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Chapter 2

Ecological Genetics of Thyroid Hormone Physiology in Humans and Wild Animals

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http://dx.doi.org/10.5772/45969

1. Introduction

Hormones are important mediators in the responses of a suite of phenotypic traits to environmental changes. Therefore, populations inhabiting different environments are expected to vary in several hormonal pathways. Such variation results from both plastic response to environments and genetic differences. Therefore, information about the genetic basis of hormonal variation is crucial to better understand the ecological and evolutionary mechanisms of phenotypic diversification in animals. Furthermore, information about the racial and geographical variation in hormone physiology is crucial for better diagnosis of hormone-related diseases in clinical fields. Thyroid hormones play key roles in regulation of many physiological and behavioral traits, such as metabolism, ion homeostasis, basal activity, and longevity. Therefore, thyroid hormone can play important roles in adaptation to external environments. In the present study, we review interspecies, racial, geographical, and interindividual variation in the thyroid hormone pathways in humans and other animals. The present review focuses on natural and subclinical variation in thyroid hormone physiology and will not cover the genetic basis for congenital hypothyroidism [1,2,3,4,5], congenital hyperthyroidism [6,7], autoimmune diseases [8], and thyroid cancers [9], for which a number of good review articles are already available. We also review what is known about the genetic basis for such variation. We found several shared features in the patterns of variation in thyroid hormone physiology in humans and other animals. This review demonstrates the importance of undertaking further integrative studies of human genetics and animal ecology for a better understanding of the ecological and genetic mechanisms of variation in thyroid hormone signaling pathways.

2. Variation in thyroid hormone physiology in humans

2.1. Interindividual, geographical, and racial variation

Geographical variation in the frequency of euthyroid endemic goiter has been extensively investigated [10,11,12]. In addition to iodine deficiency, other factors, such as smoking, age, sex, goitrogens, and body mass index, can also influence the etiology of euthyroid endemic goiter [13]. Although genetic predisposition to euthyroid goiter has been demonstrated [12,13,14], the molecular genetic mechanisms underlying the variation in susceptibility to goiter are not well understood. Polymorphism at the thyroglobulin (*TG*) [15,16] and Na^+/I^- symporter (*NIS*) loci [17] are reportedly associated with euthyroid goiter; however, linkage mapping in different families could not connect euthyroid goiter with such genetic variation [18,19].

Racial variation in the level of thyroid-stimulating hormone (TSH), one of the major hormones regulating synthesis and secretion of thyroid hormone, has been also found. Multiple studies have revealed that serum TSH levels are higher in whites and Mexican Americans than in blacks [20,21,22]. These results suggest that race-specific reference values of TSH are necessary for evaluation of thyroid hormone-related diseases. Currently, the genetic and ecological basis for the racial variation in TSH levels is not well understood. The serum levels of thyroxine-binding globulin (TBG), a major thyroid hormone-binding protein in plasma, are lower in Australian Aborigines than in Caucasians in Western Australia [23]. Aborigines have a TBG variant that has reduced affinity for thyroid hormone and is more susceptible to heat and acid denaturation [24,25,26]. Two amino acids are substituted in this variant, one of which is considered responsible for the low binding affinity for thyroid hormones [26]. Aborigines usually have lower T4 levels, but have normal TSH levels and normal or borderline T3 levels. Because Aborigines do not show any clinical symptoms of hypothyroidism, the homeostasis of thyroid hormone physiology in Aborigines differs from that in other human populations.

Although the adaptive significance of the variations remain elusive in the above cases, some interpopulation variation may result from adaptive evolution to divergent environments. Serum free T4 levels are higher in indigenous Evenki women than in nonindigenous Russian women living in the same communities in central Siberia [27]. The variation in free T4 levels was correlated with the variation in basal metabolic rate both in Evenki and Russian men and women [27]. Similar cases were also found for indigenous Nenets and nonindigenous Russians: both showed significant increases in total T4 levels during winter, but the magnitude of the increase was significantly greater in the Nenets than in the Russians [27]. Because thyroid hormones play important roles in regulating metabolic rate and adaptation to cold environments [28,29], human populations inhabiting colder environments may acquire genetic basis for more efficient thyroid hormone-induced thermogenesis and may therefore be genetically adapted to cold environments [30].

