How to Cite:
Khan, S., Yunus, M. ., Ahmad, I., Yadav, A., & Gupta, R. (2022). Association of PDE8B gene polymorphisms with thyroid disorders: A meta-analysis and systematic review. *International Journal of Health Sciences*, *6*(S9), 2364–2372. https://doi.org/10.53730/ijhs.v6nS9.12942

Association of PDE8B gene polymorphisms with thyroid disorders: A meta-analysis and systematic review

Salim Khan
Department of Biochemistry, Kurukshetra University, Kurukshetra
Email: mrsalimkhan143@gmail.com

Mohd Yunus
Department of Biochemistry, Kurukshetra University, Kurukshetra
Email: biochem2020mohad@kuk.ac.in

Imteyaz Ahmad
Department of Biochemistry, Kurukshetra University, Kurukshetra
Email: ahmadimteyaz99@gmail.com

Anita Yadav
Department of Biotechnology, Kurukshetra University, Kurukshetra
Email: ayadav@kuk.ac.in

Ranjan Gupta
Department of Biochemistry, Kurukshetra University, Kurukshetra, Kurukshetra (136119), Haryana, India
Corresponding author email: r.gupta@kuk.ac.in

***Abstract*---**Thyroid disorders are the most common endocrine disorders worldwide. PDE8B is strongly expressed in the thyroid and to a lower extent in the pituitary and hypothalamus. PDE8B gene affects the synthesis of T3 and T4 and regulates the release of TSH by the pituitary gland. Therefore, PDE8B single nucleotide polymorphisms (SNPs) rs 6885099 and rs2046045 play a crucial part in the incidence of thyroid disorders, but the existing data is insufficient and contradictory. Materials & Methods. Meta-analysis was carried out to assess the relationship between PDE8B SNP's rs 6885099 and rs 2046045 and thyroid diseases. The present meta-analysis included 9 distinct studies from January 2005 to 2021 accessible at PubMed, Embase and Google scholar. The funnel plot was used to assess the publication bias. Meta Essentials 1.5 software was employed for statistical data analysis. Q test was used to calculate heterogeneity between the studies. The heterogeneity-related variation was calculated by I^2. The association between PDE8B

polymorphism and thyroid diseases was analysed by fixed and random effect models. Results and Conclusion: An important correlation was noticed between PDE8B gene at SNP rs 6885099 and thyroid disease whereas no significant relationship was seen between PDE8B gene at SNP rs 2046045 and thyroid disease. There was significant statistical heterogeneity among the existing results (I^2 =97.70% and 99.07%).

Keywords---Phosphodiesterase 8B, Single nucleotide polymorphism, Thyroid disease, Meta-analysis, Thyroid hormones.

Introduction

The most prevalent endocrine disorders in the world are thyroid disorders. The prevalence of thyroid diseases have increased rapidly over the period. At present more than 10% of the world population is affected by thyroid disorders. Thyroid disorders have affected more than 1.6 billion people worldwide. Various studies revealed that thyroid disorders affect about 42 million people in India. According to a report by the American Thyroid Association (ATA), thyroid problems are five to eight times more common in females than males. A study conducted in 2016 in India identified that about 13.1% of pregnant women suffer from hypothyroidism. According to National Family Health Survey V (2019-2021) reports, the prevalence of thyroid disorders was 2.9% in India.

Thyroid hormones (TH) play a vital role in the metabolism and development of all human tissues. Thyroid hormones (TH) affect the metabolic pathways that manage energy balance by controling energy storage and consumption. The follicular cells of the thyroid gland produce thyroid hormones (T3&T4). Thyroxine (T4) and triiodothyronine (T3) are secreted by Thyroglobulin (Tg) proteolysis. Any abnormalities in these thyroid hormones result in thyroid diseases.

The hypothalamus-pituitary thyroid axis (HPT) controls the formation of thyroid hormones. Thyroid-stimulating hormone (TSH) regulates thyroid function by stimulating the formation and secretion of thyroid hormones by the thyroid gland. Thyrotropin-releasing hormone (TRH) is produced by the hypothalamus, which encourage the production of TSH.

Increased concentration of free T3 and T4 prevents the release of TSH and TRH through a negative feedback mechanism. The iodothyronine deiodinase (D1, D2 and D3) enzymes are present in particular tissues and control TH activation and deactivation.

