Genetic Predisposition to Rosacea

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KEYWORDS

• Human leukocyte antigen • Single-nucleotide polymorphism • HLA-DRA

KEY POINTS

- The genetics of rosacea are poorly understood; however, gene variants, susceptibility, and associations with other autoimmune diseases provide insight into the genetic predisposition to rosacea.
- Rosacea may have evolved as a genetic mutation during low UV levels to allow vitamin D–independent *CAMP* activation and, thus, provide host defense against microbial infections.
- An overlap of certain genes in the genetic profiles of rosacea subtypes suggests a developmental march from an early inflammatory stage to a hyperglandular-phymatous stage.
- Rosacea is associated with the single-nucleotide polymorphism, rs763035, and the following HLA alleles: *HLA-DRB1*03:01, HLA-DQB1*02:01*, and *HLA-DQA1*05:01*.
- Rosacea shares genetic risk loci with autoimmune diseases, including type I diabetes, sarcoidosis, ulcerative colitis, celiac disease, and multiple sclerosis.

INTRODUCTION

Rosacea is a common, chronic inflammatory skin disease characterized by facial flushing and erythema, papules, pustules, and/or telangiectasias. Secondary features of rosacea may include burning and stinging, scaling dermatitis, and edema of the face.[1] This skin disorder is easily identifiable in fair-skinned individuals and may progress to ocular involvement and rhinophyma in severe cases. Although clinical patterns of the disease often overlap, the National Rosacea Society Expert Committee recognizes the following 4 major subtypes of rosacea: erythematotelangiectatic rosacea (ETR), inflammatory papulopustular rosacea (PPR), phymatous rosacea (PhR), and ocular rosacea.[2] This variable clinical presentation of rosacea may be explained by the multifactorial basis of its pathophysiology. Specifically, the etiopathogenesis involves complex interactions within the innate immune system mediated by toll-like receptor 2 (TLR-2) and neurovascular dysregulation mediated by transient receptor potential channel vanilloid receptor 1 (TRPV1).[3] Identified triggers for this pathogenesis include physical (ultraviolet light, temperature), biological (spicy food, microbiota), and endogenous (stress, genetic) stimuli.[4]

Evidence of a family history of the disease in up to one-third of patients with rosacea suggests a strong familial inheritance of the disorder.[1] The higher incidence of rosacea in Celtic and Northern European descendants suggests that there may be a genetic predilection to this disorder.[2] However, the particular role of genetics in the development and persistence of rosacea remains poorly understood. Recent advances in research into gene loci and expression, genetic susceptibility in twin studies, and associations with other autoimmune diseases have provided

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further insight into the genetic predisposition to rosacea.

Genetic Origin

The pathophysiology of rosacea and its predominance among certain populations may be explained by the genetic origin of the disease. One of the most compelling arguments for the genetic predisposition to rosacea is its high incidence in persons of Northern European descent, particularly the Celtic population. It is hypothesized that rosacea developed as a mutation in Celts to adapt protection against life-threatening bacterial infections, such as lupus vulgaris (also known as tuberculosis luposa) during UV-deficient periods.[5] Endoplasmic reticulum (ER) stress and sphigosine-1-phosphate (S1P) signaling in rosacea may have compensated for reduced vitamin D–dependent cathelicidin antimicrobial peptide (CAMP) expression during UV-deficient Nordic winters. Under adequate UVB exposure, UVB leads to 2 actions: (1) activation of the *CAMP* promoter via a vitamin D receptor and (2) induction of ER stress causing conversion of ceramide into S1P and, subsequent, promotion of C/EBPα gene expression of CAMP. This production of CAMP is important, as it provides cutaneous defense against bacterial pathogens, such as methicillin-resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis*, as well as viral and fungal infections.[5–7] Rosacea may have evolved in Northern Europeans under exposure to environmental conditions with insufficient vitamin D–dependent *CAMP* activation. In the absence of UVB, upregulation of CAMP occurs via enhanced ER stress signaling causing intrinsic activation of the alternative C/EBP-α–regulated *CAMP* promoter (transcription factor for CAMP). Multiple rosacea pathologies can be explained by ER stress-driven transcriptional regulations, such as production of S1P and LL37. For instance, the sensation of heat and sebaceous gland dysfunction in rosacea are mediated by S1P sensitization of TRPV1. The development of telangiectasias, UV sensitivity, and inflammation over sebaceous gland–rich areas of the face may result from LL37–mediated angiogenesis and inflammation. Despite this evidence for the linkage of ER stress-driven CAMP production to the etiopathogenesis of rosacea, the genetic defect underlying increased ER stress signaling remains unknown.[5]

Gene Expression and Transcription Studies

The association between gene expression and the manifestation of rosacea has been explored by several population and genetic analysis studies. Data from epidemiologic studies comparing the prevalence, skin phenotype, and geographic distribution of rosacea suggest a genetic component to rosacea.[8–10] Transcriptome profile analysis has confirmed the existence of selective and overlapping gene profiles for subtypes of rosacea.[10] Consistent with rosacea pathogenesis, genes of the innate immune response are actively expressed in skin lesions of ETR, PPR, and PhR. However, the expression of genes of the adaptive immune response are most prominent in the PPR and PhR subtypes. Gene studies and histologic data do not reveal a significant role for known microbial agents in early phases of rosacea.[10] Rather, the overlap of certain genes in the genetic profiles of rosacea subtypes suggests that a developmental march from an early inflammatory stage to a hyperglandular-phymatous stage occurs in some patients.[3,10]

The genetic profile of rosacea subtypes has also been compared with disorders with overlapping clinical features. In a case-control observational study, gene expression varied greatly between the ETR subtype and telangiectatic photoaging (TP). Despite the shared features of facial erythema and telangiectasia in both entities, 10 genes of selected mast cell-activating neuropeptides, immune modulators, and extracellular matrix components were overexpressed in ETR compared with TP. Fifteen genes were overexpressed in ETR compared with healthy controls (**Table 1**). Identified genes of significance encoded for substance P, matrix metalloproteinases, tumor necrosis factor alpha, and chemoattractants for mast cells (*TAC1*, *MMP9*, *TNFA*, and *CXCL12*, respectively). The demonstrated increased expression of *CXCL12* and its receptor CXCR4 in ETR compared with TP and healthy skin support the important role of mast cell migration and degranulation in rosacea. Substance P is of particular interest, given its known role of vasodilation and increased vascular permeability through action on vascular smooth muscle to release nitric oxide. The greater expression of substance P in ETR may explain the greater frequency of transient and nontransient erythema in ETR compared with TP. The overexpression of MMP9 and genes for type I collagen and type III collagen in ETR, in comparison to both TP and healthy controls, provides further support for the developmental march hypothesis as ECM remodeling directly affects vascular cell biology (as seen in ETR) and MMP gene upregulation is well documented in PPR and PhR.[3,11]

Considering specific gene loci of interest, population studies have identified gene variants associated with rosacea that may provide further insight