Shared Genetic Relationships Underlying Generalized Vitiligo and Autoimmune Thyroid Disease

Richard A. Spritz

Background: Generalized vitiligo is an autoimmune disease of skin pigmentation that is associated with increased prevalence of other autoimmune diseases, particularly autoimmune thyroid disease (AITD; principally Hashimoto's disease and Graves' disease), both in vitiligo patients and their close relatives, suggesting a heritable predisposition involving, in part, shared susceptibility genes.

Summary: This review summarizes current knowledge of vitiligo epidemiology and genetics, highlighting recent findings from genome-wide approaches to disease gene identification, emphasizing susceptibility loci shared with other autoimmune diseases, particularly AITD, as well as some important differences.

Conclusions: Inherited susceptibility to generalized vitiligo involves a number of specific genes, many of which are shared with other autoimmune diseases that are epidemiologically associated with vitiligo, including AITD, confirming a longstanding hypothesis about the genetic basis of these disorders. These genes provide potential therapeutic targets for novel approaches to treatment as well as for approaches to presymptomatic diagnosis and disease prevention in individuals with inherited susceptibility to this group of autoimmune diseases.

Introduction

AUTOIMMUNE DISEASES ARE A DIVERSE GROUP of chronic disorders in which the immune system attacks one's own cells and tissues. More than 80 autoimmune diseases are known, at least one for almost every organ in the body (1). The most prevalent are the autoimmune thyroid diseases (AITD), principally Hashimoto's disease and Graves' disease (2–4), characterized by infiltration of the thyroid by thyroid-reactive T and B cells and by the production of thyroid autoantibodies (5,6). Perhaps the most recognizable autoimmune disease is generalized vitiligo, with descriptions of its visually striking clinical manifestations dating back several millennia (7).

Generalized vitiligo is characterized clinically by acquired patches of white skin and overlying hair, usually multifocal and often bilateral (7,8) (Fig. 1), resulting from progressive autoimmune loss of melanocytes from the involved areas. Development of generalized vitiligo results from a complex interaction of predisposing genetic factors and unknown environmental triggers that initiate the process of melanocyte destruction, resulting in the characteristic depigmented lesions (9,10).

It is well known that there is a tendency for multiple autoimmune diseases to occur concomitantly in some patients. Perhaps the first description was in 1855, when Addison reported a patient with idiopathic adrenal insufficiency, vitiligo, and pernicious anemia (11). In 1926 Schmidt reported co-occurrence of multiple autoimmune diseases in what came to be called Schmidt syndrome (12). In 1980 Neufeld and Blizzard suggested classification of the so-called autoimmune polyglandular syndromes based on clinical grounds (13), of which Schmidt syndrome was denoted type II. Over the past few years it has become recognized that APS II is more complex, and in particular that generalized vitiligo is part of a genetically determined, autoimmune-autoinflammatory disease diathesis that also includes AITD, rheumatoid arthritis, adult-onset type 1 diabetes mellitus, psoriasis, pernicious anemia, Addison's disease, and systemic lupus erythematosus, all of which occur at elevated frequencies both among vitiligo patients themselves, and also among their first-degree relatives, even those who are not themselves affected with vitiligo (14–16). This has led to the hypothesis that general susceptibility to this constellation of diseases is a complex trait involving various shared susceptibility genes, while other genes and exposure to environmental triggers determine specific disease occurrence in individual patients (17).

Approaches to identification of genes involved in vitiligo pathogenesis have taken a number of forms, initially focusing on biological candidates and differential expression analyses. In recent years, technological advances enabled by the human genome project, and methodological advances applied to analyses of polygenic, multifactorial diseases, have permitted

FIG. 1. A patient with generalized vitiligo. Note obvious patches of white skin in typical distribution involving the periorbital region and hands.

more global approaches, including a recent genome-wide association study. As the result, there has been considerable progress in identifying susceptibility genes for generalized vitiligo, some of which are shared with other autoimmune diseases and some of which are specific to vitiligo. These genes may thus provide novel therapeutic and even prophylactic targets for new interventional approaches to treat and prevent both generalized vitiligo and other autoimmune diseases in the APS type II constellation.

Here, we review the epidemiology of generalized vitiligo and associated autoimmune diseases, progress toward identifying vitiligo susceptibility genes and their occurrence in other, epidemiologically associated autoimmune diseases (especially AITD), and discuss biological pathways that appear to be specific to vitiligo but which may provide biological insight into other autoimmune diseases.

Epidemiology of Generalized Vitiligo and Associated Autoimmune Diseases

Generalized vitiligo is the most common depigmenting disorder, occurring with a frequency of $\sim 0.5\%$ in various populations around the world (18–20) and an average age of onset of ~ 24 years (14). Women have been overrepresented in virtually all large patient surveys, whereas men and women

are affected equally among probands' affected first-degree relatives (14,15). Large-scale epidemiological surveys have shown that most cases of generalized vitiligo occur sporadically, though about 15%–20% of patients report one or more affected first-degree relatives (14). Very rarely, large multi-generation families segregate vitiligo in an autosomal dominant pattern with incomplete penetrance (21). More typically, however, family clustering of generalized vitiligo cases exhibits a non-Mendelian pattern (14–16,22–29), with overall vitiligo prevalence among probands' first-degree relatives $\sim 7.0\%$ in Caucasians, 6.1% in Indian-Pakistanis, 4.8% in U.S. Hispanic-Latinos (14), and 2.6% in Han Chinese (16). Concordance of generalized vitiligo in monozygotic twin-pairs is $\sim 23\%$ (14), >60 times the general population risk. Together, these findings indicate that susceptibility to generalized vitiligo is a complex, polygenic multifactorial trait.

Melanocyte loss in generalized vitiligo occurs primarily on an autoimmune basis (7,30–32), although the triggers of the autoimmune response remain unknown. Many patients have circulating antibodies to various melanocyte components, most frequently tyrosinase (33), the key enzyme of melanin biosynthesis (34), as well as circulating skin-homing melanocyte-specific cytotoxic T-lymphocytes (35). Sparse infiltrates of activated and cytotoxic T cells are seen at the margins of active lesions (36–38). Moreover, generalized vitiligo is a component of the APECED (APS type I) and Schmidt (APS type II) multiple autoimmune disease syndromes, and in small studies has been associated with AITD (39,40), pernicious anemia (41,42), Addison's disease (43), and perhaps alopecia areata (44,45). Much larger surveys of vitiligo patients (14,15,46–48) have generally found elevated frequencies of AITD, pernicious anemia, rheumatoid arthritis, psoriasis, type 1 diabetes, Addison's disease, and systemic lupus erythematosus; about 15%–25% of patients with generalized vitiligo have at least one additional concomitant autoimmune disorder. Moreover, these same autoimmune diseases also occur with increased prevalence in vitiligo patients' first-degree relatives, regardless of whether or not those relatives have vitiligo themselves (14,15). Together, these findings indicate that vitiligo patients and their close relatives have a genetically determined susceptibility to this specific group of autoimmune diseases, most likely mediated by shared susceptibility genes that predispose to these diseases, with other genes and environmental triggers determining disease specificity.

