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Graves' Disease and Its Related Single Nucleotide Polymorphisms and Genes

Yuhong Lu

***Abstract*—**Graves' Disease (GD), an autoimmune health condition caused by the over reactiveness of the thyroid, affects about 1 in 200 people worldwide. GD is not caused by one specific single nucleotide polymorphism (SNP) or gene mutation, but rather determined by multiple factors, each differing from each other. Malfunction of the genes in Human Leukocyte Antigen (HLA) family tend to play a major role in autoimmune diseases, but other genes, such as LOC101929163, have functions that still remain ambiguous. Currently, little studies were done to study GD, resulting in inconclusive results. This study serves not only to introduce background knowledge about GD, but also to organize and pinpoint the major SNPs and genes that are potentially related to the occurrence of GD in humans. Collected from multiple sources from genome-wide association studies (GWAS) Central, the potential SNPs related to the causes of GD are included in this study. This study has located the genes that are related to those SNPs and closely examines a selected sample. Using the data from this study, scientists will then be able to focus on the most expressed genes in GD patients and develop a treatment for GD.

***Keywords*—**CTLA4, Graves' Disease, HLA, single nucleotide polymorphism, SNP.

I. Introduction

GD is an autoimmune disorder of which the thyroid, a butterfly-shaped organ located at the lower part of the neck, overproduces hormones. In normal condition, Thyroid-stimulating hormone (TSH) released by the brain's pituitary gland is in charge of the regulation of the function of the thyroid. But in GD patients, a malfunction in the body's immune system releases abnormal antibodies against the TSH (or thyrotropin) receptor (TSHR). This thyrotropin receptor antibody (TRAb) can mimic TSH to attach the antigen TSHR, and act like the regulatory pituitary hormone. Therefore, TRAb is able to override the normal thyroid regulation process, which then leads to an increase and overproduction of thyroid hormones including triiodothyronine (T3) and tetraiodothyronine (T4). The continuous stimulation by TRAb or stimulating immunoglobulins (TSI) is also the leading cause of hyperthyroidism [13].

A normal-sized thyroid cannot be felt by simply touching your neck, while the thyroid of a GD patient can be easily felt since it swells considerably. GD may affect the patient in different ways, such as having bulged eyes, trouble falling asleep, and an easily irritable temper [3]. Not only does GD affect the external part of the body, but it has great internal implications as well. A person with GD will have a raised overall body temperature, internal humidity, and heart rates [1].

Yuhong Lu is with Bellevue High School, United States (e-mail: luyuhong2004@gmail.com).

Numerous studies [13], [14] have concluded that GD occurs in completely random ways and suggests that there are no specific ways to avoid GD, while some data are able to demonstrate that GD often clusters within a family [10]. Even the causes of GD are unclear. Numerous studies have also been conducted in the past, but they all suggest that GD is unlikely caused by a single change of amino acid in SNP or a mutation of a single gene [3], [16], [19]. Rather, it is believed that multiple SNPs and genes are related to GD, and all of them collectively contribute to the occurrences of GD.

This study performed a systematic analysis of SNPs or single nucleotide variant (SNV) associated with GD. In total, 18 SNPs and their related genes were collected and examined in order to investigate them individually. They are then put together in a gene network in order to see the link between the connection of seemingly unrelated genes and their role in the regulation of the body.

The study compares the risks involved in each different SNP mutation, analyzes if the mutated SNP will have an effect on gene expression, sorts out genes' functions, and looks at the relationships between different genes believed to contribute to GD.

II. Material and Methods

Firstly, in order to gather potentially useful SNPs, GWAS Central was utilized [18] By clicking on the Phenotypes section, GD was searched for with -log $p \geq 2$ (p-value <= 0.01), which means that the results generated were statistically significant, having a strong correlation with the occurrence of GD unlikely caused by chance. Two studies were shown, with a total of 18 different SNPs. Every SNP has a different Odds Ratio (OR) value, which is a number that characterizes the ratio between two conditions, in which the first condition has the presence of another thing --- in this case GD --- and the second condition is the normal one, or the control. An OR value greater than 1 indicates that the targeted population, GD population, has more risk of this variation in SNP. If the OR value is equal to 1, it means that GD population will have the same risk of having the variation as the control, and if the OR value is less than 1, it means that GD population will be less likely to possess the variation in the SNP [16]. All of the SNPs this study included have OR value > 1, which further strengthened the link between GD patients and the individual SNP markers.