Any change in TSH and thyroid hormone levels may alter the functionality of the thyroid gland. Low thyroid function (hypothyroidism) leads to an increase in weight, sadness, and cold intolerance, whereas hyperthyroidism leads to weight loss, osteoporosis, atrial fibrillation etc. Demographic factors (age, sex, exercise), lifestyle factors (diet, smoking, medication) and environmental factors also influence the variation in TSH & FT4 levels. Smoking causes reduction in TSH levels and a rise in T3 and T4 levels. A study by Filis et al.(2018), revealed that

maternal smoking interferes with development the development of the foetus thyroid[12]. A recent study observed that the levels of TSH and free T4 are unaffected after physical activities [16]. TSH and thyroid hormone (TH) levels are also influenced by several genes such as sodium iodide Symporter (NIS), thyroid peroxidase (TPO), PDE8B, CAPZB and TG genes etc. Among these genes PDE8B highly affects the TSH and thyroid hormones. The level of thyroid hormones in serum are largely influenced by PDE8B and affects the TSH release via changing cAMP levels in the thyroid.

The Phosphodiesterase type 8B (PDE8B) gene is found on chromosome no. 5 and encodes a phosphodiesterase that is specific to cyclic adenosine monophosphate (cAMP) [8]. PDE8B gene is composed of 885 amino acid residues. PDE8B gene is highly expressed in the thyroid. PDE8B encodes a protein that facilitates the hydrolysis and inactivation of cyclic AMP and hence regulates cAMP levels in cells and play important role in signal transduction [9]. Cyclic AMP is a crucial regulatory signal that controls cortisol steroidogenesis. W. Roussel et al. (2013) reported that PDE8B shows a strong positive correlation with cortisol secretion [17]. A few association studies have been conducted in distinct populations to assess the association of PDE8B gene variants and risk of developing thyroid diseases. The findings of these studies are incongruent. There have been no systematic studies so far for evaluating PDE8B gene polymorphisms and the risk of thyroid diseases. Therefore a meta-analysis was carried out to find the relationship between PDE8B polymorphisms and thyroid diseases. In total, nine studies for both SNP's rs6885099 and rs2046045 were examined by appropriate software and are being described in the current analysis.

Materials and Methods

Research articles published from January 2005 to 2021 were retrieved from electronic databases namely Embase, Google Scholar, Pubmed using text based-word and keyword searches wherever possible. The references were evaluated from the retrieved papers. No unpublished literature was searched for present meta-analysis. We included only English language research papers in this meta-analysis due to limited resources for translation. When two studies reported same conclusion, the largest and latest study was included. The reference list of appropriate studies was examined to identify any missing references. Inclusion basis for the meta-analysis was to include the studies containing original data and studies with allele frequencies, effect size and standard errors. The cohort studies were also included in the study. Any studies that did not complete the inclusion norms were not included in this analysis. A flow chart of inclusion criteria is shown in fig:-

