree of the TRHR proteins.

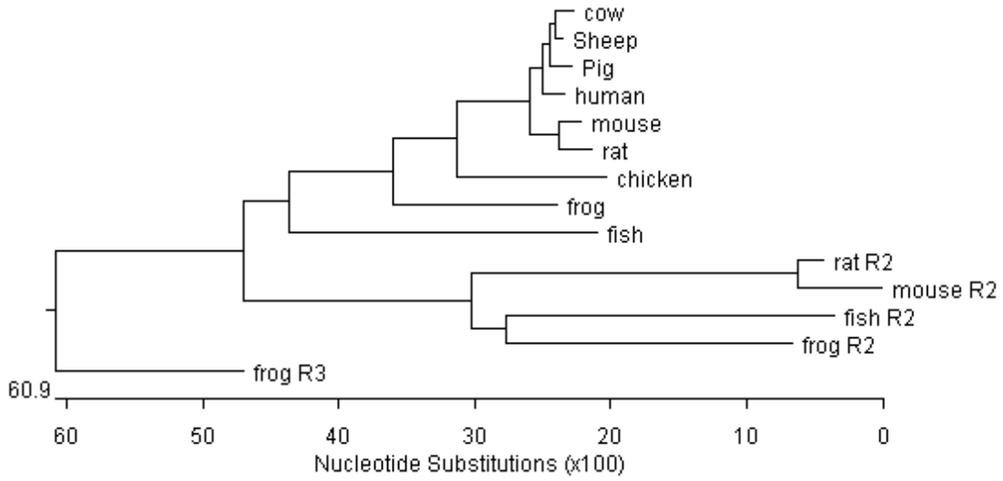

Fig. 3. Polygenetic tree of TRHR proteins, aligned with method Clustal W. The branch of fish used the TRHR sequence of *Catostomus commerson*.

Porcine *TRHR* gene (the first subtype) has been cloned and characterized recently (Jiang et al., 2011). It contains an open reading frame encoding 398 amino acids and shares 96.2%

amino acid identity to human TRHR. An intron disrupts the open reading frame in the sequence encoding the putative third intracellular loop which is between the fifth and sixth transmembrane domain. Besides, alternative spliced transcript variants and multiple transcription start sites have been observed in porcine *TRHR* gene (Jiang, 2011). The biological functions of these variants remain investigations.

2.3 Thyrotropin alpha subunit gene (*CGA*)

Thyrotropin is a member of the glycoprotein hormone family which consisting thyrotrophin, follicle-stimulating hormone and luteinizing hormone in anterior pituitary, and chorionic gonadotrophin in the placenta. Each of these hormones is a heterodimer composed of a common α subunit and a hormone specific β subunit. The common α subunit is encoded by the *CGA* gene, while the TSH specific β subunit is encoded by the *TSHB* gene.

Porcine *CGA* gene is 14 kb in length and consists of four exons and three introns (Kato et al., 1991). The coding region starts from the exon 2, and the premature peptide contains a signal peptide of 24 amino acids. Two intragenic microsatellites were found in intron 1 and intron 2. The microsatellite located in the intron 1 has been named as PGHAS or ALPHA and widely used in genetic studies as genetic marker.

2.4 Thyrotropin beta subunit gene (*TSHB*)

The porcine *TSHB* gene has at least two exons and one intron, and is 939 bp in length. Its product consists of a signal peptide of 24 amino acid residues, a mature beta subunit protein of 112 residues and an additional extension of six amino acid residues at the carboxyl terminus (Hirai et al., 1989). The TSH beta subunit noncovalently links to the alpha subunit by wrapping with its "seat belt" structure around the alpha subunit's long loop αL2.

TSH β subunit is responsible for the hormone specificity, and its translation rate directly determines the secretion and synthesis rates of the hormone TSH. Additionally, it has been reported that mature Chinese meishan pigs had 3 fold greater expressions of *TSHB* gene and greater plasma TSH concentrations than mature Western white composite pigs (Li et al., 1996).

