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Linkage and association of rs3110045 and rs28499085 variants in the thyrotropin-releasing hormone receptor (*TRHR*) gene with the risk of familial type 2 diabetes

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ABSTRACT

Type 2 diabetes (T2D) is a chronic and prevalent multisystemic disease that significantly increases morbidity and mortality. Dysfunction of the thyroid hormone system is common in patients with T2D, increasing their risk of both hyperthyroidism and hypothyroidism. Several components of the thyroid system are candidate risk genes for T2D. The thyrotropin-releasing hormone receptor (*TRHR*) gene encoding for TRHR is of particular interest since it is expressed by the dorsomedial hypothalamus neurons, which are known to regulate food intake. In humans, a variant in the *TRHR* gene has been previously reported in T2D patients in a population-based case-control study but not in familial T2D. We recruited 212 multigenerational families with T2D originated from the Italian peninsula with multiple cases of T2D and tested, via Pseudomarker 9 single nucleotide polymorphisms (SNPs) in the *TRHR* gene for linkage and linkage disequilibrium (i.e., linkage plus association) to/with T2D. We identified 2 novel risk variants (rs3110045 and rs28499085) significantly linked to and associated with the risk of T2D in the Italian families across several inheritance models. Our study is the first to confirm the previously reported association of *TRHR* gene with T2D and extends the risk to familial inheritance. However, functional and replication studies are still needed to confirm these results.

1. Introduction

Type 2 diabetes (T2D) is a chronic and prevalent multisystemic disease that significantly increases morbidity and mortality (Galicia-Garcia et al., 2020). This multifactorial disease results from a complex interplay of myriad genetic and environmental factors (Murea et al. 2012). The rising worldwide prevalence of T2D due to dietary factors is accompanied by a resurgence of T2D-related complications such as ischemic heart disease, kidney disease, and cerebrovascular accidents, as well as diseases of bidirectional pathogenesis such as mood disorders (Pan et al. 2010; Alzoubi et al. 2018), polycystic ovarian syndrome, and thyroid disorders (Zheng et al. 2018; Chen et al., 2019; Ali et al. 2022; Livadas et al. 2022). Dysfunction of the thyroid hormone system is more common in patients with T2D (Rong et al. 2021; Roa Dueñas et al. 2022), increasing their risk of both hyperthyroidism (Brandt et al. 2013) and hypothyroidism (Gronich et al. 2015). Dysfunction of the thyroid hormone systems is also more common in depressed patients with concomitant metabolic syndrome (Bode et al. 2022; Zhu et al. 2023).

The thyroid hormone system consists of: the thyrotropin-releasing hormone (TRH) which is secreted by the hypothalamus and binds to the thyrotropin-releasing hormone receptor (TRHR) on the surface of pituitary cells to mediate the release of the thyroid-stimulating hormone (TSH) (Chiamolera and Wondisford, 2009). TSH stimulates the release from the thyroid gland of the thyroid hormones (thyroxine, T4), which then is converted to triiodothyronine, T3 and free T3, which acts through the thyroid hormone receptor and plays very important physiologic and metabolic roles (Ortiga-Carvalho et al. 2016; Yavuz et al., 2019). The thyroid system is an essential regulator of food intake,

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energy expenditure (Kim, 2008), and glucose homeostasis (Eom et al., 2022). And serum TSH levels correlate with hyperglycemia and insulin resistance even in euthyroid subjects (Park et al., 2009). In rat models of T2D, impaired thyroid system (i.e., hypothyroidism) causes weight gain from increased food intake (Zhao et al. 2013), and in humans, thyroidal dysfunctions, including both hyperthyroidism and hypothyroidism, correlate with insulin resistance (Gierach et al., 2014). These effects could be mediated by any of the thyroid system components. An impaired mediation of TRH on TSH might alter TSH stimulation of the thyroid hormones secretion (Roelfsema and Veldhuis, 2013), as well as disrupt prolactin (PRL) secretion, which is also triggered by TRH (Papakostas et al. 1986), and both impaired thyroid hormones and PRL levels might contribute to the pathogenesis of T2D and its related traits (Roelfsema and Veldhuis, 2013, Ponce et al. 2020). Furthermore, mice deficient of the thyroid hormone receptor alpha are less prone to insulin resistance that is central in T2D (Jornayvaz et al. 2012), indicating the role of thyroid hormone mediation on insulin resistance and possible contribution to T2D.

The thyrotropin-releasing hormone receptor (TRHR) that is encoded by the *TRHR* gene is of particular interest since it is expressed by the dorsomedial hypothalamus neurons which are known to regulate food intake (Imoto et al. 2021). Biallelic mutations in the *TRHR* gene cause isolated congenital hypothyroidism that is resistant to TRH (Collu et al. 1997). Furthermore, research has shown that the human *TRHR* gene is an important regulator of lean body mass (Liu et al. 2009).