Secondly, with the help of SNP nexus, an engine used for SNP annotations, the discovery of a series of information was

enabled, including possible DNA variations and the genes related to those studied SNPs [14].

Thirdly, DAVID [4], [5] was used for functional enrichment analysis by the genes related to GD in order to better understand how the genes and the biological functions are tightly connected together. DAVID serves as an extremely helpful tool that provides Gene Ontology (GO) terms and allows for a deeper understanding of the biological meaning of a list of genes. Then, the functions of these genes were found using Gene Cards [2], [19] and NCBI [11]. A chart was then organized, depicting the functions of these genes.

To better understand the gene structure containing the specific SNPs, the UCSC Genome Browser [7], [8] was used. This tool helps to display the structure of the genes and allows for the discovery of the SNP position on a gene, that is to say, which intron or exon it sits upon. After that, variation in a specific SNP was studied for their potential effects on gene expression by using GTEx Portal. GTEx serves as a tool to display if a variation in a SNP causes the gene expression to increase or decrease, which can contribute to the underlying reason an individual is more vulnerable to a disease such as GD.

Finally, STRING [15], a tool widely used to discern the connections between a group of genes, was used to analyze the connection between the genes related to GD, at the same time drawing out the type of connection between individual genes, such as co-expression.

III. Results

A. Data and Statistics

In this study, a systematic analysis of genetic variants associated with GD was used with the help of online tools. The data on the GWAS Central database were queried to gather all SNPs related to GD. There are 18 SNPs associated with GD, corresponding to 18 genes (Table I), of which only one SNP is located in exon and the remaining 17 SNPs are either intergenic or intronic (Table I). However, all 18 of these SNPs have OR larger than 1 (Table I), meaning that the genetic variation in these chromosome sites will all increase the risk of an individual having GD [9]. While rs505922 only has its OR value at 1.13 (the lowest OR value included in this study), rs1521 has an OR value at 1.92 (the highest OR value included in this study), indicating a higher risk. A variation at rs1521 from C to T is likely to greatly increase the possibility of the individual possessing GD.

Next, we investigated the functions of these 18 GD-associated genes (Table I). By searching through these genes through GeneCards, the functions of encoded products by these genes are listed in Table II [12]. Among these genes, HLA-J is a pseudogene. This means it does not encode any protein products, therefore, the mechanism of how HLA-J is associated with GD still awaits further investigation.

There are several cell surface membrane proteins that belong to components of the major histocompatibility complex (MHC), such as MICA, HLA-DPB1 and HLA-DQB1. These proteins are associated with antigen processing and presentation, thereby, the presented antigen bound in the extracellular region of MHC can be recognized by TCR (T-Cell Receptor) on the cell surface of T cells. Interestingly, there is an intronic SNP in the gene locus of TSHR. The encoded protein of TSHR is a receptor for thyrotropin and thyrostimulin. If this gene is defected, it may lead to several types of hyperthyroidism. We also noted the gene CTLA4. This gene is a part of the immunoglobulin family, which sends T cells inhibitory signals. Mutations in this gene have been associated multiple kinds of autoimmune diseases as well as insulin-dependent diabetes mellitus.

