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Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo

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Summary

Generalized vitiligo is an autoimmune disorder in which acquired white patches of skin and overlying hair result from autoimmune loss of melanocytes from involved areas. Although usually sporadic, family clustering of vitiligo may occur, in a non-Mendelian pattern typical of multifactorial, polygenic inheritance. Sporadic vitiligo is associated with autoimmune thyroid disease, pernicious anemia, Addison's disease, and lupus; these same disorders occur at increased frequency in patients' first-degree relatives. Here, we studied 133 'multiplex' generalized vitiligo families, with multiple affected family members. The age of onset of vitiligo is earlier in these 'multiplex' families than in patients with sporadic vitiligo. Affected members of the multiplex vitiligo families have elevated frequencies of autoimmune thyroid disease, rheumatoid arthritis, psoriasis, adult-onset insulin-dependent diabetes mellitus, pernicious anemia, and Addison's disease. Probands' unaffected siblings have elevated frequencies of most of these same autoimmune diseases, particularly if the proband had non-vitiligo autoimmune disease. Familial generalized vitiligo is thus characterized by earlier disease onset and a broader repertoire of associated autoimmune diseases than sporadic vitiligo. This mostly likely reflects a greater inherited genetic component of autoimmune susceptibility in these families. These findings have important implications for autoimmune disease surveillance in families in which multiple members are affected with vitiligo.

Key words: multiple autoimmune disease/autoimmune polyendocrine syndrome/thyroid disease/rheumatoid arthritis/psoriasis/diabetes mellitus/pernicious anemia/Addison's disease

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Introduction

Generalized vitiligo is an acquired, non-contagious disorder in which progressive, patchy loss of pigmentation from skin, overlying hair, and oral mucosa results from loss of melanocytes from the involved areas (Hann and Nordlund, 2000; Nordlund and Ortonne, 1993). The frequency of vitiligo in Caucasians is approximately 0.38% (Howitz et al., 1977). Most cases occur sporadically, although about 20% of probands have one or more affected first-degree relatives, with cases usually occurring in a non-Mendelian pattern suggestive of polygenic, multifactorial inheritance (Alkhateeb et al., 2003; Bhatia et al., 1992; Carnevale et al., 1980; Das et al., 1985a,b; Hafez et al., 1983; Majumder et al., 1988, 1993; Mehta et al., 1973; Nath et al., 1994).

Vitiligo is widely considered to have an autoimmune basis (Harsoulis et al., 1978; Nordlund and Ortonne, 1993; Ongenae et al., 2003), although the specific triggers and precise nature of the autoimmune response remain unclear. Perhaps the strongest evidence for an autoimmune origin of vitiligo is its association with other autoimmune diseases. Vitiligo is a component of the APECED (APS1) and Schmidt (APS2) multiple autoimmune disease syndromes (Baker, 1992; Riley, 1992), and a number of studies have suggested specific association of vitiligo with autoimmune thyroid disease (Cunliffe et al., 1968; Schallreuter et al., 1994), pernicious anemia (Dawber, 1969; Grunnet and Howitz, 1970), Addison's disease (Zelissen et al., 1995), and perhaps alopecia areata (Sharma et al., 1996a,b).

We previously described epidemiologic aspects of vitiligo and associated autoimmune diseases in more than 2600 Caucasian vitiligo patients and their close relatives (Alkhateeb et al., 2003). The great majority of these cases were sporadic in occurrence. These vitiligo patients had a mean age of vitiligo onset of 23.9 ± 16.0 yr, and they had significantly increased

frequencies of autoimmune thyroid disease, pernicious anemia, Addison's disease, systemic lupus erythematosus, and perhaps inflammatory bowel disease. These same autoimmune diseases occurred at elevated frequency in the probands' first-degree relatives, whereas the frequencies of various other autoimmune diseases were not increased in either the probands or their relatives. These findings indicated that vitiligo patients and their close relatives are genetically susceptible to a specific group of autoimmune diseases – vitiligo, autoimmune thyroid disease, pernicious anemia, Addison's disease, and lupus.