Interindividual differences in TSH levels are prevalent, and have been found to be associated with variation in life span. In Ashkenazi Jews and Northern Italians, healthy

oldest-old people of around 100 years of age had higher TSH levels than elderly controls of around 70 years of age [31,32]. In addition, follow-up studies revealed that participants with abnormally high TSH levels had a lower mortality rate than those with normal or low TSH levels [33]. The offspring of Ashkenazi Jewish centenarians had significantly higher TSH levels, suggesting that higher TSH levels and longevity have heritable components [32]; however, the molecular mechanisms of this variation are unknown.

2.2. Genetic basis for variation

In addition to the case of TGB in Australian Aborigines [34], polymorphisms associated with variation in thyroid hormone physiology have been found in other populations [35]. Several studies have focused on candidate genes involved in thyroid hormone signaling pathways and revealed that single nucleotide polymorphisms (SNPs) of the TSH receptor (*TSHR*) [36], iodothyronine deiodinases (*DIO1*, *DIO2*, and *DIO3*) [36,37], thyroid hormone transporter and thyroid hormone receptor genes accounted for variation in serum TSH and thyroid hormone levels [38,39]. Genome-wide association studies have also identified several genes involved in thyroid hormone signaling. Three SNPs at intron 1 of the phosphodiesterase 8B (*PDE8B*) gene are significantly associated with serum TSH levels [40,41]. *PDE8B* encodes a high-affinity cAMP-specific phosphodiesterase catalyzing the hydrolysis and inactivation of cAMP. Because the *PDE8B* transcript is undetectable in the pituitary, it is thought that PDE8B may affect TSH levels through its effect on TSH-dependent thyroid hormone synthesis and secretion in the thyroid gland. Interestingly, other cAMP-specific phosphodiesterases have also been showed to be associated with variation in TSH levels [41]. Since there are only a few studies revealing the mechanisms by which SNPs modify thyroid hormone signaling [38], further studies are needed to confirm their actual contribution to the natural variation in thyroid hormone physiology.

If genes involved in thyroid hormone pathways were targets of natural selection, we would be able to find some signatures of natural selection in the human genome. When natural selection increases the frequency of a new beneficial mutation in a population, the neighboring regions will reduce the genetic variation and increase the level of linkage disequilibrium [42]. Two genes involved in the thyroid hormone pathway, thyroid hormone receptor interactor 4 (*TRIP4*) and iodotyrosine deiodinase (*IYD*), showed a signature of selection in the genome of African Pygmies [43]. Importantly, a low frequency (9.4%) of goiter was reported for an African Pygmy population, although they inhabit an iodine-deficient region [44]. Because another population in the same region had a much higher frequency of goiter (42.9%), López Herráez et al. (2010) concluded that the signatures of selection in these genes might reflect genetic adaptations of Pygmies to iodine-deficient diets. Another study tried to identify the genes whose allele frequencies were significantly correlated with climate. The frequency of an SNP in *TRIP6* showed strong correlation with latitude [45].

The high rate of nonsynonymous (amino acid–altering) changes compared with the rate of synonymous (silent) changes also indicates that the genes might be under positive selection

[42]. By comparing the synonymous and nonsynonymous substitutions in the human and chimp genomes, putatively positively selected genes were screened [46]. Genes expressed in the thyroid gland have an excess of rapidly evolving genes compared with other tissues, except testis, which has more putatively positively selected genes [46]. Changes in thyroid hormone physiology may contribute to some of the physiological and morphological divergence between humans and apes [47,48].

3. Inter-population and geographical variation in thyroid hormone physiology in animals

Anatomical studies conducted in the 1960s and 1970s showed interspecies morphological variation for fishes and amphibians [49,50]. Since then, natural variation in thyroid hormone physiology has been extensively investigated in diverse taxa of vertebrate (Table 1). Some of the variation results from environmental factors. For example, environmental contaminants can cause goiter. In salmon populations introduced into the Great Lakes in the late 1960s, the frequency of thyroid goiter increased in the mid-1970s [51,52,53]. In addition, herring gulls *Larus argentatus* from the Great Lakes also suffered from goiter in the 1980s [54]. It was demonstrated that laboratory rats fed with the salmons caught in the lakes exhibited hypothyroidism and goiter, suggesting the presence of goitrogenic substances in the Great Lakes fishes [55].

