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Letter to the editor Open Access

Novel rhino-like SHJH^{hr} mice with thyroid dysfunction

A new Hairless (*Hr*) gene mutant mouse line (SHJH^{hr}) was identified, which showed hairless skin in adult individuals as reported in rhino mice. Through *Hr* gene mutant identification with polymerase chain reaction (PCR) amplification and sequencing, seven mutants were identified, including nonsense mutant site 2134C→T (R467X), which produced a truncated Hr protein. Metabolic activity and heart rate were measured using a metabolic cage and blood pressure instrument, respectively. The SHJH^{hr} mice showed a strong metabolic rate, high heart rate, and low blood pressure. Histological analysis of the thyroid gland of SHJH^{hr} mice showed abnormal follicular structure and hypertrophic thyrocytes. Compared to ICR mice, thyroid function in 4-month-old SHJH^{hr} mice showed lower thyroid stimulating hormone (TSH) levels, and in 9-month-old SHJH^{hr} mice showed significantly higher TSH and thyroid hormone levels. These data indicate that SHJH^{hr} mice may be in a hyperthyroid state with increasing age. Thus, based on the above results, we successfully established a novel mouse model with thyroid dysfunction.

Hyperthyroidism is a common endocrine disease involving thyroid dysfunction. It features high thyroid hormone (TH) levels, which can influence energy metabolism, hair growth, bone maintenance, heart rate, and cardiovascular function (Bassett & Williams, 2016; Contreras-Jurado et al., 2015; Jabbar et al., 2017; Mullur et al., 2014). Thyroid disease can also manifest in pregnancy (Stagnaro-Green & Pearce, 2012), elderly health (Boelaert, 2013), and alopecia areata (Lyakhovitsky et al., 2015; Puavilai et al., 1994). Many genetic variants involved in the hypothalamus-pituitary-thyroid (HPT) axis, including TSH receptors, thyroid hormone transporters and receptors, and deiodinases, can impact thyroid hormone set points (Medici et al., 2017).

The *Hr* gene is expressed in human and rodent tissues, such as the brain and skin (Cachon-Gonzalez et al., 1994; García-Atares et al., 1998). *Hr* plays an important role in hair follicle growth, skin structure, and various cancers (Maatough et al., 2018). *Hr* mutation can result in atrichia in humans (Ahmad et al., 1998a; Ahmad et al., 1999a; Ahmad et al., 1999b) and hairlessness in rodents (Ahmad et al., 1998b; Ahmad et al., 1998c; García-Atares et al., 1998; Zhang et al., 2005). The Hr protein acts as a transcription corepressor with the thyroid hormone receptor (TR), retinoic-related orphan receptor α (RORα), and vitamin D receptor (VDR) (Moraitis & Giguere, 2003; Potter et al., 2001; Thompson, 2009; Zarach et al., 2004), and participates in the recruitment of histone deacetylases (HDACs) (Djabali & Christiano, 2004; Liu et al., 2014). Thyroid hormone can induce and regulate *Hr* transcription, and the Hr protein interacts with the TR (Thompson & Bottcher, 1997). In the brain, the Hr corepressor complex binds to the thyroid hormone response element (TRE) region of the thyroid hormone-responsive gene to regulate thyroid hormone function, thereby increasing Hr protein via TRα (Potter et al., 2002). Research has indicated that Hr levels are lower in TRα-deficient mice but do not change in TRβ-deficient mice (Potter et al., 2002). Overall, these studies indicate that Hr may be involved in thyroid hormone regulation.

Here, based on novel rhino-like SHJH^{hr} mice, we identified seven *Hr* mutant sites through PCR and sequencing analysis, including a nonsense mutant site that may result in truncated Hr protein. Physiological and histological analyses of the SHJH^{hr} mice showed higher metabolism, abnormal thyroid follicular structure, and hyperthyroid state. Thus, these SHJH^{hr} mice are a novel rhino-like strain with *Hr* mutation and thyroid dysfunction.