TABLE I
GD Related SNPs & Genes

SNP	Chromosome	Risk Allele	Function	OR Value	Gene
rs1521	6	T	Intergenic	1.92	MICA, HLA-B
rs2281388	6	T	Intergenic	1.64	HLA-DPB1
rs4947296	6	C	Intergenic	1.77	HCG22
rs6457617	6	T	Intergenic	1.4	HLA-DQB1, HLA-DQA2
rs12101261	14	T	Intronic	1.35	TSHR
rs1024161	2	T	Intergenic	1.3	CTLA4, CD28
rs6832151	4	G	Intergenic	1.24	RHOH
rs3761959	1	A	Intronic	1.23	FCRL3
rs9355610	6	G	Intergenic	1.19	RNASET2
rs370409	6	T	Intronic	1.15	BACH2
rs505922	9	T	Intronic	1.13	ABO
rs2273017	6	A	ncRNA_intronic	1.53	LOC101929163
rs3893464	6	G	Intergenic	1.53	HCG9, HLA-A
rs4313034	6	T	ncRNA_intronic	1.67	HLA-J
rs4248154	6	C	Exonic	1.38	MUC22
rs3132613	6	C	Intergenic	1.43	ABCF1
rs4713693	6	T	Intergenic	1.4	MLN
rs9394159	6	T	Intronic	1.36	ITPR3

The genes' information in Table II prompted us to investigate whether there were some functions typically enriched in these genes. The online tool, DAVID, was utilized for this purpose. As shown in Table III, as for biological process, the terms including antigen processing and presentation, immune response, MHC protein complex, and immunoglobulin-like fold, and so on, are significantly enriched in the GD-associated genes. A further survey revealed that these functions were mainly determined by some key genes, such as HLA-DQB1, MICA, HLA-J, and HLA-DPB1. As for KEGG pathway, genes related to autoimmune thyroid disease and cell adhesion molecules (CAMs) are significantly enriched (Table III). The suggested connections between genes, including HLA-DQB1, CTLA4, HLA-DPB1 and TSHR, and GD have been established. The current study revealed novel genes that were potentially related to the occurrence or development of the GD.

B. GD-Associated SNPs in Non-Exon Regions

To better understand the structures of major genes that contain the SNPs, the UCSC Genome Browser was used as a constructive tool. Figs. 1-6 display the specific positions of the SNPs on the genes. Six genes were chosen to be graphed. One of them is exonic, meaning that it is an important SNP that codes for the protein, and although the other five genes are all intronic, they can affect gene expression by increasing the

expression of the gene, impacting the gene in an important way.

TABLE II
GD RELATED GENES AND PRODUCT INFORMATION & FUNCTION

	Full Name	Subcellular Location	Function
MICA	MHC class I polypeptide-related sequence A	Cell surface	This protein act as a self-antigen that is recognized by the cytotoxic T cells, which kills epithelial tumor cells with MICA on their surface
HLA-B	Major histocompatibility complex, class I, B	Membrane	HLA-B presents the peptides form the endoplasmic recticulum lumen.
HLA-DPB1	Major histocompatibility complex, class II, DP beta 1	Cell membrane	HLA-DPB1 gene is made up of an alpha chain and a beta chain. Both chains are present in the membrane. It presents the peptides from extracellular proteins to the body.
HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	Cell membrane	HLA-DPB1 gene is made up of an alpha chain and a beta chain. Both chains are present in the membrane. It presents the peptides from extracellular proteins to the body.
HLA-DQA2	Major histocompatibility complex, class II, DQ alpha 2	Cell membrane	HLA-DQA2 is a gene that is in intracellular vesicles. It helps release CLEP from its bonding site.
TSHR	TSH receptor	Cell membrane	TSHR codes for a membrane protein that regulate the thyroid cell metabolism activity. Deffects of TSHR can result in multiple types of hyperthyroidism.
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	Cell membrane	This gene encodes for a protein that sends T cells inhibitory signals. Multiple types of autoimmune diseases are associated with the mutation of this gene, including GD.
CD28	CD28 molecule	Membrane	CD28 encodes for a protein that is critical for the survival and development of T-cell as well as the production of cytokines.
RHOH	Ras homolog family member H	Cytoplasm	RHOH encodes a protein that act as a negative regulator for cell growth.
FCRL3	Fc receptor-like 3	Cell membrane	FCRL3 encodes for a protein that is involved in the immune system regulation. Mutation of FCRL3 may result in autoimmune thyroid disease and rheumatoid arthritis.
RNASET2	Ribonuclease T2	Secreted. lysosome lumen. endoplasmic reticulum lumen.	RNASET2 is a gene that is related with a region called 6q27 that is associated with chromosomal rearrangement.
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	Cytoplasm	BACH2 codes for protein
ABO	ABO blood group (transferase A, alpha 1-3-N-acetylgalactosaminyltransferase; transferase B, alpha 1-3-galactosyltransferase)	Golgi apparatus, golgi stack membrane; single-pass type ii membrane protein. secreted.	ABO gene is associated with the production of proteins related to the ABO blood group system. Therefore, it indirectly affects the blood type of an individual.
HLA-A	Major histocompatibility complex, class I, A	Membrane	HLA-A presents peptides from the endoplasmic reticulum lumen to the cytotoxic T cells.
HLA-J	Major histocompatibility complex, class I, J	Pseudogene	HLA-J is a transcribed pseudogene.
MUC22	mucin 22	Membrane	MUC22 (Mucin 22) codes for protein and is associated with diseases such as Corneal.
ABCF1	ATP-binding cassette, sub-family F (GCN20), member 1	Isoform 2: cytoplasm. nucleus, nucleoplasm. nucleus envelope.	ABCF1 encodes for ABC proteins, which transport molecules through the cellular membranes.
MLN	motilin	Secreted.	MLN codes for a peptide hormone that is responsible for the regulation of gastrointestinal contractions.
ITPR3	inositol 1,4,5-trisphosphate receptor, type 3	Endoplasmic reticulum membrane	ITPR3 encodes for a receptor that is a second messenger responsible for the regulation of calcium inside the cell.