There are two TRHR-homologous receptors in mice: Trhr1 and Trhr2. *Trhr1*$^{-/-}$ mice are hyperglycemic (Sun et al. 2009), and knockout of both receptors causes depression-like behavior (Zeng et al., 2007, Sun et al. 2009). In humans, a variant in the *TRHR* gene has been previously reported in T2D patients in a population-based case-control study (Spracklen et al. 2020) but not in familial T2D. In this study, we report the novel implication of two variants in the *TRHR* gene in Italian families with T2D.

2. Materials and methods

We studied 212 multigenerational families (650 patients with T2D; total subjects = 1156) originated from the Italian peninsula. Diagnosis of T2D was established according to the following National Diabetes Data Group Criteria (1979): "Presence of hyperglycemia plus the classical signs and/or symptoms of diabetes, or by elevated fasting plasma glucose ≥140 mg/dl on more than one occasion," and excluding all secondary causes of diabetes (e.g., pancreatectomy) (National Diabetes Data Group, 1979). This was later corroborated by conforming to the American Diabetes Association criteria: at least two measurements of fasting glycemia at 126 mg/dl or higher, and/or random glycemia of at least 200 mg/dl or higher with symptoms, and/or at least 200 mg/dl or higher 2 h after an oral glucose tolerance test of 75 mg of glucose). The mean age of T2D diagnosis was 47.85 years (range: 7–81, median: 41). The male: female ratio was 1.04:1 and the average family size was 5.45. T2D had to be present in more than one first-degree family member.

We amplified 9 single nucleotide polymorphisms (SNPs) in the *TRHR* gene using microarray and tested them via Pseudomarker (Hiekkalinna et al., 2011) for linkage to and linkage disequilibrium (i.e., linkage joint to association) with T2D across the following models: dominant with complete penetrance (D1), dominant with incomplete penetrance (D2), recessive with complete penetrance (R1), and recessive with incomplete penetrance (R2), after excluding genotyping and Mendelian errors with PLINK (Purcell et al. 2007). Linkage analysis tests a genetic marker, i.e., a SNP, and the putative disease locus for co-segregation with the disease/trait within families, whereas association analysis focuses on the relation between a genetic marker's alleles and the disease/trait across families. The variants were amplified using the UKBB microarray platform described in https://www.thermofisher.com/order/catalog/product/902502. The list of tested variants is provided in Supplementary Table 1. *P*-value of <0.05 was the cutoff for statistical significance. By using Merlin software variance component analysis (Abecasis et al. 2002), we analyzed the two significant variants for association with the quantitative traits of age of T2D-onset, BMI at age 20, BMI at T2D-onset, and maximum lifetime BMI. Written informed consent was obtained from each participant and the study was institutionally approved by the Bios Ethical Committee.

2.1. In-silico functional analysis

We performed several bioinformatics *in-silico* SNP-related predictions for transcription-factor binding (SNP2TFBS (Kumar et al. 2017)), miRNA binding (mirSNP (Liu et al. 2012)), splicing (SNP-function prediction (Xu and Taylor, 2009)), and regulation potential (RegulomDB (Boyle et al. 2012)). These tools predict allelic-related differences in transcription-factor or miRNA binding or changes in pre-mRNA splicing by scanning the gene for regions that match the known binding motifs or patterns of specific transcription factors as well as splicing variants. These tools use algorithms, databases, and statistical models to predict likely binding sites (Xu and Taylor, 2009; Kumar et al. 2017).

3. Results

We identified 2 novel risk variants (rs3110045 and rs28499085) significantly linked to and associated with the risk of T2D in the Italian families across several inheritance models (Table 1, Fig. 1). One of the two risk variants (rs3110045) is significant at genome-wide significance level ($P < 0.0005$), and the other is suggestive for genome-wide level significance ($P < 0.0017$). The two risk variants were predicted to intersect with repressed chromatin state in the brain, pancreas, and adipose tissue (RegulomDB (Boyle et al. 2012)). The two variants were not associated with the quantitative traits of age of T2D-onset, BMI at age 20, BMI at T2D-onset, and maximum lifetime BMI (results not shown).

4. Discussion

The pleiotropy of the thyroid hormone system explains the versatility of pathological features associated with its dysfunction (Caturegli et al. 2014; Song et al. 2019; Lui et al. 2021). In this study, we reported the novel implication of two intronic variants in the *TRHR* gene in the risk of familial T2D in Italy. Our study therefore confirms the previously reported association of *TRHR* gene with T2D in a case-control study (Spracklen et al. 2020) of East Asian subjects and extends the risk to familial T2D. Within our dataset, the risk was not contributed by T2D-age of onset, BMI at age 20, BMI at T2D-onset, or maximum lifetime BMI, ruling out age of onset or BMI as driving factors,