Two male ICR mice with shedding hairlessness were identified at Shanghai Jihui Animal Care Co., Ltd. (China). After breeding for several generations, a rhino-like mouse population was established and named SHJH^{hr}. These SHJH^{hr} mice show normal hair growth from postnatal day 0 (P0) to P13 during the first hair growth wave. From P14, however, the mice begin to shed their hair, starting from the nose and head, then reaching the abdomen at 3 weeks of age, with complete hairlessness by about 4 weeks of age (Figure 1A). In 4-month-old SHJH^{hr} mice, skin wrinkles first appear on the abdomen

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and back, then increase gradually, especially in female mice that have given birth. Thus, SHJH^{hr} mice display similar characteristics to rhino mice regarding hair shedding (Ahmad et al., 1998b; Ahmad et al., 1998c) and show faster skin aging compared with ICR mice. Female SHJH^{hr} mice also only give birth once or twice, indicating poor fertility (Panteleyev et al., 1998a).

The hairlessness of adult rhino mice and certain hairless mice is reportedly due to *Hr* gene mutations, which result in hair growth failure during in the anagen phase (Panteleyev et al., 1998b). To identify the cause of hairlessness in SHJH^{hr} mice, we first detected potential *Hr* gene mutants in the coding region and analyzed whether these mutant sites influence Hr protein. After PCR amplification, sequencing, and alignment, seven mutant sites in the *Hr* transcript were identified between ICR and SHJH^{hr} mice (Figure 1B; Supplementary Table S1), including 1824A→G, 2314C→T, 2151C→T, 2443T→A, 2516-2518del, 2703T→C, and 5527T→C. The nonsense mutant site 2314C→T (R467X) in the *Hr* gene may produce a truncated Hr protein, which could explain the hairlessness of SHJH^{hr} mice.

During the feeding process, the SHJH^{hr} mice were found to have a slightly higher body temperature and were more active. As active mice expend more energy, we determined their metabolic rate using a metabolic cage. Results showed that SHJH^{hr} mice consumed significantly more food and water per day than ICR mice (Figure 1C). Furthermore, SHJH^{hr} mice excreted more feces than ICR mice and female SHJH^{hr} mice excreted more urine than female ICR mice (Figure 1C), indicating that SHJH^{hr} mice have a higher metabolic rate than ICR mice.

To further study the physiological features of SHJH^{hr} mice, we measured heart rate and blood pressure. Result showed that SHJH^{hr} mice had dramatically higher heart rates than ICR mice (Figure 1D). Furthermore, male SHJH^{hr} mice had significantly lower mean arterial pressure (MAP) and systolic blood pressure (SBP) than male ICR mice. Female SHJH^{hr} mice had mildly lower MAP, SBP, and diastolic blood pressure (DBP) than female ICR mice (Supplementary Figure S1). Therefore, SHJH^{hr} mice had higher heart rate and lower blood pressure.

In humans, hyperthyroidism shows high metabolism and tachycardia (De Leo et al., 2016). Thus, we speculated that SHJH^{hr} mice with higher metabolic and heart rates may have abnormal thyroid function. Previous studies have confirmed that the *Hr* gene is involved in thyroid hormone regulation and interacts with the thyroid hormone receptor to form a transcription complex with ROR and VDR (Thompson &

