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Hashimoto's Disease

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1. Introduction

The thyroid gland is one of the largest endocrine glands. It is prone to several very distinct pathologies, some of which are extremely common such as autoimmune thyroid diseases (AITDs). AITDs are conditions in which the immune system attacks the body's own thyroid gland which leads to a deregulation in thyroid hormones production. Because these hormones are used almost everywhere in the body, AITDs can have widespread, serious effects and many symptoms. AITDs can be broken down into two classes: i- Graves' disease (GD) characterized by hyperthyroidism and ii-Autoimmune Hypothyroidism, where the major clinical form is Hashimoto's thyroiditis (HT). In HT, the antibodies against thyroid peroxidase or thyroglobulin appear characteristically in the patients' sera, while tissue damage due to T cell-mediated cytotoxicity usually contributes to gradual development of hypothyroidism.

HT, described by Hakaru Hashimoto in 1912, is a common autoimmune disease, afflicting up to 10% of the population (Canaries et al., 2000). However, its etiology is still unknown. In fact, although environmental factors, such as infection, certain drugs, stress, smoking, can play a role in their progression, the HT- as AITDs - is generally hereditary in origin. Comprehension of physiopathological mechanism behind has been improved over the last few decades. In the literature, a number of excellent reviews have been published on the genetic background of AITDs (Eschler et al., 2011; Hadj Kacem et al., 2009). However, there is still a paucity concerning HT. Several parameters have contributed to this paucity. Some of them are general for AITDs such as genetic heterogeneity; others are rather specific to HT mainly clinical heterogeneity and diagnostic difficulties. This chapter examines the recent progress in our understanding of the genetic and environmental contributions to the etiology of Hashimoto's thyroiditis. We will also focus on epidemiology, clinical progression and physiopathological mechanism of the disease. We will shed light on our findings concerning a Tunisian multigenerational family "Akr" (Maalej et al., 2001a) which has benefited from a regular clinical follow-up, a complex segregation analysis as well as a genetic investigation using both genome screening and candidate genes approaches.

2. Epidemiology

Hashimoto's thyroiditis is a common form of chronic AITDs. The disorder affects from 2% (Wang et al., 1997) up to 10% (Canaries et al., 2000) of the general population. It is more

common in older women and ten times more frequent in women than in men (Tunbridge et al., 2000). Based on TSH (thyroid stimulating hormone) levels or anti-thyroid auto antibodies, a population-based prevalence study has reported prevalence of 3.6% and 8.8% respectively (Tunbridge et al., 1977). In the United States, Hollowell and collaborators (2002) found that 4.6% of the population had hypothyroidism and 13.0% had anti-thyroid peroxydase auto antibodies.

In Tunisian population, a study performed on 1076 patients who resorted to the Department of Endocrinology of Sfax, Hédi Chaker Universitary Hospital at Sfax, found that prevalence of HT was 22.8% (Chabchoub et al., 2006). This high value could be explained by the fact that this study has assed sedan oriented demand. In a district from the central east of Tunisia, where "Akr" family members live, the prevalence and incidence of AITDs were 4.36% and 7.2 per 1000 inhabitants per year respectively. Particularly, the prevalence of autoimmune hypothyroidism was 2.13% (Bougacha-Elleuch et al., 2011).

3. Etiology

HT results from a complex combination of genetic, environmental, and endogenous factors which interplay to initiate thyroid autoimmunity.

3.1 Environmental factors

Several environmental factors are thought to affect the incidence and the progression of HT disease. Thus, recent studies have shown the close relationship between either excessive iodine levels (Camargo et al., 2006; Doğan et al., 2011; Teng et al., 2011) or Selenium deficiency (Toulis et al., 2010) and HT. High levels of several chemical agents have also been implicated in the incidence of goiter and autoimmune thyroiditis (de Freitas et al., 2010). Moreover, the components of several viruses (hepatitis C, human parvovirus B19, coxsackie and herpes viruses) were detected in the thyroid of Hashimoto's thyroiditis patients (Mori & Yoshida 2010). Moreover, the possible involvement of the oxidative stress profile in HT pathogenesis was also reported (Baskol et al., 2007; Lassouad et al., 2010).

3.2 Epigenetic factors

Using disease discordant twin pairs, Brix and collaborators have found that the frequency of skewed X chromosome inactivation in female twins with HT was 31% (vs 8% in control population) (Brix et al., 2005). In Tunisian population, findings reported by our team suggest a possible role for X chromosome inactivation mosaicism in the pathogenesis of AITDs (GD and HT) and may, to some extent, explain the female preponderance of these diseases (Chabchoub et al., 2009).