Vitiligo Susceptibility Genes

Four very different approaches have been used to identify genes that mediate susceptibility to vitiligo: gene expression analyses, candidate gene association studies, genome-wide linkage studies, and genome-wide association studies.

Gene expression studies

Gene expression studies, either of candidate genes or via global analysis using microarrays, can identify genes that are differentially expressed, in cells from vitiligo patients versus controls, or in involved skin versus uninvolved skin. However, gene expression differences cannot distinguish between genes with primary effects versus the many more genes whose expression may be dysregulated on a secondary basis or whose expression merely varies on the outbred genetic background of humans, unrelated to vitiligo.

VIT1 (subsequently renamed *FBXO11*) was originally so-named on the basis of its apparent aberrant expression in intralesional vitiligo melanocytes (49). Similarly, *MYG1* is a widely expressed gene shown on the basis of differential hybridization to have elevated expression in melanocytes from vitiligo patients (50). Variation in *MYG1* has been found to affect levels of gene expression and to be marginally associated with active vitiligo (51), although this study did not apply appropriate correction for extensive multiple testing. A recent more global analysis of 16,000 transcripts in melanocytes cultured from vitiligo patients versus controls identified a list of 859 differentially expressed genes (52). However, neither *FBOX11* nor *MYG1*, nor any of the top-ranked genes from the more global expression analysis have been identified as potential vitiligo susceptibility genes by either genome-wide linkage studies or a recent genome-wide association study of generalized vitiligo (53), suggesting that none of these genes may be causally involved in vitiligo pathogenesis.

Candidate gene association studies

Candidate gene association studies are best suited to detecting genetic signals that represent relatively common causal variants with modest effect sizes, and hence the typical occurrence of these diseases in singleton patients who have limited or no family history of the disease. However, candidate gene association studies are highly subject to false-positive results, due to population stratification, inadequate statistical power and fluctuation, and inadequate correction for multiple testing, both within and across studies.

Apparent association of vitiligo with many different biological candidate genes has been reported in a large number of studies (Table 1). However, many of these studies reported only marginally significant nominal associations, with inadequate correction for multiple testing, and most have not been replicated in independent studies. Most of these associations thus most likely represent false-positives due to population stratification, low statistical power and fluctuation, and failure to adequately correct for multiple testing. As the result, only two biological candidate genes have been supported by positive results in multiple studies, *HLA* and *PTPN22*, and findings for a third, *CTLA4*, have been difficult to interpret.

The earliest genetic studies of vitiligo were case–control allelic association studies of genes in the major histocompatibility complex (MHC), carried out by genotyping various MHC markers in patients with various different vitiligo phenotypes versus in controls, from many different populations (e.g., 54–59). In general, these early studies found no consistent association between the occurrence of vitiligo and specific *HLA* alleles. However, re-analysis of these studies as a group shows that several found association between vitiligo and *HLA-DR4* alleles (60), and meta-analysis found association of vitiligo with *HLA-A2* (61). More recent studies that used modern analytical and statistical methods found association between generalized vitiligo and *HLA-DRB4*0101* and *HLA-DQB1*0303* in Dutch patients (62), with *HLA-DRB1*03, DRB1*04*, and *HLA-DRB1*07* alleles in Turkish patients (63), and with alleles of microsatellites located in the MHC in Colombian patients (64). In Caucasian multiplex generalized vitiligo families, the MHC class II haplotype *HLA DRB1A *04-(DQA1*0302)-DQB1*0301* is associated with both increased

risk of vitiligo and with relatively early disease onset (60), and in Han Chinese generalized vitiligo is associated with the MHC haplotype *HLA-A25-Cw*0602-DQA1*0302* (65). Association has also been reported between generalized vitiligo and genes of the *LMP/TAP* gene region of the MHC (66), although this may merely reflect long-range linkage disequilibrium with the MCH class II gene region.

Three independent candidate gene studies have shown association of the *PTPN22* R620W polymorphism with generalized vitiligo in Caucasians (67–69), thus strongly supporting true association with what is believed to be the causal variant for *PTPN22*-related autoimmune susceptibility (70). An additional study, carried out in Indians from the Gujarat region, failed to observe association of vitiligo with the R620W variant (71), an unsurprising result given the rarity of the R620W variant in non-Caucasian populations and the small size (and thus very limited statistical power) of that study.

Interpretation of findings for *CTLA4* has been more problematic. Several studies have observed apparent association of *CTLA4* and generalized vitiligo (72–74), but principally limited to the subset of patients who have other concomitant autoimmune diseases, although even in this group association has been inconsistent (74,75). A meta-analysis (74) indicated that, overall, association of *CTLA4* with vitiligo is weak, and probably is secondary, driven by primary genetic association of *CTLA4* with other autoimmune diseases that are epidemiologically associated with vitiligo, particularly AITD.

Genome-wide linkage studies

Genetic linkage studies are best suited to detecting genetic signals that represent relatively rare causal variants with large effect sizes; hence, segregation of the corresponding phenotype in the multiplex families needed for linkage analysis. However, it must be borne in mind that most vitiligo patients are singleton cases, with few or no affected relatives, and thus the susceptibility genes and variants detected by linkage in multiplex families may not be typical of the majority of cases. Moreover, in many instances it has proved difficult to identify causal genes that underlie candidate genetic linkage signals.

The first genome-wide linkage study of vitiligo was of a single large family with generalized vitiligo and other autoimmune diseases, inherited as an apparent autosomal dominant trait with incomplete penetrance. Vitiligo in this family was mapped to a 7.4 Mb interval in chromosome segment 1p31.3–p32.2 (76), and detailed studies of genes in this region of chromosome subsequently identified a promoter variant in *FOXD3*, which encodes an embryonic transcription factor that regulates melanoblast differentiation and development (77). However, this family with autosomal dominant vitiligo appears to be unique, and other generalized vitiligo patients do not have mutations of *FOXD3* or show linkage to this region of chromosome 1p.