Here, we present a similar analysis of 133 'multiplex' vitiligo families, in which multiple family members are affected with vitiligo, comparing them to an updated subject cohort of 3238 unselected, unrelated Caucasian vitiligo probands. We find that age of vitiligo onset is significantly earlier for affected members of the multiplex vitiligo families than among the unselected vitiligo probands. The multiplex vitiligo families have significantly elevated frequencies of autoimmune thyroid disease, pernicious anemia, and Addison's disease, as we had found in the unselected vitiligo probands and their relatives. In addition, the multiplex vitiligo families also have elevated frequencies of psoriasis, rheumatoid arthritis, and adult-onset insulin-dependent diabetes mellitus, autoimmune diseases that were not increased in frequency among the sporadic vitiligo probands. These results show that multiplex vitiligo families exhibit earlier disease onset and an expanded repertoire of vitiligo-associated autoimmune diseases, indicative of a greater genetic component of inherited autoimmune susceptibility in familial vitiligo than in singleton cases.

Results

Age of vitiligo onset

The 133 Caucasian multiplex vitiligo families had 2–13 affected individuals per family (mean 3.3 ± 1.8), segregation occurring in a non-Mendelian pattern. In more than three-fourths of cases the diagnosis of vitiligo had been confirmed by physician diagnosis. Only cases we also considered confirmed based on review of clinical history and lesion map are counted here as 'affected'. Among 374 affected family members for whom data were available, the mean age of vitiligo onset was 21.5 ± 15.0 yr (median 18.5), compared with 24.2 ± 16.2 yr (median 22.0) among 3238 unselected Caucasian vitiligo probands, the great majority of whom represent singleton cases. As shown in Figure 1, linear rank tests demonstrated that this difference is highly significant, with log-rank chi-square P-value = 0.0012, and Gehan (Wilcoxon) P-value = 0.0022. Thus, the age of disease onset is significantly earlier in Caucasian familial vitiligo cases than in unselected Caucasian vitiligo probands.

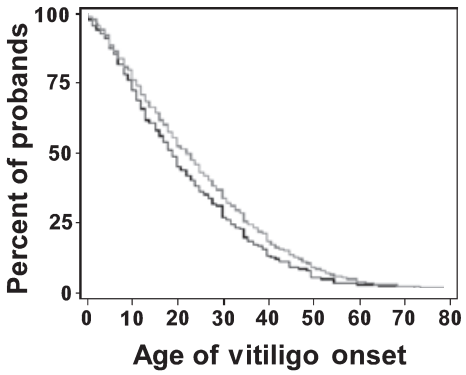

Figure 1. Kaplan–Meier survival (time to event) plot of age-of-onset for vitiligo. Black line represents the survival curve for vitiligo probands from multiplex vitiligo families and the gray line represents the survival curve for unselected, principally sporadic, vitiligo probands.

We also analyzed extent of skin involvement, self-reported in quartiles. However, there was no significant difference between the familial and unselected vitiligo probands on this parameter.

Occurrence of non-vitiligo autoimmune diseases in familial vitiligo probands

These probands were selected on the basis of multiple family members affected with vitiligo, but were unselected with respect to occurrence of other autoimmune diseases. Therefore, we could directly compare self-report of specific autoimmune diseases by familial vitiligo probands vs. by unselected vitiligo probands (Alkhateeb et al., 2003). Of the 133 familial vitiligo probands, 84 (63.2%) had only vitiligo, whereas 49 (36.8%) reported an average of 1.2 additional autoimmune diseases per individual. As shown in Table 1, the most frequent was autoimmune thyroid disease, reported by 22.6% of familial vitiligo probands, significantly more (P = 0.025) than its 17.0% frequency among unselected vitiligo probands (Alkhateeb et al., 2003), and far more (P = 0) than the ~1.90% frequency of autoimmune thyroid disease in the USA population (Canaris et al., 2000; Hollowell et al., 2002; Jacobson et al., 1997). Among the familial vitiligo probands, 73% reported hypothyroidism and 27% hyperthyroidism, very similar to the prevalence of hypothyroidism vs. hyperthyroidism in the general population (Canaris et al., 2000; Hollowell et al., 2002).

