Genetics of Graves' Disease: The Lost Concept

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ABSTRACT

A key issue of Really Significant Genes (RSG) that caused Graves Disease is unresolved. RSGs are considered likely major contributors to genetic risk for a disease. These genes should be strongly linked within families and they could become clinically useful as predictors of disease. Some Graves Disease susceptibility genes have been identified. The first identified was the Human-Leucocyte-Antigen DR (HLA-DR) gene locus, then a non-HLA genes as cytotoxic T lymphocyte antigen (CTLA-4), CD40, protein tyrosine phosphatase-22 (PTPN22), thyroglobulin, and thyroid-stimulating hormone receptor (TSHR) gene. The sites observed in different populations were not always the same. With the completion of the HapMap, which provided the geography of thousands single nucleotide polymorphisms (SNPs), the search of more minor associated genes started again although studies never revealed stronger candidates, meanwhile, the role of the environment in disease development remains poorly understood. The importance of the environment with the mechanisms involved including genetic factors is needed to be decided.

Key words: Graves' disease, genetic.

INTRODUCTION

Five decades have passed since February 28, 1953, Watson and Crick stood in their Cambridge University office marvelling at the cardboard model they had just built of the molecule of heredity: the DNA double helix —the mapping of the genome, the twisted double strand of DNA that carries the instructions for making every cell in the human body armed with blueprints for human genes, can identify the individual molecules that make us susceptible to a particular disease as among others is thyroid disease.[1]

The spectrum of clinical thyroid disease influenced by genetic factors runs from congenital hypothyroidism and thyroid agenesis, through transient gestational hyperthyroidism and autoimmune thyroid disease (AITD) with basis of germ line which is inherited and others that are inherited as complex multigenic traits such as Graves' disease.[2] Graves' disease owes its name to the Irish doctor Mathew Graves , who described a case of goiter with exophthalmos in 1835. However, the German Karl Adolph von Basedow independently reported the same constellation of symptoms in 1840. As a result, on the European Continent the term Basedow's disease is more common than Graves' disease. Graves' disease (GD) is an organ-specific autoimmune thyroid disorder characterized by hyperthyroidism, various degrees of diffuse goiter, ophthalmopathy, and, less commonly, pretibial myxedema. The etiology of GD is incompletely understood, but seems to involve complex interactions among genetic, environmental, and endogenous factors. The importance of genetic factors is evident from clustering of GD within families, and the limited twin data available suggest a higher concordance rate for GD in monozygotic (MZ) than in dizygotic (DZ) twins but 79 percent of the liability to clinically overt GD is attributable to genetic factors.[3] The trigger of Graves' disease in persons with genetic susceptibility to the disease includes stressful life events, infection, and

recent childbirth and a family history of thyroid disease, especially in maternal relatives, is associated with an increased incidence of Graves' disease and a younger age at onset.[4]

GENETIC EPIDEMIOLOGY

Twin studies show increased concordance of GD in MZ twins compared with DZ twins. Some early observations reported the prevalence of GD in a sibling of an affected GD proband as between 4 and 13 percent.[5] A measure of the heritability of a disorder can be gained from the ratio of the risk to a relative of an affected proband compared with the background population prevalence. A study by Stenzky et al.[6] done in Hungary, the country of which the background population prevalence was known, allows the calculation of the siblings for GD. In this study, 23 of 435 (5,3%) GD probands had siblings with GD, compared with a background population frequency of GD of 0.65 percent. This allows estimation of the siblings for GD as 8.1 in the Hungarian population. The slight excess of GD cases among parents and offsprings compared with sibs may reflect the effects of dominant genetic loci, or simply that the disease penetrance is greater in parental generations.

The first genome screen for AITD was completed by Tomer, Davies and coworkers using a cohort of 56 multiplex AITD families of various ethnic backgrounds.[7] This study has found significant evidence for linkage GD at one locus on chromosome 20 (20q11.2) and suggestive evidence for a further five loci (two for GD alone, two for Autoimmune Hypothyroidism and one for AITD). The chromosome 20 locus, named by the investigators as GD2, shows a multipoint limit of detection (LOD) score of 3.5 for GD under a recessive model which was greater than previous determination. Whole genome screening is a powerful tool, as it enables scanning the whole human genome for a disease gene without any prior assumptions on disease pathogenesis. Whole genome screening by linkage is performed by testing a panel of markers that span the entire human genome for linkage with a disease in a dataset of families in which the diseases aggregate. Since linkage spans large distances, one can scan the entire human genome by linkage using approximately 400-500 polymorphic markers at an average inter-marker distance of 10-20 Mb.[8] If one or more markers in a certain locus show evidence for linkage, this locus may harbour susceptibility genes for the disease studied. Recent advances have made it possible to efficiently identify complex disease genes. It became apparent that most complex diseases are influenced by numerous genes that interact with each other, in complex ways. Using both the candidate gene approach and whole genome linkage studies, six AITD susceptibility genes have been identified and confirmed: HLA_DR, CD40, CTLA-4, protein tyrosine phosphatase-22 (PTPN22), thyroglobulin (Tg) and thyroid-stimulating hormone receptor (TSHR). These genes are part of the immunological synapse, as receptors (HLA-DR, CD40, CTLA-4) or signalling pathway molecules (PTPN22), or in the form of presented peptides (Tg and TSHR).[9] The immunological synapse is a complex of molecules that orchestrate the stimulation of a T cell, by antigen-presenting cell (APCs), and it is the fundamental structure that activates the adaptive immune response. The abnormalities of the immunological synapse play a major role in the initiation of thyroid autoimmunity, and perhaps autoimmunity in general.[10]