3.3 Endogenous factors

HT could be considered as a "sex realated disease", since women are more susceptible to develop HT than men. Indeed, the Sex ratio is 7F/1M (Duron et al., 2004), with an incidence of 3,5 cases per 1000 woman in year vs 0,8 cases per 1000 men per year (vanderpump et al.,1995). The importance of pregnancy and postpartum thyroiditis in autoimmune thyroiditis is well-established (Friedrich et al., 2008).

3.4 Genetic susceptibility to HT

Evidence for genetic susceptibility to HT is strongly shown by epidemiological data from family and twin studies.

3.4.1 Family studies

The familial occurrence of AITDs (HT and GD) has been reported by investigators for many years (Hall & Stanbury, 1967; Martin, 1945). One of the large multiplex families in the world was reported in Tunisia (Akr family) (Maalej, A. et al. 2001a). The high prevalence of both GD and HT, found in the "Akr" family (17.5%), is another argument to the contribution of genetic factors in HT pathogenesis.

3.4.2 Sibling risk ratio (λs)

The λs is a useful quantitative measure of the heritability of a disease, with a λs greater than 5 usually indicating a genetic influence on the etiology of the disease (Risch, 1990; Vyse & Todd, 1996). The risk in siblings of parents with AITDs was estimated to 28.0 for HT, giving evidence for a strong genetic component (Villanueva et al., 2003).

3.4.3 Twin studies

The use of twins is a well-established method to investigate the relative importance of genetic and environmental factors to traits and diseases (MacGregor et al., 2000). Thus, for HT, the concordance rates were 55 and 0% for Monozygotic and Dizygotic twins, respectively (Brix et al., 2000). Concerning anti thyroid antibodies, monozygotic twins had 80% concordance, and dizygotic twins had only 40% concordance (Brix et al., 2000).

4. Physiopathology

It is well known that HT results from a multistep process, requiring several genetic and environmental abnormalities to converge before disease development. Thus, thyroid follicle damage may be provoked by self-antigen presentation by antigen presenting cells and specific T lymphocyte activation. On the other hand, toxic destruction of thyroid cells possibly through the generation of oxygen radicals may participate in eclosion of autoimmunity (Bagchi et al., 1995). Both proliferation and apoptosis are involved in the pathogenesis of HT. Analysis of the mechanisms by which such autoimmune pathology arises has been facilitated by the use of animal models. These include the Obese Strain (OS) chicken and the BioBreeding (BB) and Buffalo rats as spontaneous models of HT. HT can also be experimentally induced by specific immunization protocols with target auto antigens or elevation of dietary iodine.

4.1 Autoimmunity in HT

HT is considered to be a th1-mediated disease leading to aberrant infiltration of lymphoid cells and destruction of thyroid follicles (figure1). The final outcome is fibrosis replacing normal thyroid parenchyma and hypothyroidism resulting of thyroid cell destruction (Parish & Cooke, 2004). Indeed, a central phase of HT is characterized by an apparent uncontrolled production of auto reactive CD4+ T cells, CD8+ cytotoxic T cells and

immunoglobulin G auto antibodies. This immunological synapse is defined by the interface between antigen presenting cells and T-cells that is formed during T-cell activation (Chistiakov, 2005). On the other hand, existence of naturally existing CD4+ CD25+ foxp3+ T regulatory cells influencing thyroiditis development in naïve susceptible mice was recently demonstrated. Moreover, it has been shown that naturally T regulatory cells are required for induction of antigen specific tolerance, indicating that induced Murine experimental autoimmune thyroiditis tolerance is a result of activation of naturally existing T regulatory cells rather than de novo generation of induced T regulatory cells (Morris et al., 2009).

Interestingly, several of the AITDs susceptibility genes participate in the immunological synapse, suggesting that abnormalities in antigen presentation are important mechanisms leading to AITDs (Tomer, 2010).

Initially, the production of self-reactive cells and auto antibodies occurs in the draining lymph nodes. Later, the lymphoid tissue often develops directly in the thyroid gland itself. This tissue is generally very well-organized, with cords of anti-Tg-antibody- producing plasma cells in the periphery (Chistiakov, 2005). In a final, destructive step of HT, the auto reactive T cells diffusely accumulate in large numbers and infiltrate thyroid parenchyma. This phenomenon will determine clinical phenotype of the disease. In the BB-DP rat model, Th1-mediated mechanisms involving production of IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ play a major role in the destruction of thyrocytes (Blüher et al., 1999a; Mooij et al., 1993). Furthermore, it has been recently shown that pro-IL18 is constitutively expressed in thyroid cells and IL18 up regulation by INF-γ is an immunological feature of HT patients with an important role in promoting the local immune response (Liu et al., 2010).