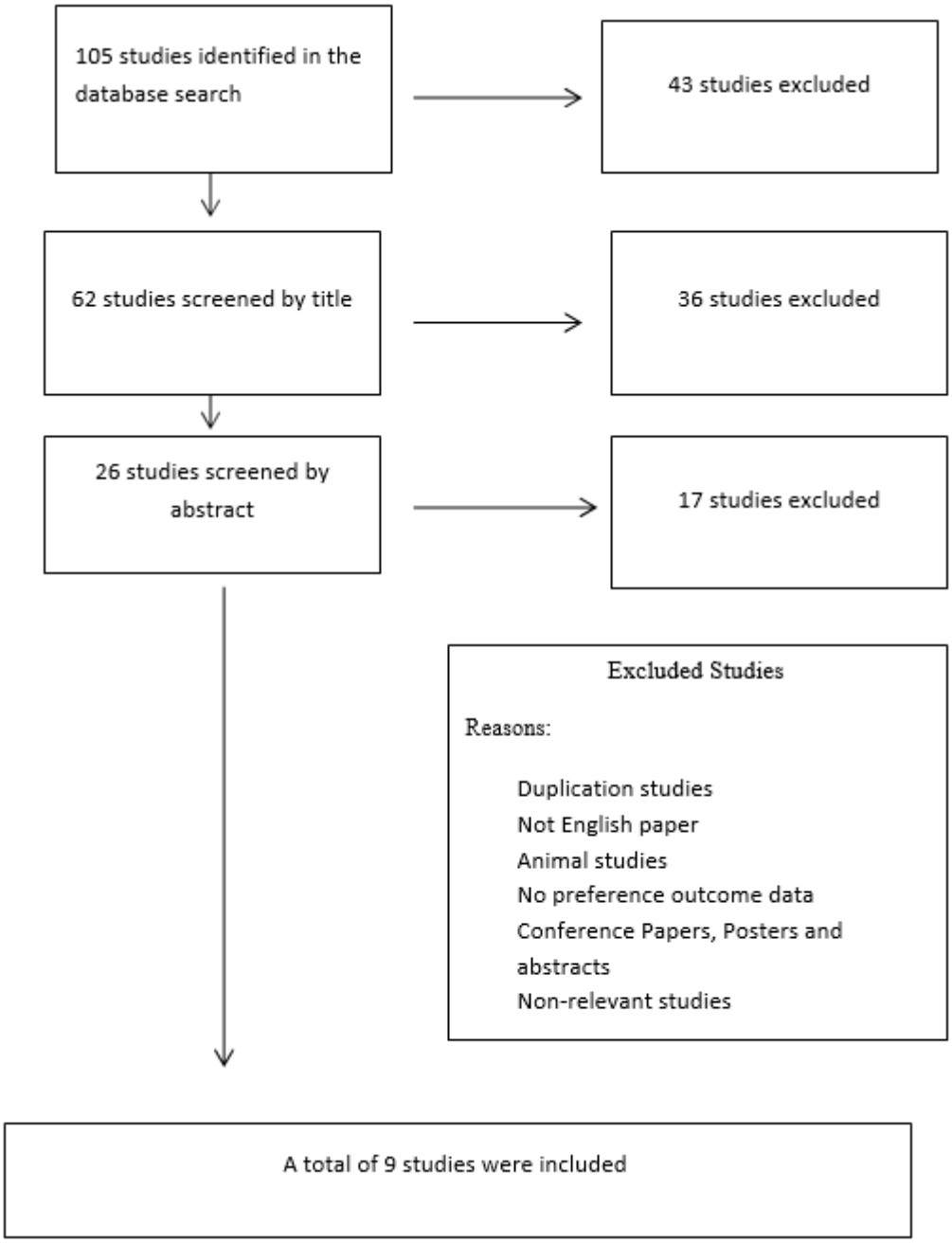

Fig (1) : A flow chart for inclusion criteria

Data Extraction

Data was extracted from retrieved research papers. For each paper, data collected included author name, publication date, effect size, standard error and sample size. 95 per cent confidence interval (CI) was calculated using the data provided.

Conference abstracts, unpublished data and animal studies were excluded from the present study. The current study comprised a total of 9 research articles. The relationship of the rs 6885099 polymorphism with thyroid diseases was studied in four research papers and the association of the rs 2046045 polymorphism with thyroid diseases was assessed in 5 studies.

Statistical Analysis

The statistical analysis for the present study was done using Meta-Essentials 1.5 software. The association of SNP's rs 6885099 and rs 2046045 of PDE8B with thyroid diseases was evaluated using weight percentage corresponding to a 95% confidence interval (CI). In the meta-analysis, we used Q test to assess statistical heterogeneity. The variation due to heterogeneity was calculated by I^2. Publication bias was calculated using Egger's regression model. To assess the publication bias, a funnel plot was used. The asymmetry in the funnel plot was evaluated by Begg's & Mazumdar's test and Egger's regression test. The significant p-value was <0.05.

Results

In this study, we retrieved a total of 105 papers from electronic searches. Out of 105 retrieved papers, we evaluated 22 full- text papers for eligibility and 9 studies were finally selected for inclusion in the meta-analysis. Thirteen findings were eliminated as these did not fall in the inclusion criteria. The reason for exclusion was non-relevant studies, duplication of data, animal studies and unpublished data etc. All nine studies met the inclusion criteria and were evaluated by weight percentage and heterogeneity. Fixed and random effect models were applied according to significant heterogeneity. Heterogeneity was high (I^2= 97.70) and significant (p=0.05) in SNP rs6885099 [Fig 2]. The SNP rs6885099 in the PDE8B gene was identified to be significantly associated with thyroid diseases. The p-value is 0.005 which is statistically significant and shown in the forest plot. Association between PDE8B gene polymorphism of SNP rs 2046045 with thyroid disorders was also studied. The value of p is 0.345 which is statistically insignificant [Fig 3].