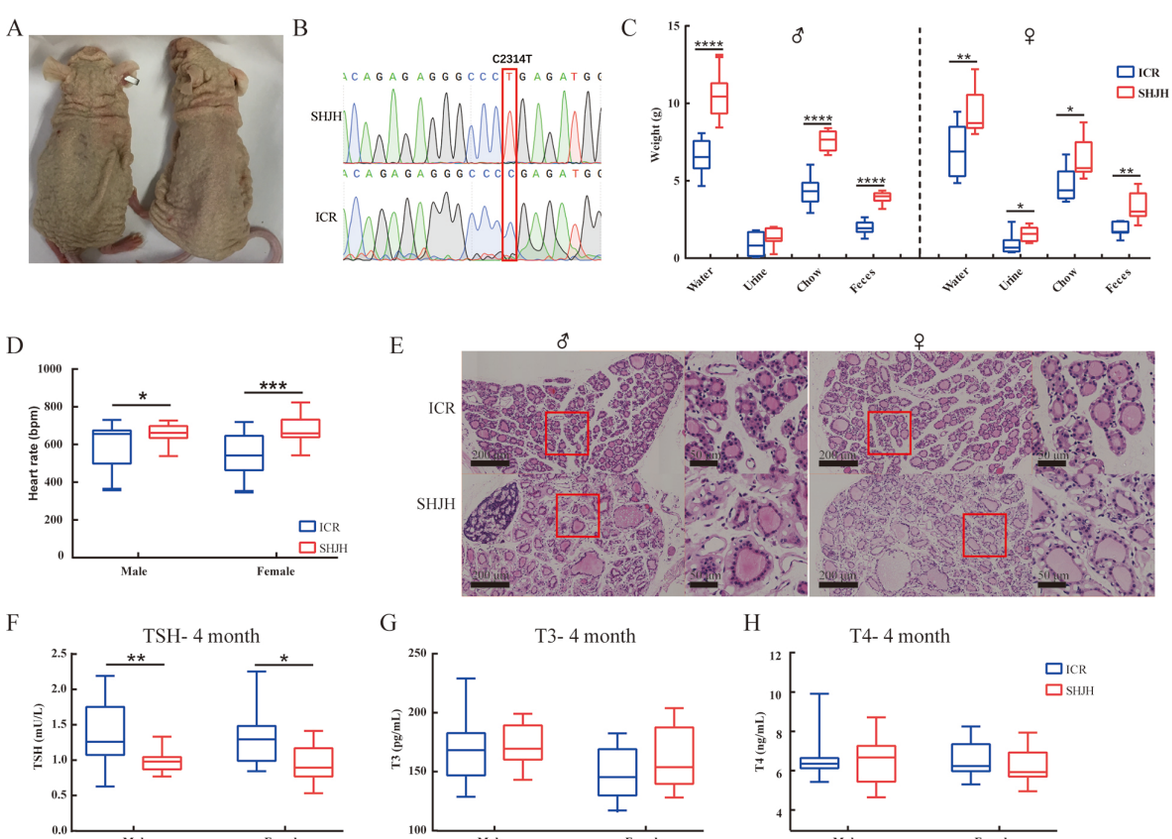

Figure 1 Adult SHJH^{hr} mice with a *Hairless* nonsense mutant site and high metabolic level, high heart rate, and thyroid dysfunction

A: SHJH^{hr} mice were hairless and wrinkled, with skin papule, long nails, and poor skin wound healing ability. B: Nonsense mutant site (2314C→T) was identified in SHJH^{hr} mice, other mutant details are provided in Supplementary Table S1. C, D: SHJH^{hr} mice had higher metabolic level and heart rate (n=18). E–H: Abnormal thyroid and follicular structure in 4-month-old SHJH^{hr} mice (H&E) (E) and (F, G, H) levels of TSH (F), T3 (G), and T4 (H) in 9-month-old SHJH^{hr} mice. ICR, ICR mice; SHJH, SHJH^{hr} mice. *: P<0.05; **: P<0.01; ***: P<0.001.

Bottcher, 1997; Thompson & Potter, 2000). Ahmad et al. (1998b) noted that in addition to the hairless and rhino phenotype, *hr*^{rhChr} mice exhibit prominent dehydration and thyroid hypertrophy. From analysis of *Hr* mutants, *hr*^{rhChr} mice also have a similar nonsense mutant site to SHJH^{hr} mice. Thus, based on previous records and the characteristics of SHJH^{hr} mice with higher metabolism, we reasoned that SHJH^{hr} mice may have abnormal thyroid function.