2.5 Thyrotropin receptor gene (*TSHR*)

The receptor of the thyrotorpin,TSHR, belongs to the glycoprotein hormone receptor (GPHR) family which is a subset of the G-protein coupled receptor (GPCR) superfamily. It contains a seven-transmembrane domain and a large ectodomain composed of many leucine-rich repeats forming TSH-binding surface (Farid & Szkudlinski, 2004).

The mRNA sequence of the porcine *TSHR* gene has been cloned in 2003 (Igarashi & Nagata, 2003) and characterized to containing an open reading frame coding 764 amino acids. However, as the genomic sequence of porcine *TSHR* gene is still unavailable so far, the genomic structure of the gene is not clear. Of human, the *TSHR* gene was found to be 190 kb in length, and contains ten exons and nine introns, of which all the first nine exons encodes the large extodomain while the last exon is in charge of the seven transmembrane domains and the intracellular tail.

3. The gene mapping and expression analysis of these genes

Quantitative trait loci (QTLs) are regions of the chromosome that are found to be associated with particular phenotypic traits by statistical analysis. Thus far, the pig QTL database (Pig QTLdb) has collected 6,344 QTLs from 281 publications in the past more than ten years. Any genes in these regions might be the positional candidate genes underlying the respective traits. Mapping the genes of HPT axis would help us to evaluate the potential genetic effects of the variations of these genes.

3.1 The electrical mapping

In April 2009, the International Swine Genome Sequencing Consortium has completed and released a 4× sequence depth draft (Sscrofa9) by a minimal tile path BAC by BAC approach. This assembly can be conveniently accessed by the web-based query on the Ensemble (http://www.ensembl.org/Sus_scrofa/Info/Index). Though a more recent assembly Sscrofa 10, a mixed BAC and WGS-based assembly of the porcine genome, has been released in April 2011, assemble errors in it remain to be resolved. Furthermore, the Pig QTLdb offered GBrowse map view of QTLs (http://www.animalgenome.org/cgi-bin/gbrowse/pig/) based on the Sscrofa 9. Thus, with the chromosome position of the candidate gene obtained by querying the Ensemble, one can easily get the information of the QTLs which were mapped onto the same genomic region (Figure 4).