Genome-wide linkage analyses of more typical small multiplex generalized vitiligo families have yielded a number of other linkage signals (Table 1), for only a few of which have corresponding genes been identified. In Caucasians, besides chromosome 1p, significant vitiligo linkage signals were detected on chromosomes 7p13–q21, 8p12, and 17p, and suggestive signals on chromosomes 9q22, 11p15, 13q33, 19p13, and 22q11, the chromosome 7 and 17p linkages deriving principally from families with other autoimmune diseases, mainly AITD (78,79). In Chinese, a major vitiligo linkage

Table 1. Genes Suggested for Involvement in Generalized Vitiligo

Chromosome	Gene or Locus	Method	Comments
1p36.23	RERE	Genome-wide association	Confirmed
1p31.3	FOXD3	Genome-wide linkage	Rare autosomal dominant
1p13.3	GSTM1	Candidate gene association	Unconfirmed
1p13.2	PTPN22	Candidate gene association, genome-wide association	Confirmed; associated with many autoimmune diseases
1q25	PTGS2 (COX2)	Candidate gene association	Unconfirmed
2p16.3	FBXO11 (VIT1)	Expression analysis	No evidence causally involved in vitiligo
2q31.2	NRF2	Candidate gene association	Unconfirmed
2q33.2	CTLA4	Candidate gene association	Associated with many autoimmune diseases; inconsistent association with vitiligo
3p13	MITF	Candidate gene linkage	No linkage
3q28	LPP	Genome-wide association	Confirmed; associated with celiac disease and rheumatoid arthritis
5q22.1	TSLP	Candidate gene association	Unconfirmed
6p21.3	HLA-A, MHC class I, class II	Candidate gene association, genome-wide linkage, genome-wide association	Confirmed; associated with many autoimmune disorders
6p21.3	TAP1, LMP2, DDR1	Candidate gene association	Unconfirmed; within MHC; may reflect linkage disequilibrium
6q25.1	ESR1	Candidate gene association	Unconfirmed
6q27	SMOC2	Genome-wide association	Unconfirmed
7	AIS2	Genome-wide linkage, association	Confirmed; autoimmunity-associated
8	AIS3	Genome-wide linkage	Unconfirmed
10p15.1	IL2RA	Genome-wide association	Associated with many autoimmune diseases
10q21.1	MBL2	Candidate gene association	Data conflicting
10q23.31	TNFRSF6 (FAS, APO1)	Candidate gene association	Unconfirmed
11p13	CAT	Candidate gene association	Data conflicting
11p11.2	LXRA	Candidate gene association	Unconfirmed
11q14.3	TYR	Genome-wide association	Confirmed
12q12-q14	VDR	Candidate gene association	Unconfirmed
12q13	MYG1	Gene expression analysis, candidate gene association	Unconfirmed
12q22	KITLG (SCF)	Candidate gene association	Unconfirmed
14q12	GZMB	Genome-wide association	Confirmed
14q22.2	GCH1	Candidate gene association	Now considered invalid
17p13	NLRP1	Genome-wide linkage, candidate gene association	Confirmed; principally in multiplex families
17q23	ACE	Candidate gene association	Data conflicting
19q13.33	SCGF	Candidate gene association	Unconfirmed
21q22.3	UBASH3A	Genome-wide association	Confirmed; associated with type 1 diabetes
21q22.3	AIRE	Candidate gene association	Data conflicting
22q11.21	COMT	Candidate gene association	Unconfirmed
22q11.23	GSTT1	Candidate gene association	Data conflicting
22q12.1	XBP1	Genome-wide linkage, candidate gene association	Unconfirmed
22q13.1	C1QTNF6	Genome-wide association	Confirmed; associated with type 1 diabetes and rheumatoid arthritis

MHC, major histocompatibility complex.

signal was detected on chromosome 4q13–q21, and weaker signals at 1p36, 6p21–p22, 6q24–q25, 14q12–q13, and 22q12 (80,81). Except perhaps for the signals on proximal chromosome 22q, none of linkages observed in Caucasians align with those observed in Chinese, suggesting that, if these linkages are valid, different genes may be involved in the pathogenesis of vitiligo in different populations around the world.

The 17p vitiligo linkage signal, detected principally in multiplex vitiligo families with other associated autoimmune diseases, principally AITD (79), coincided with the location of

SLEV1, a linkage signal originally detected in multiplex lupus families that included at least one case of vitiligo (82) and subsequently confirmed in multiplex lupus families with various other autoimmune diseases (83). Together, these findings suggested that this locus mediates susceptibility to multiple autoimmune diseases, including at least generalized vitiligo and lupus. Association analysis across the 17p linkage region, first in the same multiplex vitiligo families used for linkage and subsequently in a second set of multiplex vitiligo families, identified *NLRP1* (previously, *NALP1*) as the

vitiligo-autoimmunity gene in this region (84). *NLRP1* encodes a key regulator of the innate immune system that, on interaction with unknown bacterial or viral triggers, stimulates formation of an inflammasome complex that activates the interleukin-1β inflammatory pathway and perhaps also modulates apoptosis. Subsequent studies have confirmed association of variation in *NLRP1* with generalized vitiligo (85), as well as with Addison's disease (86,87) and type 1 diabetes (86).

A similar approach led to identification of the 22q12 locus detected in Chinese as *Xbp1* (88), encoding a DNA-binding protein, the downstream targets of which are X boxes in many genes, including several *HLA* loci. Association of *Xbp1* with vitiligo has not yet been confirmed in other populations, although variation in *Xbp1* has also been associated with inflammatory bowel disease (89).

Two of the other generalized vitiligo linkage signals, on chromosomes 7p13–q21 and 9q22, have also been subjected to detailed analysis (90). However, specific vitiligo susceptibility genes in these regions have not yet been identified.

Genome-wide association studies

Genome-wide association studies, like candidate gene association studies, are best suited to detecting genetic signals that represent relatively common causal variants with modest effect sizes. However, unlike candidate gene association studies, genome-wide association studies are sufficiently powered to minimize statistical fluctuation and permit adequate control for multiple testing within the study, and provide full-genome datasets that enable both detection of and adjustment for population stratification. As the result, genome-wide association studies have provided robust, highly replicable genetic findings for many different complex human diseases.

Two different genome-wide association studies have been reported for generalized vitiligo, both in Caucasians. The first, of a founder population in an isolated Romanian village with a high prevalence of generalized vitiligo, AITD, and other autoimmune diseases (91), detected association at chromosome 6qter near *IDDM8*, a type 1 diabetes–rheumatoid arthritis locus. This study tentatively identified the causal gene as *SMOC1* (92). The second genome-wide association study of generalized vitiligo studied over 1500 unrelated Caucasian cases in the initial genome-wide screening phase (53). This analysis detected and replicated association with at least 12 different loci (53,93). Most of these appear to represent genes with known functions in the immune response, including *HLA* class I (specifically, *HLA-A*02*), *HLA* class II, *PTPN22*, *RERE*, *FOXP1*, *LPP*, *IL2RA*, *GZMB*, *UBASH3A*, *C1QTNF6*, and probably *CCR6*. Many of these genes have been associated with susceptibility to various other autoimmune diseases. Like the Romanian study, this larger genome-wide association study also detected association at a locus at 6qter near *IDDM8*, though apparently at *CCR6*, located 1.44 Mb proximal to *SMOC2*; the relationship between these two association signals remains to be clarified. Interestingly, although association with *NLRP1* was not detected in the initial genome-wide screen, which included mostly sporadic cases, association with *NLRP1* was confirmed in a subset analysis consisting of multiplex vitiligo families, consistent with a large odds ratio for variation in *NLRP1* that enabled its original mapping by genetic linkage analysis.