To study whether SHJH^{hr} mice exhibit thyroid dysfunction, we first analyzed the thyroid follicular structure in 8-week and 4-month-old mice. Compared with the ICR mice, the SHJH^{hr} mice showed larger and more variable follicle size (Figure 1E; Supplementary Figures S2, S3). The 4-month-old SHJH^{hr} mice showed abnormal follicles and obvious thyrocyte hypertrophy (Figure 1E). Further morphometric analysis of follicular structure (Kero et al., 2007; Ock et al., 2013), including number of cells per follicle, follicle epithelia (thyrocyte) area, and follicle lumen (colloid) area, showed that SHJH^{hr} mice had an abnormal thyroid follicular structure. Compared with 8-week-old ICR mice, SHJH^{hr} mice had significantly smaller thyrocytes (ICR 158.0 μm^2 vs. SHJH^{hr} 115.8 μm^2), but larger number of thyrocytes per follicle (ICR 11.7 vs. SHJH^{hr} 14.8) and larger colloid size (ICR 1 832 μm^2 vs. SHJH^{hr} 2 863 μm^2) (Supplementary Figure S2). Based on follicle morphometry, SHJH^{hr} mice also showed differences in thyrocyte area, cell number per follicle, and colloid area compared with ICR mice (Supplementary Figure S2). Compared with 4-month-old ICR mice, SHJH^{hr} mice showed a significantly larger thyrocyte area (ICR 131.3 μm^2 vs. SHJH^{hr} 199.0 μm^2) and number of thyrocytes (ICR 13.4 vs. SHJH^{hr} 16.4), but comparable colloid size (ICR 1 387 μm^2 vs. SHJH^{hr} 1 483 μm^2) (Supplementary Figure S3). Four-month-old SHJH^{hr} mice showed differences in thyrocyte area and cell number per follicle, but comparable colloid size to ICR mice (Supplementary Figure S3). Together with the follicular structure results, SHJH^{hr} mice had a larger thyrocyte area and more atypical follicles, suggesting abnormal thyroid function.

To determine whether SHJH^{hr} mice exhibit abnormal thyroid hormones, we measured the serum levels of TSH, triiodothyronine (T3), and thyroxine (T4). Results showed that SHJH^{hr} mice had abnormal serum levels of TSH and thyroid hormones. At 4 months of age, the TSH level in SHJH^{hr} mice was significantly declined, but their T3 and T4 levels were comparable to those of ICR mice (Figure 1F–H). At 9 months of age, the SHJH^{hr} mice had significantly higher TSH, T3 and T4 levels than ICR mice (Supplementary Figure S4). Thus, based on histological and hormone analysis, SHJH^{hr} mice showed marked thyroid dysfunction characteristic of spontaneous hyperthyroidism.

Hr gene mutations have been found in rhino and other hairless mice, with the prominent phenotype involving skin, hair, and brain function (Ahmad et al., 1998c; Cachon-Gonzalez et al., 1994; García-Atares et al., 1998; Liu et al., 2010; Panteleyev et al., 1999; Seiberg et al., 1997; Tian et al., 2004; Zhang et al., 2005). Of the *Hr* polymorphisms (summarized in Supplementary Table S2), only one rhino mouse is noted with thyroid hypertrophy (Ahmad et al., 1998b). The SHJH^{hr} mice have a similar nonsense mutant site in the *Hr* coding region as that of rhino Christiano mice (*hr*^{rhChr}), which results in a truncated Hr protein (Ahmad et al., 1998b). In addition to the similar appearance of skin and loss of hair, the SHJH^{hr} mice also exhibited strong metabolism and increased consumption of food and water. Moreover, SHJH^{hr} mice had higher heart rates and lower blood pressure. The reasons for their high metabolic and heart rates could be because SHJH^{hr} mice need to consume more food to maintain body temperature and other physiological causes due to their lack of hair. Overall, in addition to hairlessness and wrinkled skin, SHJH^{hr} mice displayed several novel features, such as higher heart rate and metabolism.