Pernicious anemia was reported by 2.3% of the familial vitiligo probands, similar to (P = 0.219) its 1.8% frequency among unselected vitiligo probands (Alkhateeb et al., 2003), and far more (P = 9.1E-11) than its 0.15% frequency in the USA population (Jacobson et al., 1997). Likewise, Addison's disease was reported by 0.75% of the familial vitiligo probands, similar to (P = 0.331) its 0.38% frequency among unselected vitiligo probands (Alkhateeb et al., 2003), and far more (P = 0) than its 0.005% frequency in the USA population (Jacobson

Table 1. Associated autoimmune disorders in Caucasian familial vitiligo probands and their siblings

	Probands (n = 133)	Siblings (n = 331)	Population frequency (%)
Vitiligo	133 (100%)	128 (38.7%)	0.38
Thyroid disease	30 (21.4%), P = 0	49 (14.8%), P = 0	1.9
Undefined		7	
Hypothyroidism	22	35	
Hyperthyroidism	8	7	
Psoriasis	7 (5.3%), P = 2.4E-7	15 (4.6%), P = 9.4E-12	1.0
Rheumatoid arthritis	5 (3.8%), P = 0.00011	7 (2.1%), P = 0.0046	0.86
Adult-onset IDDM	5 (3.8%), P = 9.1E-7	4 (1.2%), NS	0.59
Pernicious anemia	3 (2.3%), P = 9.1E-11	6 (1.8%), P = 0	0.15
Alopecia areata	3 (2.3%), NS	8 (2.4%), NS	1.8
Hyper/hypoparathyroidism	3 (2.3%), ND	1 (<1%), ND	
Addison's disease	1 (<1%), P = 0	1 (<1%), P = 0	0.005
Anklyosing spondylitis	1 (<1%), NS	2 (<1%), NS	0.45
Inflammatory bowel disease	1 (<1%), NS		0.21
Sjogren's syndrome		2 (<1%), ND	0.014
Celiac disease		1 (<1%), ND	0.75
Scleroderma		1 (<1%), ND	0.0044
Uveitis		1 (<1%), ND	
None		157 (47.7%)	

P-values are for comparison of observed frequency with population frequency of each disease; NS, not significant; ND, not done.

et al., 1997), although this is based on a single case, so the absolute frequency cannot be considered reliable.

Several other autoimmune diseases that we had not found at increased frequency among unselected vitiligo probands (Alkhateeb et al., 2003) occurred at significantly elevated frequencies among the familial vitiligo probands, in fact ranking above pernicious anemia. Psoriasis occurred in 5.3% of the familial vitiligo probands, significantly more than its 1.0% frequency (P = 2.4E-7) among the unselected vitiligo probands (Alkhateeb et al., 2003) and its ~2% frequency (P = 9.4E-12) in the USA and western European populations (Naldi, 2004). Rheumatoid arthritis occurred in 3.8% of the familial vitiligo probands, significantly more than its 0.67% frequency (P = 0.00011) among unselected vitiligo probands (Alkhateeb et al., 2003) and its 0.86% frequency (P = 0.0046) in the USA population (Jacobson et al., 1997). Adult-onset insulin-dependent diabetes mellitus, which could not be assessed among the unselected vitiligo probands, also occurred in 3.8% of the familial vitiligo probands, significantly more than its frequency of ~0.59% (P = 9.1E-7) in the USA and western European populations (Koopman et al., 2005; Pozzilli and DiMario, 2001).