The mechanism of *TRHR*-related risk in T2D could be explained by several mechanisms. The *TRHR* gene encodes the receptor that binds to TRH and mediates its pituitary actions in metabolic regulation (Ortiga-Carvalho et al. 2016; Yavuz et al., 2019). Brainstem-secreted TRH is involved in food intake, and a dysfunctional TRH system (i.e., decreased expression of TRH) in T2D rat models causes obesity from decreased vagal output (Zhao et al. 2013). This suppression could potentially counter-activate the corticotropin-releasing hormone-norepinephrine system (CRH-NE), which is an important pathway implicated in T2D (Giessner et al., 2022; Walters et al., 1997; Janssen, 2022). Increased TRHR function might increase thyroid hormones-mediated sensitivity to catecholamines (Coville and Telford, 1970; Silva and Bianco, 2008). This might implicate and potentially link functional upregulation of the sympathetic system (CRHR1-NE) (Del Bosque-Plata et al., 2023) and functional downregulation of the vagus nerve due to TRHR dysfunction (Karthik et al., 2009), which might represent a future working hypothesis and lead to *in vivo* studies. On the other hand, TRHR increases cellular cAMP levels, thereby activating phosphokinase A (PKA), and up-regulates the expression of gluconeogenic genes (Li et al., 2017).

Table 1
Type 2 diabetes (T2D) *TRHR*-Risk Single Nucleotide Polymorphisms (SNPs).

Model[a]	SNP	Position	Ref	Alt	Risk Allele	Consequence	Reported in T2D?
D1, D2, R1, R2	rs3110045	109,093,891	C	T	C	Intronic	Novel
D1, R1, R2	rs28499085	109,094,932	A	G	G	Intronic	Novel

[a] Models: D1: dominant, complete penetrance, D2: dominant, incomplete penetrance, R1: recessive, complete penetrance, R2: recessive, incomplete penetrance, T2D: type 2 diabetes.

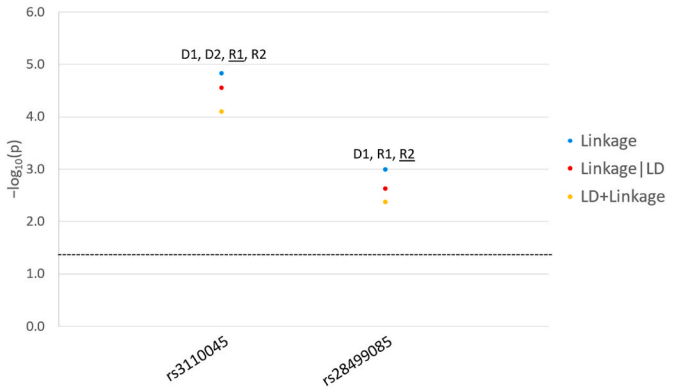

Fig. 1. Parametric Analysis Results of *TRHR*-Risk Single Nucleotide Polymorphisms (SNPs) in Type 2 diabetes (T2D)
Legend. For each *TRHR*-risk SNPs in T2D, we present the −log10(P) as a function of the significant ($p < 0.05$) test statistics [(Linkage, Linkage|linkage disequilibrium (LD) and LD + linkage] and per inheritance model. D1: dominant, complete penetrance, R1: recessive, complete penetrance, R2: recessive, incomplete penetrance. The most significant model is underlined.

The functional roles of the two intronic variants reported in our study could be explained by direct or indirect mechanisms. The risk allele (G) of the variant rs28499085 reported in our study correlates (that is it is in LD) with T allele of rs7832552 which was associated with reduced waist circumference in Chinese adults (Wu et al., 2018; Gong et al. 2021) and Mexicans (Costa-Urrutia et al. 2017). This might imply the presence of other pathogenic variants in LD with the above-mentioned variants and/or possible epistatic interaction between the variants mediating different pleiotropic effects on T2D or waist circumference. The two intronic variants could also play a role in the expression of the *TRHR* gene. Our *in-silico* analysis predicted that the two risk variants intersect with repressed chromatin state in the brain, pancreas, and adipose tissue, thereby potentially causing negative gene expression (RegulomDB (Boyle et al. 2012)). This might mediate decreased activity of the hypothalamic-pituitary-thyroid axis, decreased insulin secretion (Yamada et al. 2000), and decreased adipose tissue energy expenditure (Kim, 2008; Yau and Yen, 2020). Interestingly, this finding is consistent with the notion that subclinical hypothyroidism is the most common form of thyroid dysfunction in T2D (Chubb et al. 2005).

5. Limitations

Our study has only investigated specific variants within the *TRHR* gene and familial T2D, and direct analysis of the sequence of *TRHR* gene in T2D patients is recommended to exclude undetected but linked nearby risk variants. Furthermore, our results cannot be generalized as we have included only a monoethnic and homogeneous population in our study. Therefore, functional and replication studies are still needed to confirm these results.

Data availability statement

The study data are available on reasonable request, and due to lacking specific patients' consent and privacy restrictions, they are not publicly available.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Claudia Gragnoli, MD, PhD reports financial support was provided by Nebraska Department of Health and Human Services.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amolm.2024.100037.

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