The source of the functions of these genes is GeneCards.

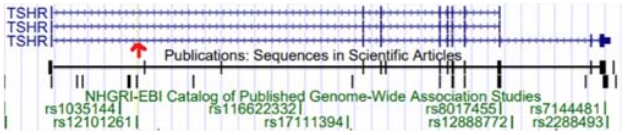

Fig. 1 rs12101261 is in the 1st intron of gene TSHR

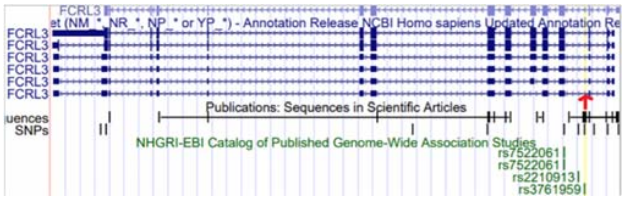

Fig. 2 rs3761959 is in the 3rd intron of gene FCRL3

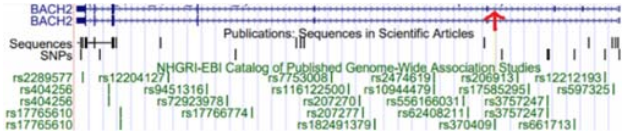

Fig. 3 rs370409 is in the 3rd intron in transcript NM 021813.4 of gene BACH2

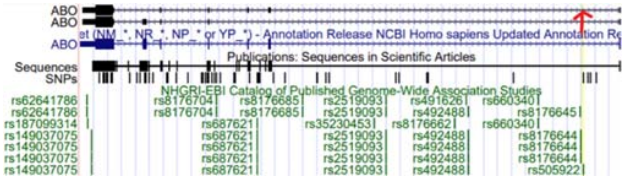

Fig. 4 rs505922 is in the 1st intron of gene ABO

TABLE III
GD ASSOCIATED GENES

Category	Term	Name	P-Value	Gene
Biological Process	GO:0019882	Antigen processing and presentation	3.38E-10	HLA-DQB1, MICA, HLA-J, HLA-A, HLA-DPB1, HLA-B, HLA-DQA2
Biological Process	GO:0006955	Immune response	3.93E-07	HLA-DQB1, MICA, HLA-J, HLA-A, CTLA4, HLA-DPB1, HLA-B, HLA-DQA2, CD28
Cellular Component	GO:0042611	MHC protein complex	4.64E-11	HCG HLA-DQB1, MICA, HLA-J, HLA-A, HLA-DPB1, HLA-B, HLA-DQA2
Cellular Component	GO:0044459	Plasma membrane part	6.13E-07	HLA-DQB1, ABCF1, MICA, HLA-J, HLA-A, CTLA4, HLA-B, ITPR3, HLA-DQA2, HLA-DPB1, CD28, RHOH, TSHR
Cellular Component	GO:0042612	MHC Class I protein complex	5.17E-06	MICA, HLA-J, HLA-A, HLA-B
Cellular Component	GO:0005886	Plasma membrane	2.77E-05	ABCF1, HLA-DQB1, MICA, HLA-J, HLA-A, CTLA4, ITPR3, HLA-DPB1, HLA-B, HLA-DQA2, FCRL3, TSHR, RHOH, CD28,
Molecular Function	GO:0032395	MHC Class II receptor activity	9.57E-07	HLA-DQB1, HLA-DPB1, HLA-B, HLA-DQA2
Structure	IPR003597	Immunoglobulin C1-set	5.81E-09	HLA-DQB1, MICA, HLA-A, HLA-DPB1, HLA-B, HLA-DQA2