The frequency of alopecia areata among the familial vitiligo probands was 2.3%, greater than both its 1.1% frequency among unselected vitiligo probands (Alkhateeb et al., 2003) and its ~1.8% frequency in the USA population (Safavi, 1992; Safavi et al., 1995). However, neither of these differences was significant. The frequencies of ankylosing spondylitis, scleroderma, Sjogren's syndrome, and inflammatory bowel disease were also not significantly increased above their population frequencies (Jacobson et al., 1997), although all of these are based on only single cases among the vitiligo probands. The frequency of autoimmune hypo/hyperparathyroidism, 2.3% among the vitiligo probands, is not known in the general population and therefore could not be evaluated. The other autoimmune disorders queried were not reported by any of the familial vitiligo probands.

Occurrence of autoimmune diseases in siblings of familial vitiligo probands

To assess whether susceptibility to autoimmunity is familial, we tabulated autoimmune diseases reported by 331 siblings of the familial vitiligo probands. In general, our findings among the probands' siblings were similar to those in the probands themselves. Among siblings, the frequency of vitiligo was 38.7%, a 6.8-fold increase (P = 0) over the 6.1% frequency of vitiligo among siblings of unselected vitiligo probands (Alkhateeb et al., 2003). However, the current families had been selected on the basis of multiplex cases of vitiligo (although not necessarily among siblings), potentially biasing this outcome. As an approach to correct for this bias, we subtracted one affected sibling from each family, a perhaps overly-stringent correction. Nevertheless, after this correction the frequency of vitiligo in probands' siblings was still 12.6%, a 2.1-fold increase (P = 0.001) over the frequency in vitiligo among siblings of unselected probands (Alkhateeb et al., 2003). This suggests that susceptibility to vitiligo is increased among siblings of familial vitiligo probands over that among siblings of sporadic vitiligo patients.

The frequencies of other vitiligo-associated autoimmune disorders were also very high among probands' siblings, regardless of whether or not those siblings had

vitiligo. Not counting vitiligo itself, 124 (37.5%) of probands' 331 siblings reported at least one (average 1.2) other autoimmune disease. These were essentially the same disorders seen at increased frequencies among the probands: autoimmune thyroid disease (frequency 14.8%; P = 0), psoriasis (frequency 4.5%; P = 0.4E-12), rheumatoid arthritis (frequency 2.1%; P = 0.0046, pernicious anemia (frequency 1.8%; P = 0), and Addison's disease (frequency 0.3%; P = 0). The 1.2% frequency of adult-onset insulin-dependent diabetes among probands' siblings was not quite significantly elevated (P = 0.069). The frequencies of alopecia areata, ankylosing spondylitis, and inflammatory bowel disease were not significantly elevated in probands' siblings, and the other autoimmune diseases queried were not reported by any of the siblings.

We also considered whether the frequency of autoimmune disease might be greater among siblings of familial vitiligo probands who themselves have other autoimmune diseases, vs. siblings of familial vitiligo probands who did not have other autoimmune diseases. Not surprisingly, this proved to be the case. There was no significant difference between the actual mean number of siblings of vitiligo-only probands (2.51) vs. probands with other autoimmune disease (2.44). The frequency of non-vitiligo autoimmune disease was 41% among siblings of probands who themselves also had non-vitiligo autoimmune disease, vs. only 14% among siblings of probands who had only vitiligo; this difference is highly significant (P = 0) and represents a relative risk of 3.2. Again, the autoimmune diseases that occurred most frequently were vitiligo and autoimmune thyroid disease. Thus, the risk of both vitiligo and other autoimmune diseases is considerably greater among siblings of familial vitiligo probands who themselves also have non-vitiligo autoimmune disease than among siblings of probands who have only vitiligo.

Discussion

The current study of 133 Caucasian multiplex vitiligo families expands on our previous survey of 2624 unselected Caucasian vitiligo probands, mostly singleton patients (Alkhateeb et al., 2003). As expected, these vitiligo families provide evidence of a greater genetic component than in unselected vitiligo probands, including earlier age of vitiligo onset and greater risk to siblings of vitiligo as well as other vitiligo-associated autoimmune diseases.