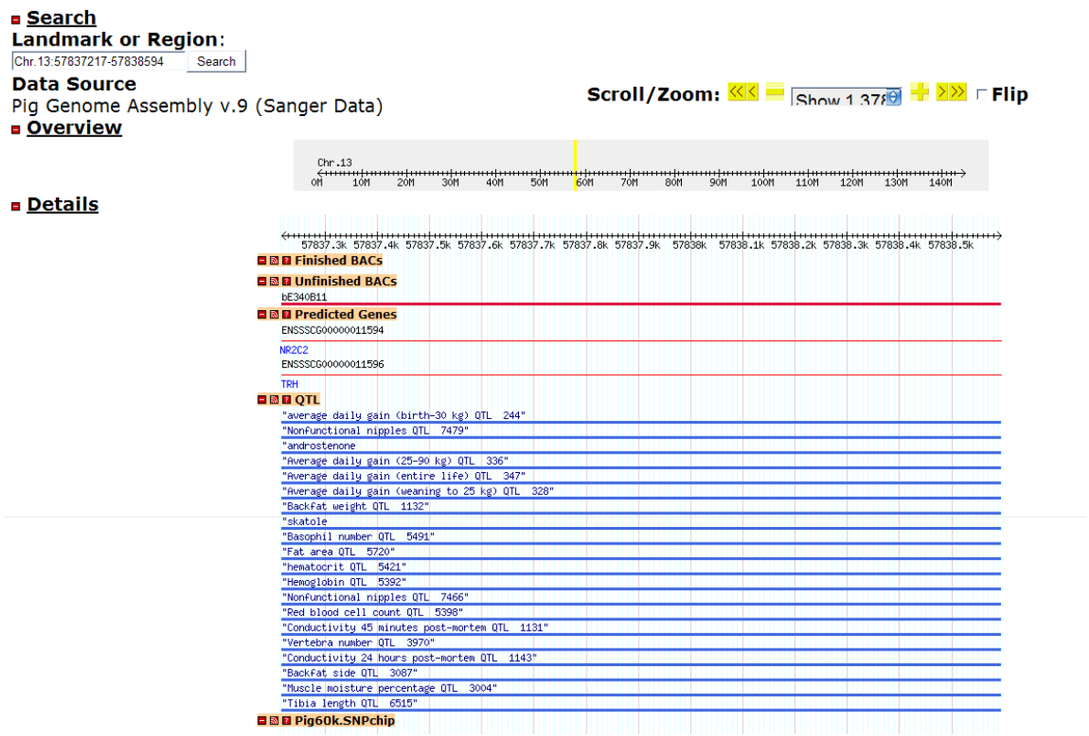

Fig. 4. Query result of pig QTLdb Gbrowse map view, using TRH as an example.

Porcine *TRH* gene is located between 57,837,217 and 57,838,594 on chromosome 13. Based on the pig QTLdb, there are 20 QTLs including average daily gain (ADG), backfat weight, meat

quality traits and blood parameters have been reported in this region. Porcine *CGA* gene is mapped between 58,190,063 and 58,192,283 on chromosome 1, and 21 QTLs have been mapped to the corresponding region, most of which are fat related traits. The position of *TSHB* gene on porcine chromosome 4 is from 109,815,329 to 109,816,276. 49 QTLs including ADG, backfat thickness (BFT) and meat quality related traits have been mapped to this position. Unfortunately, *TRHR* and *TSHR* genes had not yet been annotated in Sscrofa 9 in the year 2009.

3.2 The RH mapping

Radiation hybrid (RH) mapping is a kind of somatic cell genetics tool for mapping candidate genes into a framework of microsatellites/sequence-tagged sites. First, RH panels are constructed by using a lethal dose of X-rays to fragment the chromosomes of the donor cell and the chromosome fragments with known genetic markers are retained randomly in the host cells. The frequency of breakage between pairs of markers in a panel of RH clones can be used to calculate the relative physical distances of the genetic markers or genes. Several porcine RH panels have been produced, among which the whole-genome high-resolution IMpRH panel constructed by Yerle et al. (1998) is the most frequently used one.

The porcine *TRHR* gene was localized to the microsatellite *SW969* on chromosome 4 by RH mapping using the IMpRH panel (Jiang et al., 2011). 44 Quantitative trait loci affecting BFT, daily gain, and carcass and meat quality traits have been mapped to the same region. *TSHR* gene has been mapped between microsatellites *SW1083* and *SW581* on porcine chromosome 7 (Sato et al., 2006), and 50 QTLs including BFT, ADG, carcass length and muscle related traits have been mapped to the same position.

3.3 Expression analysis

TRH is present not only in the hypothalamus but also in many other brain loci as a neuromodulator / neurotransmitter. Besides, expression of *TRH* gene is found in gastrointestinal tract, pancreas, reproductive tissues, heart, spleen, adrenals and thymus. Its receptor, *TRHR* is also found in gastrointestinal tract, pancreas, testis and adrenals. Paracrine effects of TRH on gastrointestinal tract and pancreas have been suggested. Furthermore, *TSHR* is widely expressed in many organs and tissues such as pituitary, heart, skeletal muscle and adipose. Species-specific expression of HPT genes in certain tissues might exist. For example, *TRHR* was detected in medaka spleen (Mekuchi et al., 2010) but undetectable in bovine spleen (Takata et al., 1998), and *TSHB* has been reported in the liver and reproductive organs of red drum (Cohn et al., 2010) but undetectable in the same organs of ducks (Hsieh et al., 2007).