Study Name	Effect size	CI Lower limit	CI upper limit	Weight
A. Lopez et al.2008	0.15	0.27		22.59%
E. Porcu et al. 2013 -	-0.16	-0.12		25.86%
Jennifer et al. 2014 -	-0.16	-0.12		25.78%
S. Pedre et al. 2017 -	-0.15	-0.11		25.78%

Heterogeneity T^2 = 0.01, I^2 = 97.70% T= 0.07, Test for overall effect Z = -0.70

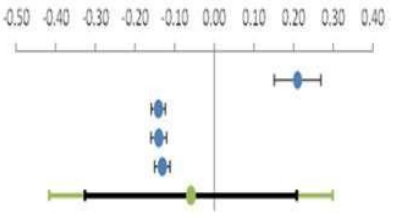

Fig (2):-The forest plot shows the relationship of PDE8B gene SNP rs 6885099 with thyroid diseases

Study Name	Effect size	CI Lower limit	CI upper limit	Weight
A. Lopez et	0.21	0.15	0.27	19.43%
M. Medici et	0.20	0.16	0.24	19.92%
R. Rawal et	-0.12	-0.13	-0.10	20.23%
Jennifer et	0.09	0.07	0.11	20.23%
P. N. Taylor et	0.14	0.12	0.16	20.19%

Heterogeneity T2 = 0.02, I^2 = 99.07%, T = 0.14, Test for overall effect Z = 1.75

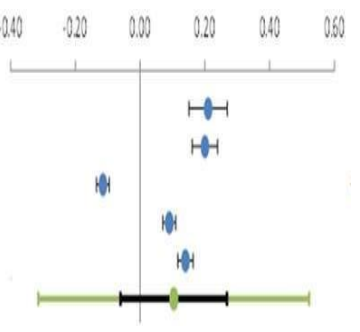

Fig (3):- The forest plot shows the relationship of PDE8B gene polymorphism of SNP rs 2046045 and thyroid diseases

Heterogeneity Testing

Heterogeneity in meta-analysis refers to the difference in results between studies. Variation percentage in many studies because of heterogeneity rather than chance is described by I^2. For PDE8B SNPs, rs 6885099 and rs 2046045, significant heterogeneity was detected under fixed or random effect models. The value of I^2 for rs6885099 is 97.70% and for rs 2046045 is 99.07%. From the present study, we observed that heterogeneity was high. According to the fixed effect model, the sampling error is the sole reason for variation in effect sizes between different studies. In other words, there is no assumption of heterogeneity. Due to this reason random effect model is used to interpret the heterogeneity.

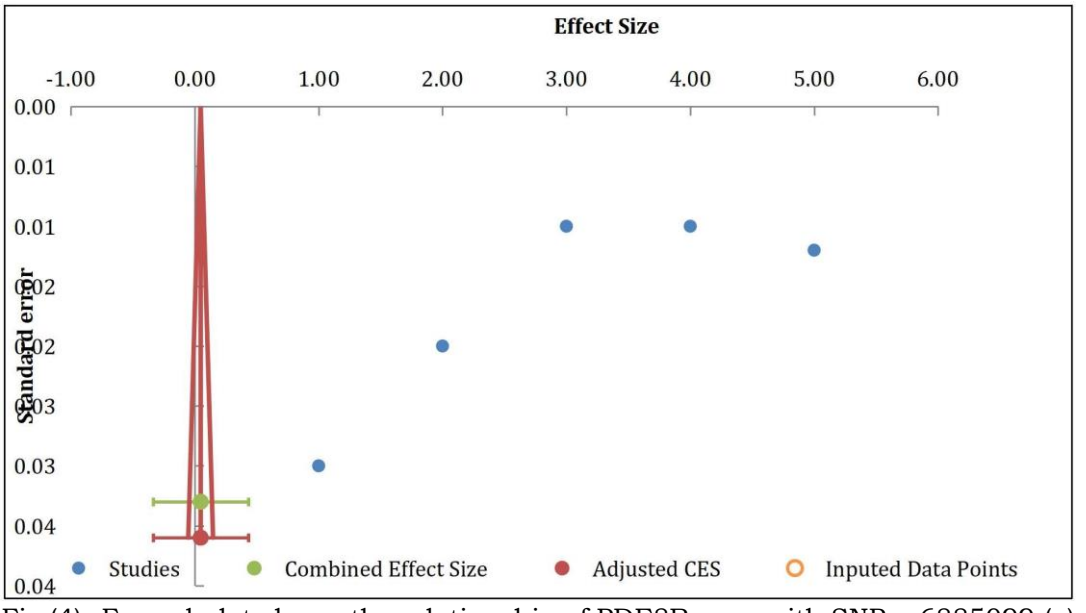

Fig (4):-Funnel plot shows the relationship of PDE8B gene with SNP rs6885099 (a) and rs2046045 (b).