Species/Family	Phenotypic variation	Potential factors and functions	Reference
Intraspecific variation			
Coho salmon	Goiter, T_4, T_3	Goitrogen	[51,53,97]
Chinook salmon	Goiter	Goitrogen	[53]
Herring gull	Goiter	Goitrogen	[54]
American alligator	T_4	Goitrogen	[98]
Japanese pond frog	Morphology		[49]
Bottlenose dolphin	T_4 and T_3	Temperature	[62]
Northern cardinal	T_4 and T_3		[61]
Alaskan husky	T_4 and T_3	Temperature	[60]
Bonnethead shark	T_4 and T_3 in yolk	Temperature	[70]
Brook charr	T_4 and T_3	Migration	[87]
Stickleback	Goiter, TSHß, T_4,T_3	Migration, metabolism	[57,58,86]
Interspecific variation			
Poeciliidae	Morphology, tumor		[50,99,100]
Spadefoot toad	T_4, T_3, sensitivity	Dry environment, metamorphosis	[63]
Big-eared mouse	T4, T3, iodide	Low iodide concentration	[59]
Rodent	T_4	Life span	[101]

Table 1. Variation in thyroid hormone physiology in natural animal populations

Goiters were also observed in hatchery fishes and possibly resulted from iodine deficiency, because iodine treatment was able to cure the goiter [56]. In the case of the threespine stickleback *Gasterosteus aculeatus*, interpopulation variation in susceptibility to goiter when reared in fresh water was observed [57,58], although whether the goiter in the sticklebacks was caused by iodine deficiency is unknown. Interestingly, a mammalian species, *Auliscomys boliviensis*, inhabiting an environment severely depleted of iodine did not show goiter [59], suggesting that genetic variation in the susceptibility to endemic goiter exists among populations and species.

Latitudinal variation in plasma concentrations of thyroid hormone has been observed in both mammals and birds, and these variations might have evolved as adaptations to environments with divergent temperatures. Plasma total T4, free T4, and total T3 levels of sled dogs living in Alaska were higher than dogs in New York, especially in winter [60]. In addition, plasma T3 increased with increasing latitude in the northern cardinals *Cardinalis cardinalis*, whereas plasma T4 did not show a simple latitudinal cline: both southern and northern birds had higher T4 levels than birds living at an intermediate latitude [61]. In mammals, bottlenose dolphins *Tursiops truncatus* show variation in thyroid hormone concentrations between populations inhabiting different latitudes [62]: plasma total T3 and T4 were higher in dolphins from South Carolina with colder year-round temperatures than those from Florida with much warmer water temperatures. Since thyroid hormones play key roles in metabolism and heat generation, evolutionary adaptation to habitats with different temperatures may account for some of the latitudinal and geographical variation in thyroid hormone levels among natural populations. The genetic basis for the latitudinal variation is currently unknown.

Several studies have demonstrated that variation in thyroid hormone physiology correlates with other potentially adaptive traits. Interspecies variation in tissue thyroid hormone levels and tissue sensitivity to thyroid hormone may be correlated with variation in the duration of the larval period in spadefoot toads [63]. For example, the tadpole of the desert-dwelling toad *Scaphiopus couchii* has higher tail and liver levels of thyroid hormone, and the tail tip is more sensitive to thyroid hormone *in vitro* than tail tips of other closely related species [63]. Because frog metamorphosis is controlled by thyroid hormone, the higher thyroid hormone levels and the higher sensitivity may explain the short larval period in this species. Rapid metamorphosis (i.e., the short period of water-dwelling at the tadpole stage) observed in the desert toad is likely adaptive for survival in the deserts where water is scarce [64,65].

Thyroid hormones also play critical roles as yolk hormones in mammalian [66], bird [67], and teleost [68,69] development. In the bonnethead shark *Sphyrna tiburo*, the concentrations of T3 and T4 in the yolk from the Tampa Bay population were consistently higher than those in the yolk from the Florida Bay population [70]. The bonnethead shark in Tampa Bay develops faster and is larger at birth than that in Florida Bay [71]. Tampa Bay is located in a more northern region and is colder than Florida Bay. Because rapid growth is generally adaptive in colder environments [72,73], higher york thyroid hormone levels in the Tampa Bay population may be adaptive.