Tissue distribution of HPT genes in pigs have been investigated by using real-time quantitative RT-PCR with RNA samples from 15 different organs/tissues including brain, hypot4halamus, pituitary, thyroid, lung, kidney, gastrointestinal tract, muscle and fat tissue (Jiang 2011). Highest expression level of *TRH* was found in the brain, and considerable level of *TRH* also expressed in testis, spleen, fat tissue, small intestine and pancreas in addition to hypothalamus. Porcine *TRHR* mRNA was detected in almost all the investigated organs/tissues except the spleen, with high expression levels in the brain, hypothalamus,

pituitary, testis and fat tissue. The two subunit genes of hormone TSH showed different tissue distribution patterns. While *CGA* was detectable in almost all the tissues, *TSHB* was mainly existed in the pituitary and undetectable or in extremely low level in the other tissues except in the fat tissue and stomach. Expression of porcine *TSHR* existed in all the fifteen organs/tissues, with highest expression level in the thyroid, then the testis and spleen.

3.4 The polymorphisms of these genes

Polymorphism in human *TRH* gene has been reported to be associated with blood pressure variations and hypertension (Kokubo et al., 2006). By re-sequencing the whole coding region of porcine *TRH* gene, eight sequence variations were identified (Jiang 2011). Among these polymorphisms, only ss325994920 (Figure 2) is a missense mutation which would bring a Val to Met amino acid mutation into pFE22 and pSE14 peptides.

Mutations in the *TRHR* could result in central hypothyroidism which causes growth retardation, pudginess and sluggishness (Collu et a., 1997). Further *TRHR* polymorphism has been identified responsible for human lean body mass variations in a genome-wide association study (Liu et al., 2009). Re-sequencing the coding sequences and flanking regions of porcine *TRHR* gene identified seven polymorphic loci (Figure 5a). Two of them locate in the intron 1 which has been proven to encompass important regulatory elements.

Mice with *CGA* gene knockout were viable, but exhibited severe growth insufficiency and infertility (Kendall et al., 1995). While no inactivating mutations of *CGA* gene has been detected in humans and mice, cases of nonsense mutations of *TSHB* gene have been continuously reported in humans which cause growth retardation and fat metabolism disorders (McDermott et al., 2002; Baquedano et al., 2010). 14 new polymorphic loci of porcine *CGA* gene (Figure 5b) and 5 polymorphisms of *TSHB* gene (Figure 5c) were identified and confirmed by re-sequencing (Jiang et al., 2011b). Four of the *CGA* polymorphisms locate in the promoter region. The single nucleotide polymorphism ss181129018 of *TSHB* gene locates on the first coding exon and brings amino acid change to the signal peptide of TSH β subunit.

TSHR is sensitive to point mutations and most of the reported human mutations existed in the last exon 10 (Davis et al., 2006). Re-sequencing the last exon of porcine *TSHR* gene detected three polymorphisms in the exon (Figure 5d), but all were synonymous mutations.

4. The association study with economic traits in the crossbred of Jinhua and Pietrain

A crossbred was established by mating the Chinese Jinhua pigs (Central China swine type) with European Pietrain pigs, and obvious segregation of growth, carcass and meat quality characters were observed in this population. Association study of the five HPT key genes' polymorphisms with the economic important traits in the crossbred of Jinhua and Pietrain were carried out by analyzing fourteen polymorphic loci with thirty traits of 463 individuals (Jiang 2011). Both PCR-RFLP and tetra-primer ARMS PCR procedure were utilized for genotyping, and haplotypes were considered as genetic effects.