Publication Bias

The funnel plot was employed to assess the publication bias. The funnel plot shows that the distribution of effect size is not asymmetric. The Begg's & Mazumdar's adjusted rank correlation test and Egger's linear regression test was used to evaluate the asymmetry of the funnel plot. The polymorphism of SNP's rs 6885099 was shown to have a considerable publication bias in the current study. Begg's and Mazumdar's z and p-value of 1.70 &0.045 and Egger's p-value of 0.005 were obtained. Fixed effect meta-regression analysis was performed for both SNP's rs6885099 and rs2046045. SNP rs6885099 show significant association with effect size and moderator (slope- 0.01,-0.33, and p-value- 0.00) [Fig (5)a].
(b)

Fig (5):- Meta –regression plots for the SNP rs6885099 (a) and rs2046045 (b).

Discussion

PDE8B gene increases the activity of the thyroid gland to generate T3 and T4 hormones. We selected two SNP's of the PDE8B gene for the meta-analysis study. We observed that SNP rs 6885099 is associated with thyroid risk (p-value 0.005). Significant heterogeneity was detected in this study. Because of sampling error, studies among different populations revealed inconsistencies with poor statistical significance. A meta-analysis was carried out to check the relationship with PDE8B variants and thyroid disease risk from the available data. It was found that using different models for both SNPs, PDE8B gene SNP rs6885099 is correlated with thyroid disease risk ($p<0.005$). Similar to our findings a meta-analysis study observed that variants at PDE8B are significantly associated with TSH [5].

Strengths of the present study include a wide literature search and the use of precise inclusion criteria and restrictions on language. The genes PDE8B and CAPZB have been linked to hypothyroidism in GWAS (Genome-Wide Association Studies)[7]. The present research findings remained disputed due to insufficient and contradictory results of a connection between PDE8B gene SNP's rs2046045 & rs6885099 and thyroid diseases. Similar to our results a study identified that variation at PDE8B is in linkage equilibrium with rs 6885099 and independent of

rs 2046045 (Taylor et al.,2014). As a result, a meta-analysis was carried out to derive useful conclusions from the available information about the link between PDE8B polymorphisms and thyroid disorders. The current study did not find any evidence of significant publication bias. In this study, all applicable research publications were used.

The present meta-analysis demonstrated an important link among PDE8B gene polymorphism at rs6885099 and thyroid disease risk based on the available study. Our results indicate that further investigation is necessary for better and more significant results.

References

Abraham R, Murugan VS, Pukazhvanthen P, Sen SK. Thyroid Disorders in Women of Pondicherry. The Indian Journal of Clinical Biochemistry 2009; 24:52-9.

Ambika Gopalakrishnan Unnikrishnan and Usha V. Menon. Thyroid Disorders in India: An epidemiological perspective. Indian Journal of Endocrinology and Metabolism 2011; 15: S78-S81.

Amit Akirov, Rouhi Fazelzad, Shereen Ezzat, Lehana Thabane and Anna M. Sawaka. A Systematic Review and Meta-Analysis of Patient Preferences for Combination Thyroid Hormone Treatment for Hypothyroidism. Frontiers in Endocrinology 2019.

Azevedo MF, Faucz FR, Bmpaki E, Horvath A, Stratakis CA. Clinical and molecular genetics of phosphodiesterase. Endocrine Review 2014.

Eleonora Porcu, Marco Medici, Giorgio Pistis, Claudia B. Volpato, Scott G. Wilson, Anne R. Cappola, Steffan D. Bos, Silvia Naitza, Serena Sanna. A Meta-Analysis of Thyroid Related Traits Reveals Novel Loci and Gender-Specific Differences in the Regulation of Thyroid Function. PLOS Genetics 2013.

Enrique Soto- Pedre, Moneeza K. Siddiqui, Ify Mordi, Cyrielle Maroteau, Jimena Soto- Hernaez, Colin N.A. Palmer, Ewan R. Pearson, Graham P. Leese. Evidence of a Causal relationship between serum thyroid stimulating hormone and osteoporotic bone fracture. European Thyroid Journal 2021.