4.2 Apoptosis in HT

Apoptosis appears to play a major role in the final stage of the disease (figure1). In fact, apoptotic molecules such as Fas and Fas ligand (FasL) expression was higher in rats with lympholytic thyroiditis indicating a possible role in thyrocyte death (Blüher et al., 1999b). Theses molecules are expressed at low level by normal thyroid cells compared to patients with HT with an increasing number of apoptotic cells (Kaczmarek et al., 2011). The mechanism and regulation of apoptosis in thyroid gland are still little known. The most studied receptor mediated apoptic pathway is the Fas/Fas ligand system. Fas is substantially expressed on lymphocytes. Fas-Fas ligand interaction could lead to the thyrocyte cell death (Kaczmarek et al., 2011). Thyroid cells express constitutively Fas but these latters are normally unaffected by Fas-mediated apoptosis. In contrast, they can be sensitised to Fas-induced destruction under certain pathologic conditions such as the release of IFN-γ, TNF-α and IL-1β, by infiltrating immune cells (Giordano et al., 2001). Over the past few years, many reports have shown that mobilisation of the Fas/Fas ligand apoptotic pathway by proinflamatory cytokines plays a pivotal role in the devastation of thyroid follicular cells in HT leading to hypothyroidism. (Kaczmarek et al.,2011). Therefore, the Fas pathway is the most important mechanism of Tlymphocyte mediated apoptosis. It is just possible that this process plays an essential role in the pathogenesis of Hashimoto thyroiditis, because cytotoxic T lymphocytes are fully present in the thyroid in places where apoptosis is located (Mitsiades et al ., 1998 ; Fountoulakis et al., 2008; Chen el al ., 2004; Baker., 1999; Bretz.,2002).

Mechanisms of regulation of this pathway include probably changes in Fas expression level, and the expression of molecules that promote survival, including the Bcl-2 gene family

(Bretz et al.,1999; Mitsiades et al.,1998). This latter antiapoptotic protein and sFas system, which normally protect thyroid cells from apoptosis, are decreased in the thyroid cells of patients with HT, creating a proapoptotic phenotype (Fountoulakis & Tsatsoulis, 2004). Thus, the rate of thyrocyte apoptosis dictates the clinical outcome of thyroid autoimmunity. Though rare in normal thyroid, it markedly increases during HT, but not in GD with a divergent phenotype. Therefore, regulation of thyrocyte survival is a crucial pathogenic determinant via the balance between Th2 and Th1 response (Chistiakov, 2005).

Despite the "crucial" role played by these apoptotic molecules, they are poorly investigated in HT pathogenesis at the genetic level. Therefore, arguments of their "real" implication in HT are still missing.