In addition to immune-related genes, the vitiligo genome-wide association study detected association to only a single non-immune-related gene, *TYR*, which encodes tyrosinase, the key enzyme of melanin biosynthesis and an important autoantigen in generalized vitiligo. Generalized vitiligo is thus analogous to type 1 diabetes and AITD, in which inherited variation in *INS* and *TG*, respectively, each encoding an important intracellular component of the target cell type, and each constituting a major autoantigen in the corresponding disease, each predisposes to disease susceptibility. For generalized vitiligo, the causal *TYR* vitiligo susceptibility variant appears to be the major allele of the common R402Q polymorphism. The minor *TYR*402R allele encodes a thermosensitive tyrosinase polypeptide that is present in greatly reduced amounts and is incorrectly glycosylated, and which thus is less available for presentation to the immune system. In fact, tyrosinase peptide is presented on the melanocyte surface by HLA-A*0201, which corresponds to the high-risk allele of *HLA-A*, and there was significant genetic interaction between the most associated single-nucleotide polymorphisms in *TYR* and *HLA-A* (53). Importantly, the *TYR*402Q allele, while conferring apparent susceptibility to generalized vitiligo, is also associated with genetic protection from malignant melanoma (94,95). A unifying hypothesis is that the *TYR* R402Q variant may mediate alternative susceptibility to vitiligo versus melanoma via modulating immune surveillance of malignant melanomas.

Genetic Relationships Between Generalized Vitiligo and AITD

There is strong epidemiological association between generalized vitiligo and AITD, which occurs (88% hypothyroidism and 12% hyperthyroidism) in 17%–25% of vitiligo probands and 6%–15% of their first-degree relatives (14,15), while the prevalence of vitiligo among patients with AITD is ∼7% (96,97). This epidemiological association strongly suggests that generalized vitiligo and AITD share common genetic susceptibility factors.

Genome-wide linkage and candidate gene association studies have identified a number of loci potentially involved in AITD (98–100). The strongest association is to *HLA-DR3* (101), in which a 74R variant allele appears to be causal for disease predisposition (102–104). In contrast, generalized vitiligo is associated with *HLA-DR4* on an MHC class II *DRB1*04–DQB1*0301* haplotype (60).

A number of non-MHC candidate genes have been associated with AITD, although only six have been confirmed in multiple studies (105). These include four immunomodulatory genes, *CTLA4* (106), *PTPN22* (107), *CD40* (108), and *FCRL3* (109), and two thyroid-specific genes, thyroglobulin (*TG*) (110), and *TSHR* (111), though undoubtedly additional unidentified genes contribute to AITD susceptibility. Of these, genetic association of *PTPN22* with generalized vitiligo is well established, whereas association of *CTLA4* with generalized vitiligo appears to be indirect, reflecting primary association with other concomitant autoimmune diseases that occur in some vitiligo patients, principally AITD. At present, there is no evidence for association of either *CD40* or *FCRL3* with generalized vitiligo, and association signals were not observed in the vicinity of these genes in the recent vitiligo genome-wide association studies (53,91). Likewise, there was

association with *TSHR* or *TG*, even in the subset of vitiligo patients with concomitant AITD, suggesting that these loci may be relevant principally to patients with isolated AITD, and that broader autoimmunity susceptibility genes may be of greater importance in patients with concomitant generalized vitiligo and AITD.

Conclusions

Recent studies have identified a number of confirmed genes that underlie susceptibility to generalized vitiligo. Whereas one of these, *TYR*, encodes a melanocyte-specific protein that likely plays a key role in target cell specificity of the autoimmune response, most vitiligo susceptibility genes encode proteins involved in immune functions. Indeed, many of these have also been identified as susceptibility genes for other autoimmune diseases with which generalized vitiligo is epidemiologically associated. The overall situation in AITD appears to be similar, with both general autoimmunity genes and thyroid-specific genes identified as conferring disease susceptibility. Generalized vitiligo and AITD are closely associated epidemiologically, and it is likely that, as additional susceptibility genes are identified for both of these autoimmune diseases, many will be shared in common, leading to a convergence of shared autoimmune susceptibility genes as well as sets of specific genes and ultimately environmental triggers that determine disease specificity and onset.

Acknowledgments

Disclosure Statement

The author declares that no competing financial interests exist.

References

1. Marrack P, Kappler J, Kotzin BL 2001 Autoimmune disease: why and where it occurs. Nat Med **7:**899–905.
2. Jacobson DL, Gange SJ, Rose NR, Graham NM 1997 Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol **84:**223–243.
3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE 2002 Serum TSH, T4 and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab **87:**489–499.
4. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR 2007 Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002) Thyroid **17:**1211–1223.
5. Davies TF 2000 Graves' diseases: pathogenesis. In: Braverman LE, Utiger RD (eds) Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. Lippincott Williams & Wilkens, Philadelphia, pp 518–530.
6. Weetman AP 2000 Chronic autoimmune thyroiditis. In: Braverman LE, Utiger RD (eds) Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. Lippincott Williams and Wilkins, Philadelphia, pp 721–732.
7. Nordlund JJ, Ortonne J-P, Le Poole IC 2006 Vitiligo vulgaris. In: Nordlund JJ, Boissy RE, Hearing VJ, King RA, Oetting WS, Ortonne J-P (eds) The Pigmentary System, 2nd edition. Blackwell, Oxford, pp 551–598.
8. Taïeb A, Picardo M 2009 Vitiligo. N Engl J Med **360:**160–169.
9. Boissy RE, Spritz RA 2009 Frontiers and controversies in the pathobiology of vitiligo: separating the wheat from the chaff. Exp Dermatol **18:**583–585.
10. Birlea SA, Spritz RA, Norris DA 2010 Vitiligo. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ (eds) Fitzpatrick's Dermatology in General Medicine, 8th edition. McGraw-Hill, New York (In press).
11. Addison T 1855 On the constitutional and local effects of disease of the suprarenal capsules. In a collection of the published writing of the late Thomas Addison, M.D., physician to Guy's Hospital, New Sydenham Society 1868, London. Reprinted in Medical Classics 1937; **2:**244–293.
12. Schmidt M 1926 Eine biglanduiare Erkrankung (Nebennieren und Schilddruse) bei Morbus Addisonii. Verh Dtsch Ges Pathol **21:**212–221.
13. Neufeld M, Blizzard RM 1980 Polyglandular autoimmune diseases. In: Pinchera A, Doniach D, Fenzi GF, Baschieri L (eds) Symposium on Autoimmune Aspects of Endocrine Disorders. Academic Press, New York, pp 357–365.
14. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA 2003 Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their relatives. Pigment Cell Res **16:**208–214.
15. Laberge, G, Mailloux CM, Gowan K, Holland P, Bennett DC, Fain PR, Spritz RA 2005 Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. Pigment Cell Res **18:**300–305.
16. Sun X, Xu A, Wei X, Ouyang J, Lu L, Chen M, Zhang D 2006 Genetic epidemiology of vitiligo: a study of 815 probands and their families from south China. Int J Dermatol **45:**1176–1181.
17. Spritz RA 2008 The genetics of generalized vitiligo. Curr Dir Autoimmun **10:**244–257.
18. Howitz J, Brodthagen H, Schwartz M, Thompsen K 1977 Prevalence of vitiligo: epidemiological survey of the Isle of Bornholm, Denmark. Arch Dermatol **113:**47–52.
19. Das SK, Majumder PP, Chakraborty R, Majumdar TK, Halder B 1985 Studies on vitiligo. I. Epidemiological profile in Calcutta, India. Genet Epidemiol **2:**71–78.
20. Lu T, Gao T, Wang A, Jin Y, Li Q, Li C 2007 Vitiligo prevalence study in Shaanxi Province, China. Int J Dermatol **46:**47–51.
21. Alkhateeb A, Stetler GL, Old W, Talbert J, Uhlhorn C, Taylor M, Fox A, Miller C, Dills DG, Ridgway EC, Bennett DC, Fain PR, Spritz RA 2002 Mapping of an autoimmunity susceptibility locus (*AIS1*) to chromosome 1p31.3-p32.2 Hum Mol Genet **11:**661–667.
22. Mehta NR, Shah KC, Theodore C, Vyas VP, Patel AB 1973 Epidemiological study of vitiligo in Surat area. Indian J Med Res **61:**145–154.
23. Carnevale A, Zavala C, Castillo VD, Maldonado RR, Tamayo L 1980 Analisis genetico de 127 families con vitiligo. Rev Invest Clin **32:**37–41.
24. Hafez M, Sharaf L, El-Nabi SMA 1983 The genetics of vitiligo. Acta Derm Venereol (Stockh) **63:**249–251.
25. Das SK, Majumder PP, Majumder TK, Haldar B 1985 Studies on vitiligo. II. Familial aggregation and genetics. Genet Epidemiol **2:**255–262.