Eriksson N, Tung JY, Kiefer AK, Hinds DA, Francke U, et al. Novel Associations for Hypothyroidism Include Known Autoimmune Risk Loci. PLoS 2012.

Hayashi M, Shimada Y, Nishimura Y, Hama T, Tanaka T. Genomic organisation, chromosomal localization and alternative splicing of the human phosphodiesterase 8B gene. Biochem Biophys Res Commun 2002; 297(5): 1253-1258.

Lakics V, Karran EH & Boess FG. Quantitative comparison of phosphodiesterase mRNA distribution in the human brain and peripheral tissues. Neuropharmacology 2010; 59: 367-374.

Lisette Arnaud- Lopez, Gianluca Usala, Graziano Ceresini, Braxton D. Mitchell, Maria Grazia Piras, Natascia Sestu, Andrea Maschio, Fabio Busonero, Mariano Dei, Sandra Lai et al. Phosphodiesterase 8B Gene Variants are Associated with Serum TSH Levels and Thyroid Function. The American Journal of Human Genetics 2008; 82: 1270-1280.

Nicholas Mikolajewicz and Svetlana V. Komarova. Meta-Analytic methodology for basic research: A Practical Guide. Frontiers in Physiology 2019; 10: 203.

Panagiotis Fillis, Sabine Hombach- Klonisch, Pierre Ayotte, Nalin Nagrath, Ugo Soffientini, Thomas Klonisch, Peter O'Shaughnessy, Paul A. Fowler. Maternal smoking and high BMI disrupt thyroid gland development. BMC Medicine 2018; 16: 194.

Panicker V, Wilson SG, Walsh JP, Richards JB, Brown SJ, Beilby JP et al. A locus on chromosome 1p36 is associated with thyrotropin and thyroid function as identified by a genome-wide association study. Am J Hum Genet 2011; 87: 430-5.

Peter N. Taylor, Eleonora Porcu, Shelby Chew, Purdey J. Campbell, Suzanne J. Brown, Jie Huang et al. Whole-genome sequence-based analysis of thyroid function. Nature Communications, 2015.

Prue J. Hardefeldt, Guy D. Eslick, Senarath Edirimanne. Benign thyroid disease is associated with breast cancer: a meta-analysis. Breast Cancer Res Treat 2012; 133: 1169-1177.

Roa Dueñas, O.H. Koolhaas, C. Voortman, T. Franco, O.H. Ikram, M.A. Peeters, R.P. Chaker et al. Thyroid function and physical activity: A population-based cohort study. Thyroid 2020, 31, 870–875.

Roussel HW, Delphine Vezzosi, Marthe Rizk-Rabin, Olivia Barreau, Bruno Ragazzon, Fernande Rene- Corail et al. Identification of gene expression profiles associated with cortisol secretion in adrenocortical adenomas. The Journal of Clinical Endocrinology& Metabolism 2013; 98:1109-1121.

Sana Abd Elgany Yousif, Hanan Babiker Eltahir, Mariam Abbas Ibrahim and Amar Mohamed Ismail. Association of Phosphodiesterase 8B Gene Polymorphism (rs4704397) in Sudanese Women with Hyperthyroidism. World Journal of Pharmaceutical Research 2016; 9: 93-101.

Sharma A, Shivgotra VK. Risk and Prevalence of thyroid disorder among Indian population: A meta-analysis. International Journal of Recent Trends in Science and Technology. 2018; 26(2)P: 16-20.

Soto – Pedre, Enrique, Siddiqui, Moneeza K., Doney, Alex S., Palmer, Colin N.A., Pearson, Ewan R., Graham P. Replication confirms the association of loci in FOXE1, PDE8B, CAPZB and PDE10A with thyroid traits. Pharmacogenetics and Genomics 2017.

Vikas Kumar, Jaswinder Singh, Ashish Aneja, Jasbir Singh. Association of RETN gene polymorphism at+299G>A with type 2 diabetes mellitus: a meta-analysis. International Journal of Diabetes in Developing Countries 2019.

Yul Hwangbo, Young Joo Park. Genome-wide association studies of autoimmune thyroid diseases, thyroid function and thyroid cancer. Endocrinology and Metabolism, 2018; 33:175-184.