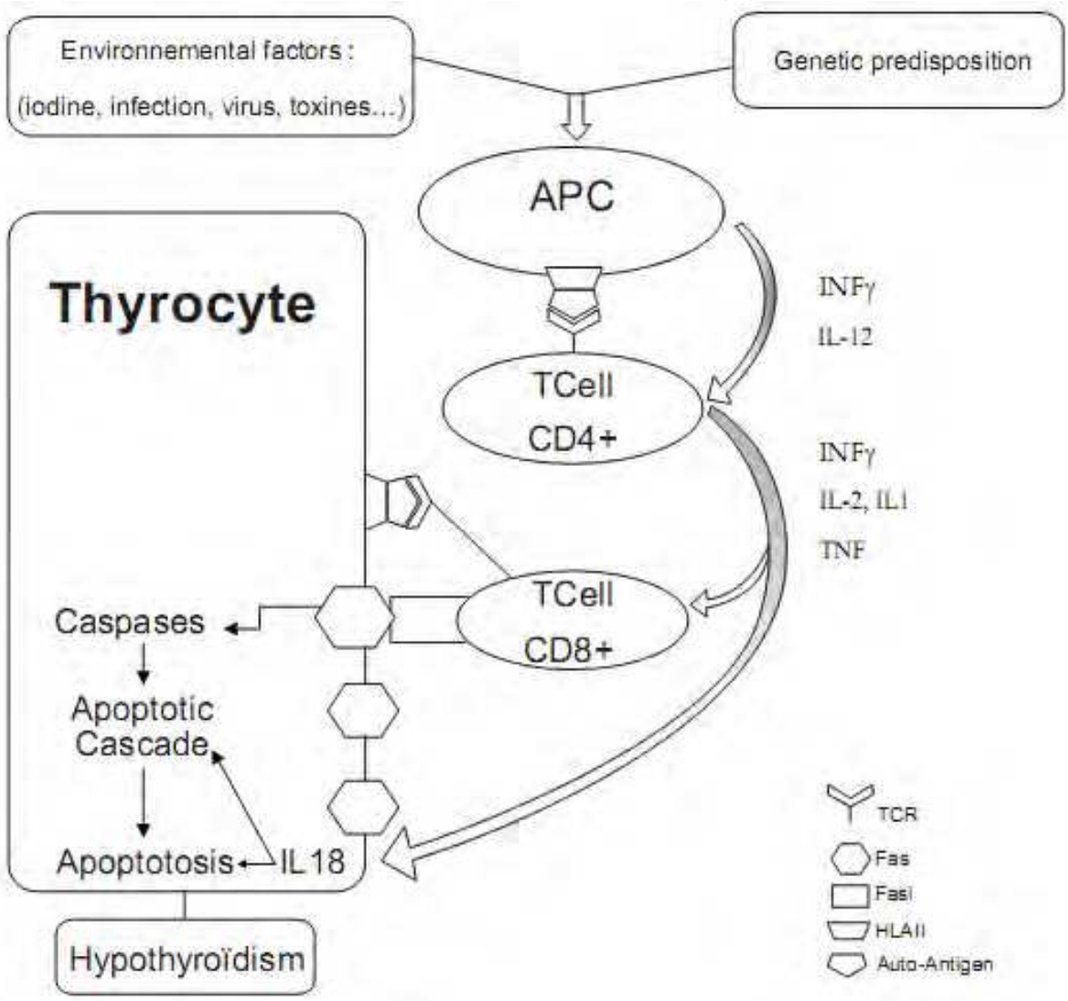


Fig. 1. Autoimmune events in Hashimoto's thyroiditis.

At the onset of disease, (HLA) class II-positive Antigen-presenting cells (APC), present thyroid-specific autoantigens to the naïve T cells, leading to the maturation of autoreactive T cells. Interaction with auto antigen leads to the production of different cytokines inducing T-helper type 1 (Th1)-mediated cell immune response. The stimulation of the Fas/Fas ligand apoptotic pathway by pro-inflammatory cytokines is the most important mechanism of

T lymphocyte mediated apoptosis. The caspase cascade ultimately induces enzymes that progressively destroy the cell, leading to thyroid cell death and hypothyroidism

5. Clinical data

HT occurs especially during the decades from 30 to 50 but no age is exempt, although the prevalence increases with age (Akamizu et al.,2008) The Sex ratio is 7F/1M, (Duron et al.,2004), with an incidence of 3.5 cases per 1000 women per year vs 0.8 cases per 1000 men per year (Vanderpump et al.,1995).

This disease is primarily associated with symptoms of altered thyroid function. Early in the course of the disease, the patient is usually euthyroid, but may show clinical hyperthyroidism, due to the inflammatory breakdown of thyroid follicles with release of thyroid hormones. Thyrotoxicosis may be present in 20% of patients when first seen (Akamizu et al.,2008),or commonly develop over a period of several years. In contrast, late in the disease, the patient is often hypothyroid because of progressive destruction of the thyroid gland. The most common eventual outcome of HT is hypothyroidism (Bottazzo & Doniach 1986).

In HT, the association of goiter with hypothyroidism is the most frequent condition of the diagnosis. Most often the gland is hypertrophic; two to four times the normal size, firm and nubbey. It is usually symmetrical, although much variation in symmetry can occur (Duron et al.,2004). Ultrasound may display an enlarged gland with normal texture, a characteristic picture with very low echogenity, or a suggestion of multiple well-defined nodules (Pedersen et al., 2000).

The goiter of HT may remain unchanged for decades (Akamizu et al., 2008), but usually it gradually increases in size. However, in some cases there is an involution of the goiter with evolution. Hence, the two major forms of the disorder are goitrous and atrophic autoimmune thyroiditis. A fast increase of the volume of the goiter and a very firm consistence of a fibrous goiter in aging patients, have to be taken with particular attention due to possible existence of a malignancy or a thyroid lymphoma (Duron et al., 2004).

Generally the progression from euthyroidism to hypothyroidism has been considered an irreversible process due to thyroid cell damage and loss of thyroidal iodine stores. However, it is now clear that up to one-fourth of patients who are hypothyroid may spontaneously return to normal function over the course of several years. This sequence may reflect the initial effect of high titers of thyroid stimulation blocking antibodies which fall with time and allow thyroid function to return (Takasu et al., 1992). Progression from subclinical hypothyroidism (normal FT4 but elevated TSH) to overt hypothyroidism occurs in a certain fraction (3-5%) each year. In Akr family, 11 patients (30%) had subclinical hypothyroidism (unpublished results).