Structure	IPR003006	Immunoglobulin / MHC, conserved site	2.04E-08	HLA-DQB1, MICA, HLA-A, HLA-DPB1, HLA-B, HLA-DQA2
Structure	IPR013783	Immunoglobulin-like fold	2.62E-08	HLA-DQB1, MICA, HLA-A, CTLA4, HLA-DPB1, HLA-B, HLA-DQA2, FCRL3, CD28
Structure	IPR001039	MHC Class I, alpha chain, alpha1 and alpha2	2.54E-06	MICA, HLA-J, HLA-A, HLA-B
Structure	IPR011161	MHC Class I, like antigen recognization	2.85E-06	MICA, HLA-J, HLA-A, HLA-B
Structure	IPR010579	MHC Class I, alpha chain, C-terminal	5.87E-06	MICA, HLA-A, HLA-B
Structure	IPR007110	Immunoglobulin-like	6.70E-06	HLA-DQB1, MICA, HLA-A, HLA-DPB1, HLA-B, HLA-DQA2, FCRL3
KEGG Pathway	hsa05320	Autoimmune thyroid disease	2.13E-12	HLA-DQB1, HLA-A, CTLA4, HLA-DPB1, HLA-B, TSHR, HLA-DQA2, CD28
KEGG Pathway	hsa04514	Cell adhesion	1.13E-07	HLA-DQB1, HLA-A, CTLA4, HLA-DPB1, HLA-B, TSHR, HLA-DQA2, CD28

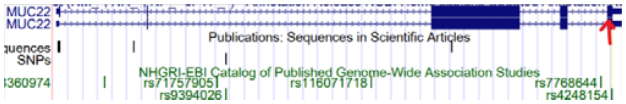

Fig. 5 rs4248154 is the 5th exon in transcript NM 001318484.1 of gene MUC22

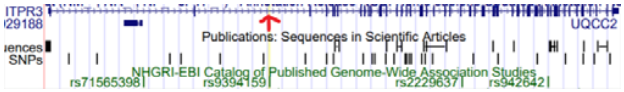

Fig. 6 rs9394159 is in the 2nd intron of gene ITPR3

C. GD-Associated SNPs' Effect on Gene Expression

Variation on some of the SNPs can either increase, decrease, or have no effects on the expression of a gene. The gene combination could be both homozygous or heterozygous, and if an individual inherited the variated form from both parents, it could have a more notable effect on gene expression. As Fig. 7 A and B suggest, at these SNPs, variations could result in an increased amount of gene expression. However, a variation could also decrease the gene expression, as suggested in Fig. 7 C.