26. Majumder PP, Das SK, Li CC 1988 A genetical model for vitiligo. Am J Hum Genet 43:119–125.

27. Bhatia PS, Mohan L, Pandey ON, Singh KK, Arora SK, Mukhija RD 1992 Genetic nature of vitiligo. J Dermatol Sci 4:180–184.

28. Majumder PP, Nordlund JJ, Nath SK 1993 Pattern of familial aggregation of vitiligo. Arch Dermatol 129:994–998.

29. Nath SK, Majumder PP, Nordlund JJ 1994 Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. Am J Hum Genet 55:981–990.

30. Harsoulis P, Kanakoudi-Tsakalidis F, Vyzantiadis A, Minas A, Cassimos C 1978 Autoimmunity and vitiligo. Arch Dermatol 114:1554.

31. Ongenae K, Van Geel N, Naeyaert J-M 2003 Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res 16:90–100.

32. Le Poole CI, Wankowicz-Kalinska, van den Wijngaard RMJGJ, Nickoloff BJ, Das DK 2004 Autoimmune aspects of depigmentation in vitiligo. J Investig Dermatol Symp Proc 9:68–72.

33. Kemp EH, Gavalas NG, Gawkrodger DJ, Weetman AP 2007 Autoantibody responses to melanocytes in the depigmenting skin disease vitiligo. Autoimmun Rev 6:138–142.

34. Spritz RA, Chiang P-W, Oiso N, Alkhateeb A 2003 Human and mouse disorders of pigmentation. Curr Opin Genet Dev 13:284–289.

35. Ogg GS, Rod Dunbar P, Romero P, Chen JL, Cerundolo V 1998 High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo. J Exp Med 188:1203–1208.

36. Gross A, Tapia FJ, Mosca W, Perez RM, Briceno L, Henriquez JJ, Convit J 1987 Mononuclear cell subpopulations and infiltrating lymphocytes in erythema dyschromicum perstans and vitiligo. Histol Histopathol 2:277–283.

37. Badri AM, Todd PM, Garioch JJ, Gudgeon JE, Stewart DG, Goudie RB 1993 An immunohistological study of cutaneous lymphocytes in vitiligo. J Pathol 170:149–155.

38. Le Poole IC, van den Wijngaard RM, Westerhof W, Das PK 1996 Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. Am J Pathol 148:1219–1228.

39. Cunliffe W, Hall R, Newell J, Stevenson CJ 1968 Vitiligo, thyroid disease and autoimmunity. Br J Dermatol 80:135–139.

40. Schallreuter KW, Lemke R, Brandt O, Schwartz R, Westhofen M, Montz R, Berger J 1994 Vitiligo and other diseases: coexistence or true association? Dermatology 188:269–275.

41. Dawber R 1969 Integumentary associations of pernicious anemia. Br J Dermatol 82:221–222.

42. Grunnet I, Howitz J 1979 Vitiligo and pernicious anemia. Arch Dermatol 101:82–85.

43. Zelissen PMJ, Bast EJEG, Croughs RJM 1995 Associated autoimmunity in Addison's disease. J Autoimmun 8:121–130.

44. Sharma VK, Dawn G, Kumar B 1996 Profile of alopecia areata in Northern India. Int J Dermatol 35:22–27.

45. Sharma VK, Kumar V, Dawn G 1996 A clinical study of childhood alopecia areata in Chandigarh, India. Pediatr Dermatol 13:372–377.

46. Handa S, Kaur I 1999 Vitiligo: clinical findings in 1436 patients. J Dermatol 26:653–657.

47. Handa S, Dogra S 2003 Epidemiology of childhood vitiligo: a study of 625 patients from north India. Pediatr Dermatol 20:207–210.

48. Onunu AN, Kubeyinje EP 2003 Vitiligo in the Nigerian African: a study of 351 patients in Benin City, Nigeria. Int J Dermatol 42:800–802.

49. Le Poole IC, Sarangarajan R, Zhao Y, Stennett LS, Brown TL, Sheth P, Miki T, Boissy RE 2001 "VIT1," a novel gene associated with vitiligo. Pigment Cell Res 14:475–484.

50. Kingo K, Philips MA, Aunin E, Luuk H, Karelson M, Ratsep R, Silm H, Vasar E, Koks S 2006 MYG1, novel melanocyte related gene, has elevated expression in vitiligo. J Dermatol Sci 44:119–122.

51. Philips MA, Kingo K, Karelson M, Ratsep R, Aunin E, Reimann E, Reemann P, Porosaar O, Vikesaa J, Nielsen FC, Vasar E, Silm H, Koks S 2010 Promoter polymorphism −119C/G in MYG1 (C12orf10) gene is related to vitiligo susceptibility and Arg4Gln affects mitochondrial entrance of Myg1. BMC Med Genet 11:56.

52. Strömberg S, Björklund MG, Asplund A, Rimini R, Lundeberg J, Nilsson P, Pontén F, Olsson MJ 2008 Transcriptional profiling of melanocytes from patients with vitiligo vulgaris. Pigment Cell Melanoma Res 21:162–171.

53. Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, Holland PJ, Mailloux CM, Sufit AJD, Hutton SM, Amadi-Myers A, Bennett DC, Wallace MR, McCormack WT, Kemp EH, Gawkrodger DJ, Weetman AP, Picardo M, Leone G, Taïeb A, Jouary T, Ezzedine K, van Geel N, Lambert J, Overbeck A, Spritz RA 2010 Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. N Engl J Med 362:1686–1697.