Various auto antibodies may be present in sera of patients with HT: anti-thyroid peroxidase antibodies and, less frequently, anti-thyroglobulin antibodies. These later are positive in about 80% of patients and their prevalence increases with age. Anti- thyroid peroxidase antibodies are positive in 90% of patients; their frequency is higher in women and aging subjects. If both anti-thyroglobulin and anti-thyroid peroxidase antibodies are measured, 97% are positive. In contrast to the anti-thyroglobulin antibodies, the presence of anti-thyroid peroxidase antibody is correlated with the occurrence of hypothyroidism (duron et al.,2004).

The titles of anti -thyroid peroxidase antibodies are typically higher in atrophic form than in goitrous one.Young patients tend to have lower or occasionally negative levels. In this age group, even low titles evolve the presence of thyroid autoimmunity (Akamizu et al., 2008).

In the Tunisian study achieved by our group, 70 patients belonging to "Akr" famiy, were included. This family is actually composed of about 400 members with high level of consanguinity (60.5% vs 38.3% in controls from the same region) (Bougacha-Elleuch et al., 2011). Among these patients, 63 have benefited from a regular clinical follow up during these two last decades. Strikingly, we have found in this large family a co segregation of the two AITDs: 38 cases of HT (60.3%) and 25 cases (39.6%) of GD. Given the genetic predisposition of AITDs in this large family and occurrence of HT precisely at later ages, 115 healthy members of "Akr" family were carefully followed up by physicians, during 2 decades. We have found that 13 subjects (11,3%) developed AITDs. HT was seen in 77% of the cases while GD was found in only 23% (Charfi et al., 2009). In these patients, HT was in a hyperthyroid state in 13. 6% vs only 5% in literature (Duron et al., 2004)

6. Genetic susceptibility to HT

In complex diseases such as HT, it's well-established now that genetic susceptibility exists and represents an important piece in the general puzzle. However, determining both the "true" involved genes and the importance of contribution of each gene in the physiopathology of the disease, remains a laborious task which is not achieved yet.

To dissect the genetic component of HT, the major technologies used were mainly candidate gene analysis and whole-genome linkage screening. However, and unlike GD, at the genetic level, HT was poorly investigated as an individualized clinical entity. A general methodological problem has been disease definition. Indeed, HT encompasses a spectrum of manifestations, ranging from the simple presence of thyroid auto antibodies to the presence of goitrous or atrophic thyroiditis, characterized by gross thyroid failure (Davies et al., 1993). A second problem is lack of families composed only of HT patients. Thus, in most studies, AITDs are explored as a whole and in a second step, HT is considered aside. This situation is well encountered in genome scans where the investigated families usually comprise both GD and HT patients. This approach may identify more easily the common than the specific HT or GD gene susceptibility.

Another issue in genetic investigation of complex diseases such as HT, is search of a major gene in the general genetic entity. Possible existence of such a major gene could be evidenced by a particular type of statistical analysis: ie complex segregation analysis.

In our previous work, we have analyzed genetic susceptibility of AITDs (HT and GD) at the two levels: i-determination of involved genes using the two complementary approaches: ie whole genome screening and candidate genes analysis and ii- complex segregation analysis to search for possible major genes. In the following sections, we will focus on our findings concerning HT.

6.1 Dissection of genetic susceptibility

6.1.1 Whole genome screening

Genome-wide linkage analysis was the first approach employed to screen the genome for the genetic contribution to AITDs and particularly HT. Thus, the first genome linkage scan

in AITDs was performed in 1999. There were two areas of linkage to HT, designated HT-1 and HT-2 on chromosome 13q32 and 12q22, respectively (Tomer et al., 1999). Since, many genome screenings were conducted and revealed regions with suggestive linkage (MLS<3.3), except the chromosomal region 8q23-q24 which has given a value of MLS=3.77 (Reviewed in Hadj Kacem et al., 2009). Therefore, it could be considered as "significantly linked" to HT. Indeed, according to Lander and Kruglyak, in complex diseases (such as HT) a lod score of >1.9 is suggestive of linkage, while a lod score of >3.3 indicates significant linkage in studies using the parametric approach. Linkage is confirmed if evidence for linkage is replicated in two separate data sets (Lander & Kruglyak, 1995).

Among linked regions, only 12q22 and 8q23-q24 were replicated. If we examine these replications, we will find that for the first region (12q22), we could not consider that replication was done in two separate data sets, since the second data set already contains the first one (Tomer et al., 2003; 2007). Concerning the second region (8q23-q24), replication was rather reported with AITDs and not HT (Tomer et al., 2002). In Tunisian population, genome screening, performed on Akr family, has revealed a genetic linkage of AITDs as a whole with the chromosomal region 2p.21. There were no regions linked to HT (Maalej et al., 2001a).