Thyroid hormone is also implicated in the regulation of longevity in animals [74,75]. Long-lived species of squirrels, deer mice, bats and mole-rats maintain low levels of thyroid hormone [76,77,78,79]. Hypothyroid Wister rats live longer than hyperthyroid rats [80]. Furthermore, investigations in the Ames and Snell dwarf mice have demonstrated that mutation at the *Prop-1* and *Pit-1* genes lead to defects in the generation of pituitary cells including thyrotrope and the dwarf mice have extended longevity [81,82,83,84,85]. Thus, it is possible that changes in the thyroid hormone pathway are involved in variation of life span among wild animals, as is observed among human races (see above). Further research on the genetic basis for the low thyroid hormone levels observed in the long-lived animals should be conducted.

Divergence in thyroid hormone physiology may also be important for adaptation of stickleback fishes to marine and freshwater environments [86]. Stream-resident populations of the threespine stickleback have repeatedly evolved from ancestral marine populations. First, Kitano et al. (2010) found plasma thyroid hormone levels and metabolic rate were lower in stream-resident populations than in ancestral marine populations [86]. Since thyroid hormones regulate metabolic rate in sticklebacks [86], it is likely that lower thyroid hormone in stream-resident sticklebacks is adaptive for permanent residency in small streams where oxygen and food are often scarce. In addition, the expression level of thyroid stimulating hormone *TSHß2* gene was significantly lower in the pituitary gland of stream-resident fish than in that of marine fish. Allele-specific expression analysis with F1 hybrids revealed that some of the differences in *TSHß2* expression levels were caused by *cis*-regulatory changes at the *TSHß2* locus. Importantly, a signature of natural selection was found at *TSHß2* locus: several SNPs within the *cis*-regulatory region exhibited marked differences in the allele frequency between marine and stream-resident populations. Thus, changes in the thyroid hormone pathways may play important roles in genetic adaptation to freshwater environments. In other fishes exhibiting alternate life history style, such as the brook charr *Salvelinus fontinalis* anadromous and resident forms show differences in thyroid hormone concentrations, although genetic factors seem to be of little importance in the interpopulation variation seen in the brook charr [87].

Other than the *TSH* loci in sticklebacks, there are few studies that have examined whether thyroid hormone-related genes are under selective pressure in wild animal populations. However, domestication seems to be a strong artificial selection on thyroid hormone-related genes. Very strong selective sweeps were found at the *TSHR* loci in chickens [88] and sheep [89]. Because TSH is found to regulate photoperiodic control of reproduction [90,91,92,93,94], artificial selection favoring continuous reproduction under domestication might act on the *TSH* locus.

4. Conclusions and future directions

We found similar features in the patterns of variation in thyroid hormone physiology in humans and other animals. First, genetic variation in the susceptibility to endemic goiter exists among populations and species. Second, some of the latitudinal and racial variation in

thyroid hormone physiology likely results from adaptation to environments with divergent ambient temperatures. Third, variation in thyroid hormone physiology may be associated with variation in longevity. Fourth, genomic scan of signatures of selection have revealed that some thyroid hormone-related genes experience selective pressure during evolution or domestication.

In humans, it is very difficult to experimentally test the adaptive significance of such variation. However, ecological experiments can be conducted using animals. For example, reciprocal transplant experiments on divergent populations or species with different thyroid hormone physiology can test whether wild animals have higher fitness in native habitats than in foreign habitats [95,96]. We can also investigate whether the fitness is correlated with the thyroid hormone levels. In addition, hormonal manipulation would be able to directly test whether the higher or lower thyroid hormone levels can change the fitness in a variety of environments.

Until recently, it has been difficult to study the genetic basis for physiological differences between natural animal populations. However, it is now becoming increasingly easier to conduct genomic studies because of the recent progress in genomic technologies. Therefore, we can test whether candidate loci involved in thyroid hormone signaling pathways are correlated with fitness in natural environments or laboratory conditions. Furthermore, ecological and genomic studies of wild animal populations will help answer fundamental evolutionary questions, such as whether the same environmental variables are strong agents of natural selection on the thyroid hormone pathways and whether genetic variation in the same genes caused the adaptive divergence in thyroid hormone physiology across diverse taxa, including humans.

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Acknowledgement

This research is supported by JST PRESTO program, the Naito Foundation, Grant-in-Aid for Scientific Research on Innovative Areas (23113007 and 23113001) from the Ministry of Education, Science, Sports, and Culture to JK. AI is a Fellow of the Japan Society of Promotion of Science.

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