In addition, the multiplex vitiligo families provide support for an expanded repertoire of autoimmune diseases that are significantly associated with vitiligo. Small-scale studies provided initial evidence of associations between vitiligo and autoimmune thyroid disease (Cunliffe et al., 1968; Schallreuter et al., 1994), pernicious anemia (Dawber, 1969; Grunnet and Howitz, 1970), Addison's disease (Zelissen et al., 1995), and perhaps alopecia areata (Sharma et al., 1996a,b). Our previous survey of unselected vitiligo probands (Alkhateeb et al., 2003) found an overall frequency of self-reported non-vitiligo autoimmune disease among probands of about 20%, with significantly elevated frequencies of autoimmune thyroid disease (both hypothyroidism and hyperthyroidism), pernicious anemia, Addison's disease, and systemic lupus erythematosus, but no increase in the frequencies of alopecia areata, multiple sclerosis, myasthenia gravis, psoriasis, rheumatoid arthritis, scleroderma, and Sjogren's syndrome. We observed these increases in both the unselected vitiligo probands and their first-degree relatives, indicating that susceptibility to this group of autoimmune disorders involves a significant genetic component. Recent retrospective studies of large vitiligo patient series in India (Handa and Dogra, 2003; Handa and Kaur, 1999) and Nigeria (Onunu and Kubeyinje, 2003) have generally confirmed our findings in Caucasians, but reported much lower frequencies of associated autoimmune diseases, particularly thyroid disease, most likely because of under-diagnosis of many of these autoimmune diseases in these populations.

In the 133 multiplex vitiligo families studied here, one-third of family probands reported at least one other autoimmune disease besides vitiligo. Among the probands, the frequencies of autoimmune thyroid disease, pernicious anemia, and Addison's disease were again elevated, as we had found among the unselected vitiligo probands. Surprisingly, we also observed significantly elevated frequencies of psoriasis, rheumatoid arthritis, and adult-onset insulin-dependent diabetes mellitus, diseases whose frequencies had not been elevated among the unselected vitiligo probands. Again, the frequencies of alopecia areata, ankylosing spondylitis, scleroderma, and Sjogren's syndrome were not elevated among the family probands, and the many other autoimmune diseases queried were not reported at all.

The general risk of autoimmune disease is clearly heritable in multiplex vitiligo families, with the siblings of familial vitiligo probands having a frequency of vitiligo much greater than the overall 6.1% risk we found in the siblings of unselected vitiligo patients, although the magnitude of the increased risk in the multiplex vitiligo families is difficult to estimate with precision. The risk of non-vitiligo autoimmune disease is also very high among the probands' siblings. In fact, the frequency of non-vitiligo autoimmune disease was essentially the same among probands (36%) and their siblings (37%), with the frequency being substantially greater (41%) among siblings of probands who themselves reported additional autoimmune diseases than the 14% among siblings of probands with only vitiligo. In general, the non-uniform risk of autoimmune disease in probands' relatives is inconsistent with Mendelian inheritance and more consistent with multifactorial inheritance.

Overall, our findings provide strong support for a greater genetic component of risk for both vitiligo and

specific vitiligo-associated autoimmune diseases in familial vitiligo than in unselected, principally singleton vitiligo cases. This is an important consideration for future investigations of environmental risk factors for vitiligo, implied by a concordance for vitiligo in monozygotic twins of only 23% (Alkhateeb et al., 2003). Our current findings expand the repertoire of autoimmune diseases associated with vitiligo to include autoimmune thyroid disease, pernicious anemia, psoriasis, rheumatoid arthritis, adult-onset insulin-dependent diabetes mellitus, Addison's disease, and systemic lupus erythematosus, and establish vitiligo as an important component of so-called 'multiple autoimmune disease'. These findings have important implications for surveillance for individual autoimmune diseases in families at risk, and suggest that screening for at least autoimmune thyroid disease should become standard medical practice in patients with vitiligo and perhaps also their first-degree relatives.

