Clustering of autoimmune diseases in patients with rosacea

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Background: Rosacea is a common inflammatory skin condition that shares genetic risk loci with autoimmune diseases such as type 1 diabetes mellitus (T1DM) and celiac disease. A recent genomewide association study identified 90 genetic regions associated with T1DM, celiac disease, multiple sclerosis, and/or rheumatoid arthritis, respectively. However, a possible association with rosacea was not investigated.

Objective: We evaluated the association between rosacea and T1DM, celiac disease, multiple sclerosis, and rheumatoid arthritis, respectively.

Methods: We performed a population-based case-control study. A total of 6759 patients with rosacea were identified and matched with 33,795 control subjects on age, sex, and calendar time. We used conditional logistic regression to calculate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: After adjustment for smoking and socioeconomic status, patients with rosacea had significantly increased ORs for T1DM (OR 2.59, 95% CI 1.41-4.73), celiac disease (OR 2.03, 95% CI 1.35-3.07), multiple sclerosis (OR 1.65, 95% CI 1.20-2.28), and rheumatoid arthritis (OR 2.14, 95% CI 1.82-2.52). The association was mainly observed in women.

Limitations: We were unable to distinguish between the different subtypes and severities of rosacea.

Conclusions: Rosacea is associated with T1DM, celiac disease, multiple sclerosis, and rheumatoid arthritis, respectively, in women, whereas the association in men only reached statistical significance for rheumatoid arthritis. (J Am Acad Dermatol 2016;74:667-72.)

Key words: celiac disease; diabetes; epidemiology; multiple sclerosis; rheumatoid arthritis; rosacea.

Rosacea is an inflammatory skin condition characterized primarily by persistent or recurrent episodes of centrofacial erythema. Clinically, papules, pustules, and telangiectases can be observed, but patients may also develop rhinophyma and ocular symptoms including xeropthalmia.[1-4] However, distinct clinical patterns exist and the National Rosacea Society Expert Committee recognizes 4 subtypes of rosacea that frequently

Abbreviations used:

CI:	confidence interval
GWAS:	genomewide association study
ICD-8:	*International Classification of Diseases, Revision 8*
ICD-10:	*International Statistical Classification of Diseases, 10th Revision*
OR:	odds ratio
SLE:	systemic lupus erythematosus
T1DM:	type 1 diabetes mellitus

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Funding sources: None.

Disclosure: Dr Hansen is supported by a grant from the LEO Foundation. Dr Gislason is supported by an unrestricted research scholarship from the Novo Nordisk Foundation. Dr Egeberg is currently employed by Pfizer. Dr Thyssen is supported by a grant from the Lundbeck Foundation. This research was performed independently through the authors' academic university affiliations.

Accepted for publication November 3, 2015.

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Published online January 30, 2016.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.11.004

overlap, ie, erythematotelangiectatic, inflammatory papulopustular, phymatous, and ocular rosacea, respectively.[5] The exact prevalence of rosacea in Denmark is unclear, and although reported worldwide prevalences of rosacea differ markedly between countries, fair-skinned Europeans have increased risk of rosacea when compared with darker-skinned individuals and a rosacea prevalence of 10% has been reported from Sweden.[2,6] Distinct environmental triggers including *Demodex folliculorum*, ultraviolet irradiation, temperature changes, spicy foods, and alcohol consumption have been identified.[5] There is currently little definitive insight into comorbidities of rosacea although rosacea has been associated with migraine, depression, hypertension, dyslipidemia, coronary artery disease, and other chronic systemic illnesses.[7-10] However, although observational register studies enable examination of associations, these may also be explained by shared environmental or lifestyle factors rather than by a common genetic disposition, and such studies cannot establish a causal relationship.

CAPSULE SUMMARY

- Genomewide association studies have identified risk loci for rosacea that were also associated with several autoimmune disease.
- Rosacea is associated with type 1 diabetes mellitus, celiac disease, multiple sclerosis, and rheumatoid arthritis, particularly in women.
- Increased focus on autoimmune diseases in patients with rosacea may be warranted.

Although few studies have investigated the inheritance of rosacea, a study from Estonia showed that patients with rosacea often have a strong family history of rosacea and a very recent twin study from the United States suggested that approximately half of the risk of rosacea was accounted for by genetic factors.[11,12] Importantly, a very recent genomewide association study (GWAS) identified genetic risk loci for rosacea that were also associated with type 1 diabetes mellitus (T1DM) and celiac disease.[13] Because several studies have shown clustering of selected autoimmune diseases such as rheumatoid arthritis, celiac disease, multiple sclerosis, and T1DM, and a very recent GWAS identified 90 shared genetic regions associated with 1 or more of these 4 conditions,[14-16] it is tempting to speculate that rosacea could also be associated with these autoimmune diseases. Therefore, we evaluated the relationship between rosacea and rheumatoid arthritis, celiac disease, multiple sclerosis, and T1DM, respectively, in nationwide registers from Denmark.

METHODS

Data sources and study population

Study approval was obtained from by the Danish Data Protection Agency (reference 2007-58-0015, internal reference GEH-2014-018, I-Suite 02736). Review of an ethics committee is not required for register studies in Denmark. Conduct of this study was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[17]

All Danish citizens have free, equal, and universal access to health care. The unique personal identification number, which is assigned to all Danish citizens at immigration or birth, allows for unambiguous cross-linkage of administrative registers, and information on date of birth, gender, and vital statistics are available from the Civil Personal Register.[18] The Danish National Patient Register contains information on 99.4% of all hospital admissions, procedures, and diagnosis since 1978. Diagnoses are registered according to *International Classification of Diseases, Revision 8* (*ICD-8*) before 1994 and *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) thereafter.[19] Moreover, the Danish Civil Registration System contains information such as date of birth, sex, vital status, and Statistics Denmark records information on tax-reported household income.[20]

We identified all patients between January 1, 1997, and December 31, 2011, with an inpatient or outpatient (ambulatory) hospital diagnosis of rosacea (*ICD-8* code 695.3 and *ICD-10* code L71). We defined the index date as the time of the first diagnosis of rosacea for each individual patient. Each patient (case) was matched (on age, sex, and calendar time) with 5 healthy control subjects. The index date for the control subjects was defined as the date of first rosacea diagnosis for the corresponding case. From the Danish National Patient Register, we identified all patients with a diagnosis of T1DM, celiac disease, multiple sclerosis, and rheumatoid arthritis, respectively. The appropriate *ICD-8* and *ICD-10* codes are provided in the Appendix (available at http://www.jaad.org)