6.1.2 Candidate genes

Candidate genes analyzed in HT can be classified into two groups: (i) immune regulatory genes (MHC, CTLA-4, PTPN-22, cytokines..) and (ii) thyroid-specific genes (Tg, TPO, PDS..). Investigation of these genes in HT pathogenesis was done (for most of them) since they are functional candidates (they are selected by virtue of their physiological functions as possible contributors to disease pathogenesis). Among these genes, there are only two (CTLA-4 and Tg genes) which are both functional and positional genes (Table 1). In fact, they are localized in chromosomal regions found linked using the genome scan approach (2q33 and 8q23 respectively). At the statistical level, these two regions share a significant value of lod score (MLS= 4.2 and 3.77 for 2q33 and 8q23 respectively) (reviewed in Hadj Kacem et al., 2009).We have to get in mind that the chromosomal region 2q33 (harboring CTLA-4 gene) was linked with positive antibody rather than HT.

On the other hand, what we can note is that genetic associations reported with candidate genes were less definitive than in GD. Indeed, genetic investigation of AITDs since early 1990, has given arise to “significantly associated genes” either with AITDs or GD, but not HT. This could be explained by limited investigated samples. Thus, until now, there is no consortium in HT.

In table 1, we have only reported candidate genes which have been associated with HT and for which, potential mechanisms were proposed. In this regard, genes showing no association were not included. Potential mechanisms of associated genes variants were proposed by authors. They mainly involve higher production of either anti-thyroid antibody or the protein encoded by the gene itself. What we can note is that explored candidate genes are mainly those of immunoregulatory pathway. However, genes involved in apoptosis are poorly studied in HT in spite of their functional involvement in thyroid destruction in HT.

Gene	Chromosome	Associated variant (p<0.05)	Populations showing association	Potential mechanism	References
Immunoregulatory genes					
MHC classI genes (HLA-A, B, C)	6p21	A2, B16,B35, B46,B51,B54,C3	Asians		Chistialov, 2005
		A2-B50	Tunisian**		Bougacha-Elleuch et al., 2004
MHC classII genes (HLA-DP, DQ, DR)		DR3, DR4,	Caucasians	direct thyroid auto antigen presentation	Tandon N et al. 1991;
		DRw53	Japanese		Honda K et al. 1989
		DR9	Chinese		Hawkins et al; 1987
		DQw7 (DQB1*0301)	Caucasians		Badenhoop et al; 1990
		DRB1*04, DQB1*03	Caucasians		Zeitlin et al., 2008
		DR11, DR12	Tunisian**		Bougacha-Elleuch et al., 2004
CTLA-4*	2q33.2	-318C/T	Caucasians (Slovenians)	Higher thyroid autoantibody concentrations	zaletel et al., 2006
		49A/G	Caucasians (Slovenians)		
		CT60	Caucasians	reduced production of soluble CTLA-4	Udea et al., 2003
PTPN22	1p13	1858C/T	Slovenians (children)	Inhibition of T cell activation	Dallos et al., 2008
		R620W	Caucasians	Higher thyroid auto antibody concentrations	zaletel et al., 2010
IFN-gamma	12q15	874A/T	Japanese	High producing IFN gamma	Ito et al., 2006
			Indian		Rekha et al., 2006

Gene	Chromosome	Associated variant ($p<0.05$)	Populations showing association	Potential mechanism	References
TGF	19q13	869T/C	Japanese	Suppression of cytotoxic T cells actions and IFN-g expressions leading to thyroid destruction in HT	Yamada et al., 2008
IL6	7p15.3	-572 C/G	Japanese	High producing IL6	Inoue et al., 2011
IL4	5q31.1	-590C/T	Japanese	higher activity of inflammatory Th1 cytokines and more rapid progression of thyroid destruction	Nanba et al., 2008
TNF	6p21	-308A/G	Tunisian**	high constitutive and inducible levels of the TNFα chain	Bougacha-Elleuch et al., 2004
		−1031C/T	Japanese	high TNF-α production	Inoue et al., 2009
Thyroid specific genes					
Tg	8q24.22	Tgms2	Japanese	Interaction between HLA-DR3 and Tg polymorphisms	Ban et al., 2004
PDS	7q31	D7S2459	Tunisian	Low level of gene expression and/or protein activity in the thyroid tissue	Hadj-Kacem et al., 2003

*: Candidate genes harbored in linked regions found by genome scans.
**: The studied sample in Tunisian population is "Akr" family

Table 1. Functional and positional candidate genes associated with HT pathogenesis.