54. Foley LM, Lowe NJ, Misheloff E, Tiwari JL 1983 Association of HLA-DR4 with vitiligo. J Am Acad Dermatol 8:39–40.

55. Finco O, Cuccia M, Mantinetti M, Ruberto G, Orecchia G, Rabbiosi G 1991 Age of onset in vitiligo: relationship with HLA supratypes. Clin Genet 39:448–454.

56. Orecchia G, Perfetti L, Malagoli P, Borghini F, Kipervarg Y 1992 Vitiligo is associated with a significant increase in HLA-A30, Cw6 and Dqw3 and a decrease in C4AQ0 in northern Italian patients. Dermatology 185:123–127.

57. Ando I, Chi HI, Nakagawa H, Otsuka F 1993 Difference in clinical features and HLA antigens between familial and non-familial vitiligo of non-segmental type. Br J Dermatol 129:408–410.

58. Schallreuter KU, Levenig C, Kuhnl P, Loliger C, Hohl-Tehari M, Berger J 1993 Histocompatibility antigens in vitiligo: Hamburg study on 102 patients from northern Germany. Dermatology 187:186–192.

59. al-Fouzan A, al-Arbash M, Fouad F, Kaaba SA, Mousa MA, al-Harbi SA 1995 Study of HLA class I/IL and T lymphocyte subsets in Kuwaiti vitiligo patients. Eur J Immunogenet 22:209–213.

60. Fain PR, Babu SR, Bennett DC, Spritz RA 2006 HLA class II haplotype DRB1*04-DQB1*0301 contributes to risk of familial generalized vitiligo and early disease onset. Pigment Cell Res 19:51–57.

61. Liu JB, Li M, Chen H, Zhong SQ, Yang S, Du WD, Hao JH, Zhang TS, Zhang XJ, Zeegers M 2007 Association of vitiligo with HLA-A2: a meta-analysis. J Eur Acad Dermatol Venereol 21:205–213.

62. Zamani M, Spaepen M, Sghar SS, Huang C, Westerhof W, Nieuweboer-Krobotova L, Cassiman JJ 2001 Linkage and association of HLA class II genes with vitiligo in a Dutch population. Br J Dermatol 145:90–94.

63. Tastan HB, Akar A, Orkunoglu FE, Arca E, Inal A 2004 Association of HLA class I antigens and HLA class II alleles

with vitiligo in a Turkish population. Pigment Cell Res **17:**181–184.

64. Arcos-Burgos M, Parodi E, Salgar M, Bedoya E, Builes JJ, Jaramillo D, Ceballos G, Uribe A, Rivera N, Rivera D, Fonseca I, Camargo M, Palacio LG 2002 Vitiligo: complex segregation and linkage disequilibrium analyses with respect to microsatellite loci spanning the HLA. Hum Genet **110:**334–342.

65. Xia Q, Zhou WM, Liang YH, Ge HS, Liu HS, Wang JY, Gao M, Yang S, Zhang XJ 2006 MHC haplotypic association in Chinese Han patients with vitiligo. J Eur Acad Dermatol Venereol **20:**941–946.

66. Casp CB, She JX, McCormack WT 2003 Genes of the LMP/TAP cluster are associated with the human autoimmune disease vitiligo. Genes Immun **4:**492–499.

67. Cantón I, Akhtar S, Gavalas NG, Gawkrodger DJ, Blomhoff A, Watson PF, Weetman AP, Kemp EH 2005 A single-nucleotide polymorphism in the gene encoding lymphoid protein tyrosine phosphatase (PTPN22) confers susceptibility to generalised vitiligo. Genes Immun **6:** 584–587.

68. LaBerge GS, Bennett DC, Fain PR, Spritz RA 2008 *PTPN22* is genetically associated with risk of generalized vitiligo, but *CTLA4* is not. J Invest Dermatol **128:**1757–1762.

69. Laberge GS, Birlea SA, Fain PR, Spritz RA 2008 The *PTPN22*-1858C>T (R620W) functional polymorphism is associated with generalized vitiligo in the Romanian population. Pigment Cell Melanoma Res **21:**206–208.

70. Brand O, Gough S, Heward J 2005 HLA, CTLA-4, and PTPN22: the shared genetic master-key to autoimmunity? Expert Rev Mol Med **7:**1–15.

71. Laddha NC, Dwivedi M, Shajil EM, Prajapati H, Marfatia YS, Begum R 2008 Association of PTPN22 1858C/T polymorphism with vitiligo susceptibility in Gujarat population. J Dermatol Sci **49:**260–262.

72. Blomhoff A, Kemp EH, Gawkrodger DJ, Weetman AP, Husebye ES, Akselsen HE, Lie BA, Undlien DE 2005 CTLA4 polymorphisms are associated with vitiligo, in patients with concomitant autoimmune diseases. Pigment Cell Res **18:**55–58.

73. Birlea SA, Laberge GS, Procopciuc LM, Fain PR, Spritz RA 2009 *CTLA4* and generalized vitiligo: two genetic association studies and a meta-analysis of published data. Pigment Cell Melanoma Res **22:**230–234.

74. Pehlivan S, Ozkinay F, Alper S, Onay H, Yuksel E, Pehlivan M, Ozkinay C 2009 Association between IL4 (-590), ACE (I)/(D), CCR5 (Delta32), CTLA4 (+49) and IL1-RN (VNTR in intron 2) gene polymorphisms and vitiligo. Eur J Dermatol **19:**126–128.

75. LaBerge GS, Bennett DC, Fain PR, Spritz RA 2008 *PTPN22* is genetically associated with risk of generalized vitiligo, but *CTLA4* is not. J Invest Dermatol **128:**1757–1762.

76. Alkhateeb A, Stetler GL, Old W, Talbert J, Uhlhorn C, Taylor M, Fox A, Miller C, Dills DG, Ridgway EC, Bennett DC, Fain PR, Spritz RA 2002 Mapping of an autoimmunity susceptibility locus (*AIS1*) to chromosome 1p31.3-p32.2. Hum Mol Genet **11:**661–667.

77. Alkhateeb A, Fain PR, Spritz RA 2005 Candidate functional promoter variant in the *FOXD3* melanoblast developmental regulator gene in a family with autosomal dominant vitiligo. J Invest Dermatol **125:**388–391.

78. Fain PR, Gowan K, LaBerge GS, Alkhateeb A, Stetler GL, Talbert J, Bennett DC, Spritz RA 2003 A genomewide screen for generalized vitiligo: confirmation of *AIS1* on

79. Spritz RA, Gowan K, Bennett DC, Fain PR 2004 Novel vitiligo susceptibility loci on chromosomes 7 (*AIS2*) and 8 (*AIS3*), confirmation of *SLEV1* on chromosome 17, and their roles in an autoimmune diathesis. Am J Hum Genet **74:**188–191.

80. Chen JJ, Huang W, Gui JP, Yang S, Zhou FS, Xiong OG, Wu HB, Cui Y, Gao M, Li W, Li JZ, Yan KL, Yuan WT, Xu SJ, Liu JJ, Zhang XJ 2005 A novel linkage to generalized vitiligo on 4q13-q21 identified in a genomewide linkage analysis of Chinese families. Am J Hum Genet **76:**1057–1065.

