Genetics of Vitiligo

Richard A. Spritz, MD*, Genevieve H.L. Andersen, BS

KEYWORDS

• Vitiligo • Autoimmunity • Gene • Genomewide association study • Genetic linkage
• Genetic epidemiology

KEY POINTS

- Vitiligo is a complex disorder (also termed polygenic and multifactorial), reflecting simultaneous contributions of multiple genetic risk factors and environmental triggers.
- Large-scale genomewide association studies, principally in European-derived whites and in Chinese, have discovered approximately 50 different genetic loci that contribute to vitiligo risk, some of which also contribute to other autoimmune diseases that are epidemiologically associated with vitiligo. At many of these vitiligo susceptibility loci the corresponding relevant genes have now been identified and, for some of these genes, the specific DNA sequence variants that contribute to vitiligo risk are also now known.
- A large fraction of these genes encode proteins involved in immune regulation, several others play roles in cellular apoptosis, and still others are involved in regulating functions of melanocytes.
- Although many of the specific biologic mechanisms through which these genetic factors operate to cause vitiligo remain to be elucidated, it is now clear that vitiligo is an autoimmune disease involving a complex relationship between programming and function of the immune system, aspects of the melanocyte autoimmune target, and dysregulation of the immune response.

INTRODUCTION, BACKGROUND, AND GENETIC EPIDEMIOLOGY

The disorder now known as vitiligo was first described by Claude Nicolas Le Cat in 1765.[1] However, the first specific consideration of a genetic component in vitiligo did not come until 1950, when Stűttgen[2] and Teindel[3] simultaneously reported a total of 8 families with multiple relatives affected by vitiligo. Stűttgen[2] noted that, in his affected family, vitiligo seemed to exhibit dominant inheritance after intermarriage to a family with apparent recessive thyroid disease, a very early recognition of what would now be considered complex (polygenic, multifactorial) inheritance. Mohr,[4] Siemens,[5] and Vogel[6] subsequently reported concordant identical twin-pairs affected by vitiligo, pointing to a major role for genetic factors. Early clinical case series reported a frequency of vitiligo in probands' relatives of 11% to 38%,[7–10] highlighting the importance of genetic factors even in typical vitiligo cases.

Nevertheless, formal genetic epidemiologic studies of vitiligo came much later. Hafez and colleagues,[11] and Das and colleagues,[12] suggested a polygenic, multifactorial mode of inheritance, and estimated vitiligo heritability at 46%[12] to 72%.[11] Subsequent investigations likewise supported a polygenic, multifactorial model,[13–18] with heritability approximately 50%.[18] A twin study of vitiligo in European-derived whites[17] found that the concordance of vitiligo was 23% in monozygotic twins, underscoring the importance of nongenetic factors as well as genetic factors in vitiligo pathogenesis. In this same study, large-scale genetic

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Human Medical Genetics and Genomics Program, University of Colorado School of Medicine, 12800 East 19th Avenue, Room 3100, MS8300, Aurora, CO 80045, USA
* Corresponding author.
E-mail address: richard.spritz@ucdenver.edu

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epidemiologic analyses[17] indicated that in European-derived whites the overall frequency of vitiligo in probands' first-degree relatives was 7%, with the risk 7.8% in probands' parents and 6.1% in siblings, consistent with polygenic, multifactorial inheritance and age-dependency of vitiligo onset. Importantly, among vitiligo probands' affected relatives, the frequency of vitiligo was equal in male and female subjects, eliminating the female sex bias found in most vitiligo clinical case series. Moreover, a careful study of families with multiple relatives affected by vitiligo[19] showed earlier age-of-onset and greater skin surface involvement than in singleton cases,[17] as well as greater frequency of other autoimmune diseases, suggesting that in such multiplex families genes likely contribute more to vitiligo risk than in singleton cases.

RELATIONSHIP TO OTHER AUTOIMMUNE DISEASES

The genetic basis of vitiligo is deeply intertwined with the genetic basis of other autoimmune diseases with which vitiligo is epidemiologically associated. Indeed, the earliest clue to the autoimmune origin of vitiligo came in the original 1855 report of Addison disease,[20] which included a patient with idiopathic adrenal insufficiency, generalized vitiligo, and pernicious anemia, a co-occurrence of autoimmune diseases that suggested shared etiologic factors. Subsequently, the co-occurrence of different autoimmune diseases, including vitiligo, was reported by many investigators, particularly Schmidt,[21] and key combinations of concomitant autoimmune diseases were later codified by Neufeld and Blizzard.[22] Beginning with the vitiligo case series reported by Steve,[23] numerous investigators have since documented prevalent co-occurrence of vitiligo with various other autoimmune diseases, particularly autoimmune thyroid disease (both Hashimoto disease and Graves disease), pernicious anemia, Addison disease, systemic lupus erythematosus,[17] rheumatoid arthritis, adult-onset type 1 diabetes mellitus, and perhaps psoriasis.[19] Of particular importance, these same vitiligo-associated autoimmune diseases also occur at increased frequency in first-degree relatives of vitiligo probands who do not themselves have vitiligo, indicating that these autoimmune diseases share at least some of their genetic underpinnings with vitiligo.[19]

EARLY GENETIC MARKER STUDIES

The earliest attempts to identify genetic markers associated with vitiligo began in the mid-1960s, assaying polymorphic blood proteins, such as the ABO and other blood group antigens[24–30]; secretor status[26,27,31]; and, later, serum alpha 1-antitrypsin and haptoglobin phenotypes,[32] with no positive results. A decade later, numerous investigators reported association studies of vitiligo with human leukocyte antigen (HLA) types, which have also been associated with many other autoimmune diseases. Initial association studies of vitiligo and HLA yielded inconsistent and largely spurious findings due to testing different ethnic groups, inadequate statistical power, and inadequate correction for multiple-testing of many different HLA types.[33–37] Nevertheless, Foley and colleagues[38] correctly identified association of the HLA-DR4 class II serotype with vitiligo, borne out by subsequent studies, the first known genetic association for vitiligo. Importantly, HLA-DR4 is also strongly associated with several other autoimmune diseases.

A large number of additional HLA association studies of vitiligo were published subsequently, again with generally inconsistent findings. Nevertheless, Liu and colleagues[39] conducted a careful meta-analysis of 11 previous studies of HLA class I serotypes and found robust association of vitiligo with HLA-A2 with odds ratio (OR) 2.07, a finding borne out by subsequent studies. Specific associations of vitiligo with the class I and class II gene regions of the major histocompatibility complex (MHC) were subsequently replicated and refined by detailed molecular genetic and genomewide association studies (GWASs), even to the point of identifying apparently causal genetic variation (see later discussion).

NON-MAJOR HISTOCOMPATIBILITY COMPLEX CANDIDATE GENE ASSOCIATION STUDIES

The development of DNA technology in the late 1970s ushered in an era of testing candidate genes for association with a great many diseases, including vitiligo. Unfortunately, numerous retrospective studies have shown that well over 95% of published case-control genetic association studies represent false-positives, due to inadequate sample size and statistical fluctuation, genotyping errors, occult population stratification, inadequate correction for multiple-testing, and publication bias of positive results.[40,41] As the result, this type of study is no longer considered appropriate for primary discovery of genetic association. Accordingly, of the approximately 70 genes for which association with vitiligo has been claimed based on such studies, this article discusses only those 2 non-MHC candidate gene