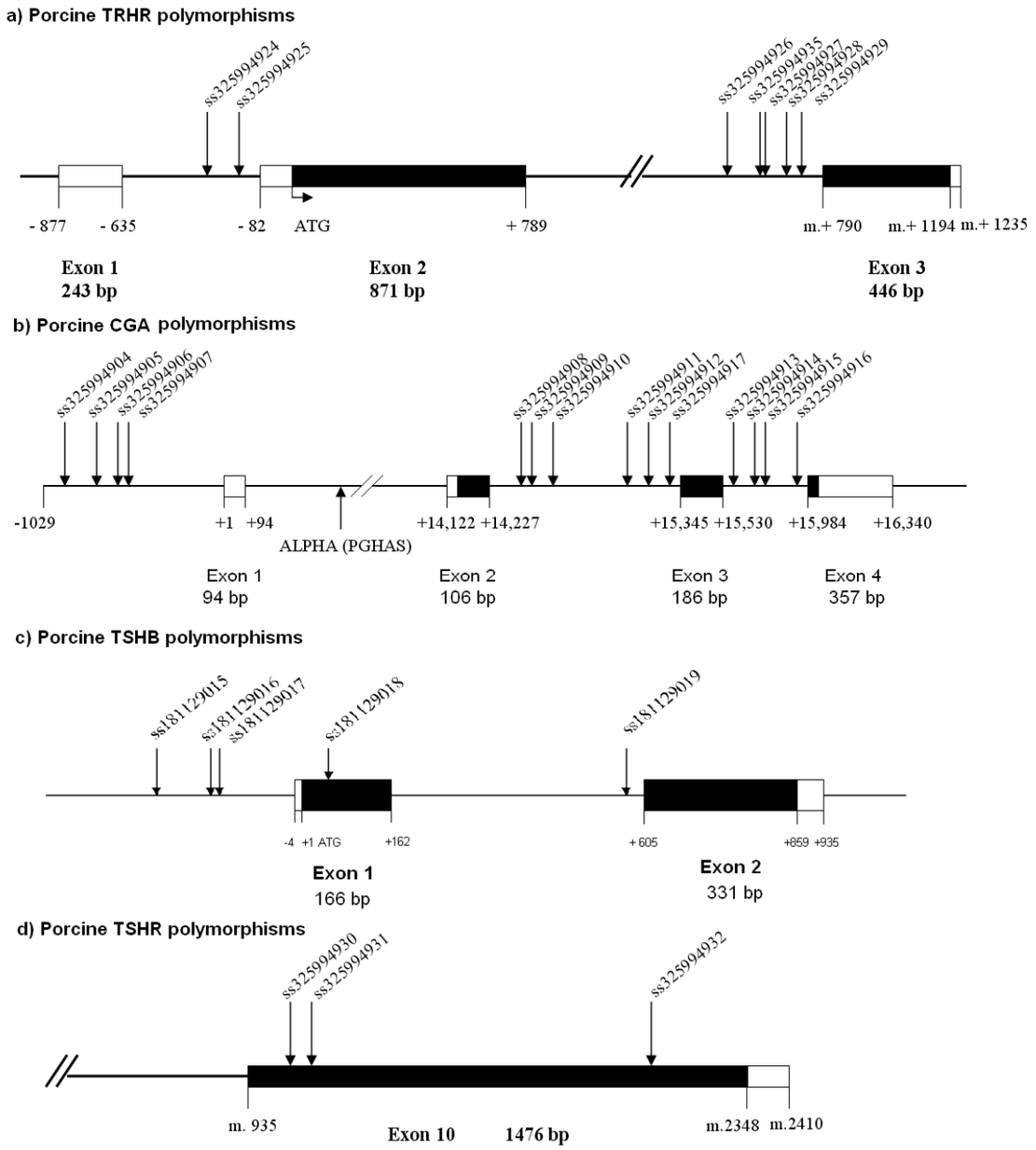

Fig. 5. Genetic Polymorphisms of porcine HPT axis

4.1 Thyrotropin releasing hormone gene (*TRH*)

Polymophisms of porcine *TRH* gene were divided into two linkage disequilibrium (LD) blocks. One of the LD block contained locus ss325994933 which was significantly ($P < 0.05$) associated with daily weight gain. Homozygous individuals with the insertion allele showed higher daily weight gain than the ones with the deletion allele. TRH could be considered functional and positional candidate gene of the ADG QTL reported by de Koning et al. (de Koning et al., 2001). However, further investigation on the allele frequencies in different purebreds showed that the insertion allele mainly existed in the

Chinese breeds, while the Western pig breeds those normally grow faster than the Chinese breeds were almost fixed with the deletion allele. Another LD block consisted of the other *TRH* polymorphisms investigated. No significant associations of this LD block with the economical traits were observed.