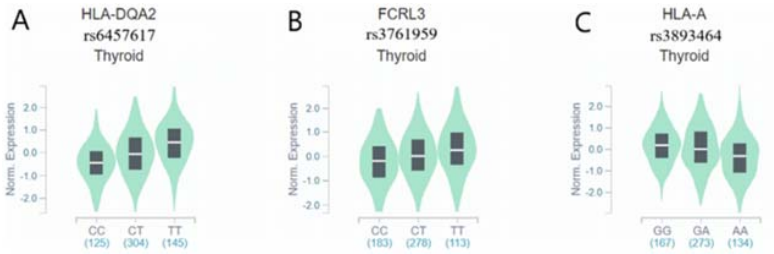

Fig. 7 GD-associated genetic variations can affect gene expression. All of those graphs come from the variations in thyroid: A) Gene HLA-DQA2 B) Gene FCRL3 C) Gene HLA-A

D. Network Analysis among GD-Associated Genes

The study extended further to understand the relationships between these genes, utilizing STRING as a helpful tool. Not surprisingly, the different HLA groups showed many more connections with each other than other genes do.

Some notable connections also exist between, for example, CTLA4 and CD28; CTLA4 and HLA-A, etc. Co-expression also exists between multiple genes like CTLA4 & TSHR; CTLA4 & HLA-A etc. This indicates that an increase in one of those related genes will likely have a cascade effect on other related genes as well. For example, when CTLA4 increases, HLA-A, TSHR, FCRL3, and multiple other genes will simultaneously increase, by the same amount or not.

The HLA-A and HLA-B proteins associated with GD are a

part of a larger group called the MHC Class I molecules. The MHC Class I molecules are almost present on every cell's surface, and along with a part of the antigen, in this case the TSHR, they bind to the CD8 receptors on Cytotoxic T cells, ensuring the appropriate T-cell is activated for the presented pathogen. In GD, if the links between MHC Class I molecules are disturbed, it can result in the production of antibody against TSHR called TRAb. TRAb molecules compete with TSH to bind to TSHR, resulting in the inability for TSH to regulate the production of T3 and T4 molecules. The increase of T3 and T4 molecules would not only decrease the production of TSH, initiating a negative feedback loop, but also increase the metabolism rate, one of the many indicators for GD.

The MHC Class 2 molecules, in comparison, binds to the CD4 receptor on the Helper T cells, and this interaction is therefore widely considered as the initiation of autoimmune response in GD [6].