6.1.2.1 Immune regulatory genes

6.1.2.1.1 HLA

Data on HLA haplotypes in HT have been less definitive than in GD. In patients with HT, HLA associations have been found with the HLA'DR4' haplotypes (Tandon et al., 1991). Interestingly, it was shown that substitution of the neutral amino acids Ala or Gln with arginine at position beta 74 in the HLA-DR peptide-binding pocket is a key to the etiology of both GD and HT (Ban et al., 2004; Menconi et al., 2008).

In the Tunisian "Akr" family, using transmission disequilibrium test, we have reported a genetic association of AITDs with HLA-B37and HLA-DR11 alleles (Elleuch-Bougacha et al., 2001). Sequencing of the rare allele HLA-B37 in Akr family, has given evidence that it is not a new variant, but rather the known subtype HLA-B37*01 (unpublished results). In a second step, investigation of MHC (class I, II and III) genes polymorphisms has shown that TNF-308 A/G polymorphism was involved in GD and HT with different alleles.

Thus, TNFA allele was associated with GD, whereas TNFG, HLA-DR11 and DR12 were rather implicated in HT pathogenesis giving evidence for particular component for each disease (GD or HT) (Bougacha-Elleuch et al., 2004).

6.1.2.1.2 CTLA-4 gene

CTLA-4 (cytotoxic T lymphocyte-associated 4) is a cell surface immunoglobulin like receptor involved in the regulation of T-lymphocyte activation. CTLA-4 gene polymorphisms have been shown to be associated with a variety of autoimmune conditions. The most consistent reported association was with AITDs (Taylor et al., 2006). A recent investigation of patients with HT provided evidence that -318C/T promoter, 49A/G exon 1 and CT60 CTLA-4 gene SNPs were associated with higher thyroid autoantibody concentrations (Zaletel et al., 2006; 2010). In "Akr" family, CTLA-4 gene did not reveal any associated variant with HT (Maalej et al., 2001b).

6.1.2.1.3 PTPN22 gene

The PTPN22 (protein tyrosine phosphatase N22) molecule is involved in the activation of both naïve and activated T cells. The association of PTPN22 1858C/T polymorphism with HT is much weaker than the association with GD (Kahles et al., 2005). T-allele carriers were reported to be at particularly high risk of developing HT (Dultz et al., 2009). In a recent study performed in Japanese population, a novel protective effect of a haplotype containing five SNPs in this gene was observed for HT (Ban et al., 2010).

In Akr family, stratifying patients according to their phenotype (HT) did not show any significant association with PTPN22 R620W allele (Chabchoub et al., 2006).

6.1.2.1.4 VDR gene

VDR (vitamin D receptor) plays an immunoregulatory role based on the fact that the activation of human leucocytes causes the expression of VDR. The VDR gene, lies on chromosome 12q12-14 and harbors several polymorphisms and was found to be associated with several autoimmune diseases, (Huang et al., 2002; Mc Dermott et al., 1997; Pani et al., 2000; 2002)

Our previous results, in Tunisian population, showed no significant association of the Vitamin D receptor gene polymorphisms with HT in the "Akr" family (Maalej et al. 2008).

6.1.2.1.5 Cytokine genes

Local release of cytokines within the thyroid gland is important in regulating antigen presentation and lymphocyte trafficking by enhancing the expression of MHC class II and adhesion molecules on thyroid follicular cells (Kelso, 1998)

Studies, interested in cytokine gene polymorphisms with HT, are limited in literature. Thus, Ito C and collaborators (2006), have reported that the +874A/T polymorphism in the IFN-gamma gene was associated with severity of HT. Moreover, a significant association between high IFN-gamma-producing genotype TT (+874 A/T) and HT was found (Rekha et al., 2006). A recent study, exploring IL-1B, IL-1RN, IL-6 and TNFA genes polymorphisms, has given evidence that only IL-6 gene promoter (-572) C/G polymorphism could represent a potential "candidate" genetic marker to predict an individual's susceptibility to HT (Chen et al., 2006). It has been later revealed that the IL6-572G allele carriers, which have higher producibility of IL-6, were more frequent in severe HT (Inoue et al., 2011). Concerning IL4 gene, it was shown that the-590CC genotype appears to be a strong predictive factor for the development of hypothyroidism in HT (Nanba et al., 2008).

In "Akr" family, investigation of IL-1RN VNTR, IL-1B-511 C/T and IL-1A-889 C/T SNPs in the IL1 gene cluster and TNFRI ((GT)17 (GA)n microsatellite marker has not revealed any association with HT (Kammoun-Krichen et al., 2007; 2008).