81. Liang Y, Yang S, Zhou Y, Gui J, Ren Y, Chen J, Fan X, Sun L, Xiao F, Gao M, Du W, Fang Q, Xu S, Huang W, Zhang X 2007 Evidence for two susceptibility loci on chromosomes 22q12 and 6p21-p22 in Chinese generalized vitiligo families. J Invest Dermatol **127:**2552–2557.

82. Nath SK, Kelly JA, Namjou B, Lam T, Bruner GR, Scofield RH, Aston CE, Harley JB 2001 Evidence for a susceptibility gene, *SLEV1*, on chromosome 17p13 in families with vitiligo-related systemic lupus erythematosus. Am J Hum Genet **69:**1401–1406.

83. Johansson CM, Zunec R, Garcia MA, Scherbarth HR, Tate GA, Paira S, Navarro SM, Perandones CE, Gamron S, Alvarellos A, Graf CE, Manni J, Berbotto GA, Palatnik SA, Catoggio LJ, Battagliotti CG, Sebastiani GD, Migliaresi S, Galeazzi M, Pons-Estel BA, Alarcon-Riqauelme ME, Collaborative Group on the Genetics of SLE, Argentine Collaborative Group 2004 Chromosome 17p12-q11 harbors susceptibility loci for systemic lupus erythematosus. Hum Genet **115:**230–238.

84. Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC, Fain PR, Spritz RA 2007 *NALP1* and vitiligo-associated multiple autoimmune disease. N Engl J Med **365:**10–18.

85. Jin Y, Birlea SA, Fain PR, Spritz RA 2007 Genetic variations in *NALP1* are associated with generalized vitiligo in a Romanian population. J Invest Dermatol **127:**2558–2562.

86. Magitta NF, Bøe Wolff AS, Johansson S, Skinningsrud B, Lie BA, Myhr KM, Undlien DE, Joner G, Njølstad PR, Kvien TK, Førre Ø, Knappskog PM, Husebye ES 2009 A coding polymorphism in NALP1 confers risk for autoimmune Addison's disease and type 1 diabetes. Genes Immun **10:**120–124.

87. Zurawek M, Fichna M, Januszkiewicz-Lewandowska D, Gryczyńska M, Fichna P, Nowak J 2010 A coding variant in NLRP1 is associated with autoimmune Addison's disease. Hum Immunol **71:**530–534.

88. Ren Y, Yang S, Xu S, Gao M, Huang W, Gao T, Fang Q, Quan C, Zhang C, Sun L, Liang Y, Han J, Wang Z, Zhang F, Zhou Y, Liu J, Zhang X 2009 Genetic variation of promoter sequence modulates XBP1 expression and genetic risk for vitiligo. PLoS Genet **5:**e1000523.

89. Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, Tilg H, Nieuwenhuis EE, Higgins DE, Schreiber S, Glimcher LH, Blumberg RS 2008 XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. Cell **134:**743–756.

90. Jin Y, Riccardi SL, Gowan K, Fain PR, Spritz RA 2010 Fine-mapping of vitiligo susceptibility loci on chromosomes 7 and 9 and interactions with *NLRP1* (*NALP1*). J Invest Dermatol **130:**774–783.

91. Birlea SA, Fain PR, Spritz RA 2008 A Romanian population isolate with high frequency of vitiligo and associated autoimmune diseases. Arch Dermatol **144:**310–316.

92. Birlea SA, Gowan K, Fain PR, Spritz RA 2010 Genome-wide association study of generalized vitiligo in an isolated European founder population identifies *SMOC2*, in close proximity to *IDDM8*. J Invest Dermatol **130:**798–803.

93. Jin Y, Birlea SA, Fain PR, Mailloux CM, Riccardi SL, Gowan K, Holland PJ, Bennett DC, Wallace MR, McCormack WT, Kemp EH, Gawkrodger DJ, Weetman AP, Picardo M, Leone G, Taïeb A, Jouary T, Ezzedine K, van Geel N, Overbeck A, Spritz RA 2010 Common variants in *FOXP1* are associated with generalized vitiligo. Nat Genet 2010 Jun 6 [Epub ahead of print] doi 10.1038/ng.602.

94. Gudbjartsson DF, Sulem P, Stacey SN, Goldstein AM, Rafnar T, Sigurgeirsson B, Benediktsdottir KR, Thorisdottir K, Ragnarsson R, Sveinsdottir SG, Magnusson V, Lindblom A, Kostulas K, Botella-Estrada R, Soriano V, Juberías P, Grasa M, Saez B, Andres R, Scherer D, Rudnai P, Gurzau E, Koppova K, Kiemeney LA, Jakobsdottir M, Steinberg S, Helgason A, Gretarsdottir S, Tucker MA, Mayordomo JI, Nagore E, Kumar R, Hansson J, Olafsson JH, Gulcher J, Kong A, Thorsteinsdottir U, Stefansson K 2008 ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet **40:**886–891.

95. Bishop DT, Demenais F, Iles MM, Harland M, Taylor JC, Corda E, Randerson-Moor J, Aitken JF, Avril MF, Azizi E, Bakker B, Bianchi-Scarrà G, Bressac-de Paillerets B, Calista D, Cannon-Albright LA, Chin-A-Woeng T, Debniak T, Galore-Haskel G, Ghiorzo P, Gut I, Hansson J, Hocevar M, Höiom V, Hopper JL, Ingvar C, Kanetsky PA, Kefford RF, Landi MT, Lang J, Lubiński J, Mackie R, Malvehy J, Mann GJ, Martin NG, Montgomery GW, van Nieuwpoort FA, Novakovic S, Olsson H, Puig S, Weiss M, van Workum W, Zelenika D, Brown KM, Goldstein AM, Gillanders EM, Boland A, Galan P, Elder DE, Gruis NA, Hayward NK, Lathrop GM, Barrett JH, Bishop JA 2009 Genome-wide association study identifies three loci associated with melanoma risk. Nat Genet **41:**920–925.

96. Shong YK, Kim JA 1991 Vitiligo in autoimmune thyroid disease. Thyroidology **3:**89–91.

97. Artanaş S, Gül U, Kiliç A, Gül S 2009 Skin findings in thyroid disease. Eur J Intern Med **20:**158–161.

98. Tomer Y, Davies TF 2003 Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. Endocr Rev **24:**694–717.

99. Tomer Y, Huber A 2009 The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun **32:**231–239.

100. Weetman AP 2009 The genetics of autoimmune thyroid disease. Horm Metab Res **41:**421–425.

101. Jacobson EM, Huber A, Tomer Y 2008 The HLA gene complex in thyroid autoimmunity: from epidemiology to etiology. J Autoimmun **30:**58–62.

102. Ban Y, Davies TF, Greenberg DA, Concepcion ES, Osman R, Oashi T, Tomer Y 2004 Arginine at position 74 of the HLA-DRb1 chain is associated with Graves' disease. Genes Immun **5:**203–208.