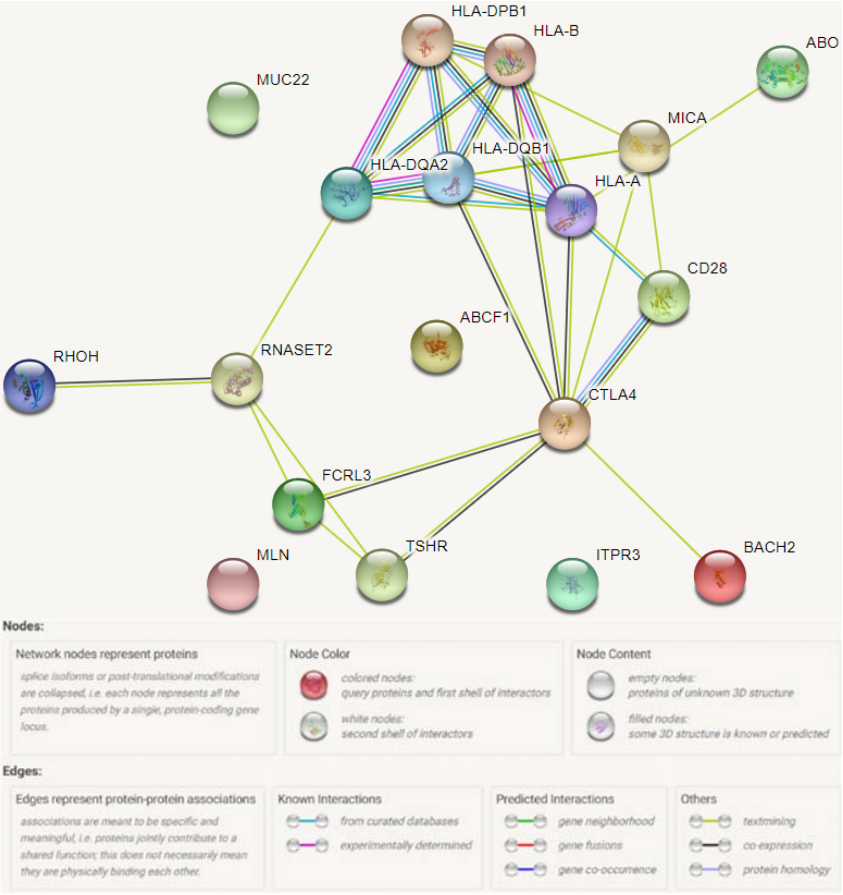

Fig. 8 GD related Gene Connections. Since sometimes there are multiple genes having the connection with the same SNP, this figure included all the genes that is related to the 18 SNPs, even the ones not shown in Table I

IV. Discussion

Normally, the body produces TSH like a normal body as a means to regulate the body's internal levels, shown in Fig. 9 (a). MHC cells, from both class I and class II, will bind on to the cells in order to recognize potentially foreign things, like bacterium. However, a malfunction will occur, causing the antigen receptor to recognize TSHR as non-self rather than self, depicted by Fig. 9 (b). This will cause the HLA that attached to the cell to signal the T cells to take action. Helper T cells then send a note for the need of antibody against TSHR, and in this case, the antibody would be TRAb. TRAb will then be released into the body, and since TRAb has very similar functions as TSH, it will continue to stimulate the TSH receptor, causing an overproduction of thyroid hormone in the individual's body. In this case, the HLAs contribute greatly to the occurrence of GD. In addition, CTLA4 is a gene which suppresses the function of T cells; a normally functioning CTLA4 will largely decrease the probability of developing autoimmune disease [17]. However, a mutation in CTLA4 will cease to suppress T cells, thus letting the T cells function, even when they are not needed. The mutation of CTLA4 will result in a more intense and hostile reaction toward TSHR, thus allowing B cells to produce the antibody, TRAb, in an unrestrained way. The overproduction of TRAb will largely increase the production of thyroid hormone, therefore resulting in GD.

The most important part of the whole mechanism is TSHR, which initially serves as a receptor for TSH; but when the body

recognizes TSHR as non-self, it will start making TRAb, an antibody for TSHR. And when TRAb binds to the TSHR, it would also produce thyroid hormone. However, since TRAb lacks regulation, the binding of TRAb on TSHR will cause the body to produce uncontrollable amounts of thyroid hormone, leading to GD.

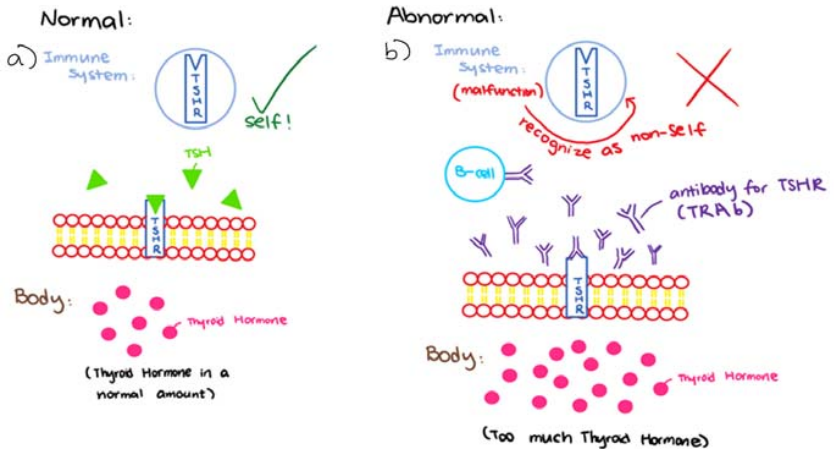

Fig. 9 GD Potential Mechanism: Fig. 9 (a) shows how a normal body would function between TSHR and TSH; Fig. 9 (b) shows when a malfunction occurs in the immune system, TRAb (antibody for TSHR) is made, causing more thyroid hormone to be produced

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