Materials and methods

Study families

The 133 multiplex Caucasian families with multiple members affected with generalized vitiligo were ascertained principally from the memberships of the Vitiligo Society, UK and the National Vitiligo Foundation, USA. All available affected and unaffected family members filled out a questionnaire that reported age of disease onset, stability of lesions, physician diagnosis of vitiligo, laterality of lesions, degree of skin involvement, whether white spotting was congenital, and occurrence of heterochromia irides, deafness, and chemical exposure. Each study participant (both affected and unaffected with vitiligo) filled out a skin lesion map. All clinical data and lesion maps were carefully reviewed by the study investigators, and most family members (affected and unaffected) were personally examined by the study staff. The few individuals in whom the diagnosis of generalized vitiligo was considered uncertain were excluded from the data presented here.

Each study participant also completed an extensive questionnaire list of other autoimmune diagnoses, providing age of disease onset and additional details for each. These included: Addison's disease, allergies/asthma/eczema, ankylosing spondylitis (Strümpell-Marie disease/Bekhterev-Strümpel syndrome/spondyloarthritis), antiphospholipid syndrome (anti-cardiolipin syndrome), autoimmune polyendocrine syndrome type 1 (APS1/autosomal recessive APECED), autoimmune hemolytic anemia, autoimmune hepatitis (non-infectious chronic active hepatitis), Behçet's disease, bullous pemphigoid, cardiomyopathy, celiac disease (celiac sprue/gluten enteropathy), chronic inflammatory demyelinating polyneuropathy, Churg-Strass syndrome (allergic granulomatosis), cicatrical pemphigoid (mucous membrane pemphigoid/benign pemphigoid), CREST syndrome, cold agglutinin disease, diabetes (specifying age of onset and type, including insulin-dependent diabetes mellitus/type 1/juvenile diabetes, non-insulin-dependent diabetes mellitus/type 2/adult-onset, unknown, and type of treatment (pills/diet/insulin/none), essential mixed cryoglobulinemia, fibromyalgia–fibromyositis syndrome, Guillain-Barré syndrome, IgA nephropathy, idiopathic thrombocytic purpura (ITP), inflammatory bowel disease (Crohn's disease/ulcerative colitis/irritable bowel syndrome), hypo- or hyperparathyroidism, kidney disease (glomerulonephritis/nephrosis/nephritic syndrome), juvenile arthritis, lichen planus, multiple sclerosis, myasthenia gravis, pernicious anemia, pemphigus vulgaris, piebaldism, polyarteritis nodosa, polychondritis, polymyalgia rheumatica, polymyositis and dermatomyositis (PM–DM syndrome), primary biliary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome (APS2), Sjogren's syndrome, Stiff-man syndrome (Moersch–Woltmann syndrome), systemic lupus erythematosus (lupus, SLE), Takayasu arteritis, temporal arteritis (giant cell arteritis), thyroid disease (graves disease/myxedema/hyperthyroidism, Hashimoto's thyroiditis/goiter/hypothyroidism), uveitis, and Waardenburg syndrome. In some cases specific diagnoses were checked by review of clinical records and clinical tests; diagnoses considered questionable based on standard diagnostic criteria were excluded.

These studies were approved by the Colorado Multiple Institutional Review Board (COMIRB) and the Multicentre Research Ethics Committee (UK), and were performed in accord with Declaration of Helsinki principles. Written informed consent was obtained from all study participants prior to their participation.

Statistics

We used Fisher's exact test and chi-square analyses to calculate P-values as appropriate. For comparisons with disease frequencies in the general population, we considered the population frequency as a virtually fixed constant, given that it was calculated with a very large sample; consequently, we used the formula:

$$Z = (f1 - f2)/\sqrt{[f2(1 - f2)/n]}$$

where z is the standard normal variate, $f1$ the frequency in our sample, $f2$ the frequency in the general population, and n is the number of individuals in our sample.

Statistical analysis of age at onset was conducted using the LIFETEST procedure implemented in the SAS system. Kaplan–Meier estimates were used to construct survival (time to event) curves for each group. Non-parametric comparisons of survival distributions were obtained by the log rank and Gehan (Wilcoxon) tests implemented in the LIFETEST procedure.

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