6.1.2.2 IDDM6 locus

The IDDM6 locus (on 18q21 chromosome) was found to be linked to many autoimmune diseases: (Davies et al., 1994), (Cornelis et al., 1998), (Shai et al., 1999) (Vaidya et al., 2000), providing evidence that it is likely to harbor important autoimmunity loci. This locus was also examined in "Akr" family. Genetic linkage was found associated with both AITDs and HT (Hadj kacem et al., 2006) confirming again its key role in autoimmunity.

6.1.2.3 Thyroid specific genes

6.1.2.3.1 Thyroglobulin gene

Genetic-linkage studies have reported chromosome 8q24, containing the thyroglobulin (Tg) gene, as a susceptibility locus for AITDs in two different family samples (Sakai et al. 2001; Tomer et al., 2002). Later, association of the thyroglobulin intragenic marker (Tgms2) was found with HT (Ban et al., 2004). In a previous study, our group has examined the genomic region (11.5 cM) containing the Thyroglobulin gene by genotyping seven microsatellite markers and four SNPs in "Akr" family. Analysis of data did not show linkage of the Thyroglobulin gene with AITDs nor did analysis of HT and considered separately (Belguith-Maalej et al. 2008).

6.1.2.3.2 PDS gene

The PDS gene (7q31), responsible for Pendred syndrome (congenital sensorineural hearing loss and goiter), encodes a transmembrane protein known as pendrin (Everett et al., 1997). Pendrin functions as a transporter of iodide and chloride (Scott et al., 1999). In the Tunisian population,

PDS gene was reported to be associated with sporadic HT (goitrous and non goitrous forms) patients. In "Akr" family, there was an absence of linkage between HT and the PDS gene which could be explained by the reduced number of patients in the studied sample or by the weak contribution of the PDS gene in HT development (Hadj Kacem et al., 2003).

6.2 Complex segregation analysis

This kind of analysis aims to foresee whether the genetic susceptibility of complex diseases is governed by either a major gene or several minor genes. In AITDs, two previous studies have reported evidence for genetic transmission of thyroid peroxidase auto antibodies in old order Amish families using the Pointer program (Jaume et al., 1999; Pauls et al., 1993).

In "Akr" family, we have thought for a long time that segregation of both GD and HT with such prevalence could only reflect existence of at least a major gene behind. In order to decide between existence and absence of such a component, we have recently performed a complex segregation analysis of AITDs in the region harbouring Akr family. Our results gave evidence for a polygenic character of these diseases suggesting that genetic susceptibility to AITDs results from numerous loci, each contributing with small effects rather than a major one (Bougacha-Elleuch et al., 2011).

7. Conclusion

Based on “Akr” family studies, it seems that natural history but also the clinical and immunological feature of HT disease are not so different between familial and sporadic cases. Nevertheless, this multigenerational family remains a particular one with its high prevalence of AITDS, its high level of consanguinity and endogamy.

Regarding the literature, and despite extensive efforts, association studies often failed to reach consensus. Many reasons could be advanced for non replication of association studies, such as inadequate sample sizes, population stratification, variation in study design, confounding sampling bias and misclassification of phenotypes. Concerning HT, besides these parameters, there are some difficulties in disease definition. Additionally, co segregation of the two clinical forms (HT and GD) in the same family could be considered as another element making HT diagnosis more difficult. In such families, genome scan carried out tend to reveal chromosomal regions predisposing to AITDs rather than HT. Indeed, this approach may identify more easily the common than the specific HT or GD gene susceptibility. These observations might advocate setting up separate genome screening studies for GD and HT.

On the other hand, we can also postulate that among important reasons for non replication of many linked and/or associated regions/genes is that all these components of AITDs or HT "puzzle" contribute with minor effects (as it was evidenced in "Akr" family). Consequently, the appropriate approach to detect these small pieces of the puzzle would be genome wide association study in large samples. Indeed, as risk factors become more common and have smaller effect sizes, GWA studies emerge as a more powerful approach, There still is a paucity of GWAS in AITD in general and particularly in HT. A full genome-wide association analysis solely on AITD has not been published yet.

It is clear then, that we have to search for these genes in a large cohort composed only of HT patients with restricted clinical criteria to have a homogeneous sample. In this sample, investigation will not only be at the genetic level, but also at the transcriptomic one.

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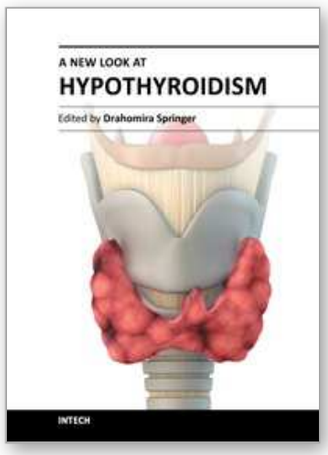
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A New Look at Hypothyroidism

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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