4.2 Thyrotropin releasing hormone receptor gene (*TRHR*)

All the four *TRHR* polymorphisms studied existed in one LD block. Significant associations of porcine *TRHR* gene with head weight, carcass length, and electric conductivity, pH value, water holding capacity, intramuscular water and fat content of loin muscle were observed. QTLs of carcass length (Wimmers et al., 2002; Murani et al., 2006) and intramuscular fat content (de Koning et al., 1999) have been reported previously. Individuals with the haplotypes originating from the Pietrain had smaller head weight, longer carcass length and lower conductivity of loin muscle. However, no significant difference among the haplotypes was observed after bonferroni corrections.

4.3 Thyrotropin alpha subunit gene (*CGA*)

As the existence of microsatellites in the porcine *CGA* gene, QTL mapping results around the *CGA* gene from different studies were instable. In the crossbred of Jinhua and Pietrain, haplotypes of *CGA* was only associated with intramuscular water content. But if further dissecting by dividing the gene with the microsatellites, the promoter region of this gene showed significant associations with growth and backfat thickness traits.

4.4 Thyrotropin beta subunit gene (*TSHB*)

Haplotypes of porcine *TSHB* gene were significantly associated daily weight gain between 90 to 120 days, ham muscle weight, and extremely significantly ($P<0.01$) associated with carcass weight, carcass length and average backfat thickness. Corresponding QTLs have also been reported in this chromosome region (Grindflek et al., 2001; Knott et al., 2002; Malek et al., 2001; Nagamine et al., 2003; van Wijk et al., 2007; Walling et al., 2000). The homozygous individuals with haplotype originating from Jinhua pig had significantly lower daily weight gain and thicker average BFT than the homozygous individuals with the haplotype originating from Pietrain, which were in accordance with the observations in the two purebreds. Further verification in a Duroc population confirmed the association of *TSHB* gene with the average BFT trait and showed that the allele A of ss181129015 which was popular in Western breeds was associated with lower average BFT. Porcine *TSHB* gene, especially the locus ss181129015 is worthwhile for further study and to be developed as genetic marker for the BFT trait.

4.5 Thyrotropin receptor gene (*TSHR*)

Individuals with allele A of *TSHR* ss325994932 showed higher daily gain between 120 to 180 days old and lower muscular pH value than the ones with allele G in the crossbred of Jinhua and Pietrain. Several QTLs on ADG around the *TSHR* gene have been reported previously (Edwards et al., 2008; Nagamine et al., 2003). Though individuals with allele A showed better performance in growth and meat quality in the crossbred, investigation on the allele frequencies in different purebreds showed that the allele A appeared in fairly low

frequencies in all the purebreds studied. Verification in Landrace population confirmed the association of *TSHR* with ADG, but allele A was associated with slower growth rate in this breed. Possible explanations were interactions of alleles of *TSHR* with other genes' might exist, or recombination might have occurred between the causative polymorphism and ss325994932 in some breeds.

5. Acknowledgment

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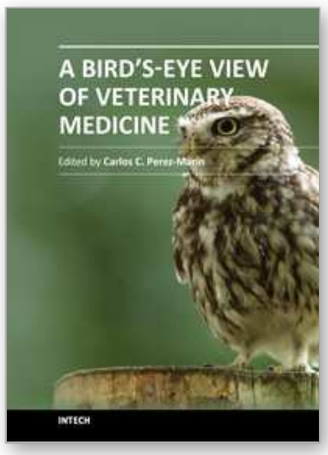

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