In humans, HR mutations result in congenital atrichia, atrichia with popular lesions, and Marie Unna hereditary hypotrichosis (Ahmad et al., 1999b; Mehmood et al., 2016; Yun et al., 2014). Moreover, some patients with alopecia areata show hyperthyroidism (Patel et al., 2017; Puavilai et al., 1994), suggesting that HR mutations could be involved in thyroid dysfunction. Hyperthyroidism also shows high metabolism and tachycardia (De Leo et al., 2016). We found that SHJH^{hr} mice showed high metabolic and heart rates, raising the question of whether SHJH^{hr} mice have thyroid dysfunction. Based on thyroid histology, we found that SHJH^{hr} mice showed an abnormal thyroid follicular structure at 8 weeks and 4 months of age. Compared with ICR mice, 8-week-old SHJH^{hr} mice had a smaller average thyrocyte area and larger colloid area, while 4-month-old SHJH^{hr} mice had a significantly larger average thyrocyte area but comparable colloid area. These results suggest that SHJH^{hr} mice have an abnormal follicular structure and hypertrophic thyrocytes. Previous studies have found that IGF-1- and Gq/G11-deficient mice show an increase in thyrocyte area after TSH treatment (Kero et al., 2007; Ock et al., 2013). TSH can induce thyrocyte proliferation and hypertrophy in thyroid cell cultures (Kimura et al., 2001). Compared with ICR mice, 4-month-old SHJH^{hr} mice showed lower serum levels of TSH, but no significant differences in T3 and T4. However, 9-month-old SHJH^{hr} mice showed a dramatic increase in the serum levels of TSH, T3, and T4, suggesting that SHJH^{hr} mice may develop from subclinical hyperthyroidism to overt hyperthyroidism, according to clinical standards (Biondi & Cooper, 2018; Jones et al., 2010). Although SHJH^{hr} mice showed abnormal thyroid follicles and thyroid hormone levels, two questions need further study: i.e., whether other *Hr* mutant mice have similar thyroid dysfunction, and how *Hr* mutants influence follicular structure and thyroid function.

The Hr protein plays an important role in skin and hair growth, as well as the cell cycle and apoptosis (Kim & Yoon, 2013; O'Driscoll & Bressler, 2010; Thompson, 2009; Thompson et al., 2006). The Hr protein contains a zinc-finger domain, nuclear localization signal domain, nuclear matrix targeting motif, and JmjC domain (Maatough et al., 2018). Current knowledge about Hr interactions with proteins includes nuclear receptors (TR, RORα, and VDR), HDAC, and p53 (Maatough et al., 2018). As the Hr protein contains a TR interaction domain and nuclear receptor corepressor (Thompson, 2009), the *Hr* gene nonsense mutant in SHJH^{hr} mice produces a truncated protein without the TR domain, which prevents it from forming the TR complex and thus regulating thyroid hormone. Therefore, SHJH^{hr} mice exhibit

thyroid hormone dysregulation, which may result from the nonsense mutant of the *Hr* gene. Due to the lack of genetic analysis, the relationship between thyroid dysfunction and *HR* mutations in patients with alopecia areata is still unclear. However, given that SHJH^{hr} mice show obvious hyperthyroidism at 9 months of age, people with *HR* mutants should monitor their thyroid function at around 35 years of age, according to the age transition of humans and mice.

In conclusion, we identified a novel *Hr* mutant mouse with abnormal follicular structure and thyroid function, as well as hairless and wrinkled skin. These mice could be applied as animal models of thyroid disease.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.C.L., J.F.G., Y.L.G., X.Y.W., X.J.L., Y.F.L., Z.Q.H., and S.H.L. performed the experiments. P.X. established the SHJH^{hr} mouse strain. Y.C.L., analyzed the data. G.L. and Y.Z. designed the project. Y.C.L. wrote the manuscript. G.J.P. and Y.Z. revised the manuscript. All authors read and approved the final version of the manuscript.

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