103. Simmonds MJ, Howson JM, Heward JM, Cordell HJ, Foxall H, Carr-Smith J, Gibson SM, Walker N, Tomer Y, Franklyn JA, Todd JA, Gough SC 2005 Regression mapping of association between the human leukocyte antigen region and Graves disease. Am J Hum Genet **76:**157–163.

104. Menconi F, Monti MC, Greenberg DA, Oashi T, Osman R, Davies TF, Ban Y, Jacobson EM, Concepcion ES, Li CW, Tomer Y 2008 Molecular amino acid signatures in the MHC class II peptide-binding pocket predispose to autoimmune thyroiditis in humans and in mice. Proc Natl Acad Sci U S A **105:**14034–14039.

105. Jacobson EM, Tomer Y 2007 The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future. J Autoimmun **28:**85–98.

106. Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, Rainbow DB, Hunter KM, Smith AN, Di Genova G, Herr MH, Dahlman I, Payne F, Smyth D, Lowe C, Twells RC, Howlett S, Healy B, Nutland S, Rance HE, Everett V, Smink LJ, Lam AC, Cordell HJ, Walker NM, Bordin C, Hulme J, Motzo C, Cucca F, Hess JF, Metzker ML, Rogers J, Gregory S, Allahabadia A, Nithiyananthan R, Tuomilehto-Wolf E, Tuomilehto J, Bingley P, Gillespie KM, Undlien DE, Rønningen KS, Guja C, Ionescu-Tîrgovişte C, Savage DA, Maxwell AP, Carson DJ, Patterson CC, Franklyn JA, Clayton DG, Peterson LB, Wicker LS, Todd JA, Gough SC 2003 Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature **423:**506–511.

107. Velaga MR, Wilson V, Jennings CE, Owen CJ, Herington S, Donaldson PT, Ball SG, James RA, Quinton R, Perros P, Pearce SH 2004 The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. J Clin Endocrinol Metab **89:**5862–5865.

108. Jacobson EM, Concepcion E, Oashi T, Tomer Y 2005 A Graves' disease-associated Kozak sequence single-nucleotide polymorphism enhances the efficiency of CD40 gene translation: a case for translational pathophysiology. Endocrinology **146:**2684–2691.

109. Wellcome Trust Case Control Consortium; Australo-Anglo-American Spondylitis Consortium (TASC), Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand WH, Samani NJ, Todd JA, Donnelly P, Barrett JC, Davison D, Easton D, Evans DM, Leung HT, Marchini JL, Morris AP, Spencer CC, Tobin MD, Attwood AP, Boorman JP, Cant B, Everson U, Hussey JM, Jolley JD, Knight AS, Koch K, Meech E, Nutland S, Prowse CV, Stevens HE, Taylor NC, Walters GR, Walker NM, Watkins NA, Winzer T, Jones RW, McArdle WL, Ring SM, Strachan DP, Pembrey M, Breen G, St. Clair D, Caesar S, Gordon-Smith K, Jones L, Fraser C, Green EK, Grozeva D, Hamshere ML, Holmans PA, Jones IR, Kirov G, Moskivina V, Nikolov I, O'Donovan MC, Owen MJ, Collier DA, Elkin A, Farmer A, Williamson R, McGuffin P, Young AH, Ferrier IN, Ball SG, Balmforth AJ, Barrett JH, Bishop TD, Iles MM, Maqbool A, Yuldasheva N, Hall AS, Braund PS, Dixon RJ, Mangino M, Stevens S, Thompson JR, Bredin F, Tremelling M, Parkes M, Drummond H, Lees CW, Nimmo ER, Satsangi J, Fisher SA, Forbes A, Lewis CM, Onnie CM, Prescott NJ, Sanderson J, Matthew CG, Barbour J, Mohiuddin MK, Todhunter CE, Mansfield JC, Ahmad T, Cummings FR, Jewell DP, Webster J, Brown MJ, Lathrop MG, Connell J, Dominiczak A, Marcano CA, Burke B, Dobson R, Gungadoo J, Lee KL, Munroe PB, Newhouse SJ, Onipinla A, Wallace C, Xue M, Caulfield M, Farrall M, Barton A; Biologics in RA Genetics and Genomics Study Syndicate (BRAGGS) Steering Committee, Bruce IN, Donovan H, Eyre S, Gilbert PD, Hilder SL, Hinks AM, John SL, Potter C, Silman AJ, Symmons DP, Thomson W, Worthington J, Dunger DB, Widmer B, Frayling TM, Freathy RM, Lango H, Perry JR, Shields BM, Weedon MN, Hattersley AT, Hitman GA, Walker M, Elliott KS, Groves

CJ, Lindgren CM, Rayner NW, Timpson NJ, Zeggini E, Newport M, Sirugo G, Lyons E, Vannberg F, Hill AV, Bradbury LA, Farrar C, Pointon JJ, Wordsworth P, Brown MA, Franklyn JA, Heward JM, Simmonds MJ, Gough SC, Seal S; Breast Cancer Susceptibility Collaboration (UK), Stratton MR, Rahman N, Ban M, Goris A, Sawcer SJ, Compston A, Conway D, Jallow M, Newport M, Sirugo G, Rockett KA, Bumpstead SJ, Chaney A, Downes K, Ghori MJ, Gwilliam R, Hunt SE, Inouye M, Keniry A, King E, McGinnis R, Potter S, Ravindrarajah R, Whittaker P, Widden C, Withers D, Cardin NJ, Davison D, Ferreira T, Pereira-Gale J, Hallgrimsdo'ttir IB, Howie BN, Su Z, Teo YY, Vukcevic D, Bentley D, Brown MA, Compston A, Farrall M, Hall AS, Hattersley AT, Hill AV, Parkes M, Pembrey M, Stratton MR, Mitchell SL, Newby PR, Brand OJ, Carr-Smith J, Pearce SH, McGinnis R, Keniry A, Deloukas P, Reveille JD, Zhou X, Sims AM, Dowling A, Taylor J, Doan T, Davis JC, Savage L, Ward MM, Learch TL, Weisman MH, Brown M 2007 Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet **39:**1329–1337.

110. Ban Y, Greenberg DA, Concepcion E, Skrabanek L, Villanueva R, Tomer Y 2003 Amino acid substitutions in the thyroglobulin gene are associated with susceptibility to human and murine autoimmune thyroid disease. Proc Natl Acad Sci U S A **100:**15119–15124.

111. Brand OJ, Barrett JC, Simmonds MJ, Newby PR, McCabe CJ, Bruce CK, Kysela B, Carr-Smith JD, Brix T, Hunt PJ, Wiersinga WM, Hegedüs L, Connell J, Wass JA, Franklyn JA, Weetman AP, Heward JM, Gough SC 2009 Association of the thyroid stimulating hormone receptor gene (TSHR) with Graves' disease. Hum Mol Genet **18:**1704–1713.

Address correspondence to:
Richard A. Spritz, M.D.
Human Medical Genetics Program
University of Colorado School of Medicine
Aurora, CO 80113

E-mail: richard.spritz@ucdenver.edu