MHC

MHC, major histocompatibility complex, which contains the human leucocyte antigen (HLA) genes, is located on chromosome 6p21.[7] It is subdivided into three regions: 1) the class I region, which encodes HLA antigens A,B and C; 2) the class II region, which encodes HLA antigens DR, DQ and DP, each with one or more á and ß chains; and 3) the class III region, encoding several immuno-regulatory molecules including complement components, heat shock protein70 (HSP70), and TNF. The class II region also contains the peptide transporters associated with antigen processing (TAP) and large multifunctional protease (LMP) genes. Tight linkage disequilibrium exists between the alleles of the MHC region. The MHC class II molecules play a critical role in the initiation of adapted immune responses. Peptide antigens can only be recognized by T cell receptors when they are attached to the binding groove of an MHC molecule on the surface of an antigen-presenting cell. This, together with the presence of several other immuno-regulatory genes in the region, makes the MHC a strong candidate locus for AITD and other autoimmune diseases[5] and Grumet et al. first showed the association between GD and the alleles of MHC class I, with a higher frequency of HLA-B8 in GD patients (47%) compared with controls (21%).[11] However, a stronger association of GD was found with the MHC class II allele, HLA-DR3 which is in strong linkage disequilibrium with HLA-B8.[12] In non-white populations, GD has been found to be associated with different HLA alleles. GD has been shown to be associated with HLA B35, B46, A2 and DPB1*0501 in

Japanese,[13] and B46, DR9, DRB1*303 and DQB1*0303 in Hong Kong Chinese.[14]

CD40

CD40 signaling cascade has been shown to play a role in a number of autoimmune conditions. It has been identified CD40 as a novel susceptibility gene for GD. It is the first GD-specific gene.[9] Linkage study performed showed that the CD40 gene locus was linked and associated with GD. Sequencing the entire CD40 gene led to the identification of a C/T polymorphism, at the 5' untranslated region (UTR) of CD40, with the CC genotype of this SNPs which was strongly associated with GD.[15]

AN END ROAD OR NEW HORIZON?

The familial occurrence of GD was first reported more than a century ago [(16)]. The past few years have witnessed significant advances in understanding of the genetic contribution to the etiology of autoimmune thyroid disease (AITD) including GD. Important genes in AITD in 2007 :

• Class 1~consistently found: HLA class II, CTLA-4, PTPN22, Thyrotropin receptor
• Class 2~strong evidence building: Thyroglobulin, CD40, CD25 and FCRL3.

It is likely that there are 20 or more genes contribution for GD. There are many reports of important additional sites. Many genes are at work, but major genes those essential to disease development, do not appear to be involved. This multitude of genes, both thyroid disease specific and non-specific genetic influences are involved in the evolution of these disorders. The thyroid-specific genes may include thyroglobulin and thyrotropin (TSH) receptor. The non-specific genes appear to be primarily immune related or influence signal transduction. One of the most looked for pieces of evidence to sustain validity in genetics of GD is reasonable, but the complexity of their analysis and the high cost of these studies have raised more problems,[17] while the Really Significant Genes (RSGs) never exist. Is this an end road?

Maybe it is not ! To understand the disease is strongly needed, particularly in the making effort of prevention. Genes should be strongly linked within families and they could become clinically useful as predictors of disease. Proceeding to understand how these gene associations translated and linked into disease with the role of the environment in disease development is highly required. To decide the importance of the environment in GD and the mechanisms involved is going to be a big challenge, and the genetic contribution in Graves disease will not be a lost concept.

CONCLUSION

The development and the subsequent course of Graves' disease are greatly influenced by heredity. Because there are a number of genetic loci that may contribute to GD susceptibility, it is often referred to as polygenic disorder. The search for thyroid specific genetic susceptibility has led to only small influences exerted by polymorphisms. More things remain to be learned about thyroid disease specificity in genetic susceptibility including its connection with environment.

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