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Lessons learned from twins in autoimmune and chronic inflammatory diseases

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ABSTRACT

Autoimmunity and chronic inflammation recognize numerous shared factors and, as a result, the resulting diseases frequently coexist in the same patients or respond to the same treatments. Among the convenient truths of autoimmune and chronic inflammatory diseases, there is now agreement that these are complex conditions in which the individual genetic predisposition provides a rate of heritability. The concordance rates in monozygotic and dizygotic twins allows to estimate the weight of the environment in determining disease susceptibility, despite recent data supporting that only a minority of immune markers depend on hereditary factors. Concordance rates in monozygotic and dizygotic twins should be evaluated over an observation period to minimize the risk of false negatives and this is well represented by type I diabetes mellitus. Further, concordance rates in monozygotic twins should be compared to those in dizygotic twins, which share 50% of their genes, as in regular siblings, but also young-age environmental factors. Twin studies have been extensively performed in several autoimmune conditions and cumulatively suggest that some diseases, i.e. celiac disease and psoriasis, are highly genetically determined, while rheumatoid arthritis or systemic sclerosis have a limited role for genetics. These observations are necessary to interpret data gathered by genome-wide association studies of polymorphisms and DNA methylation in MZ twins. New high-throughput technological platforms are awaited to provide new insights into the mechanisms of disease discordance in twins beyond strong associations such as those with HLA alleles.

Contents

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1. Introduction

Autoimmune diseases cumulatively affect 5% of Western countries' population, with a significant impact on the patient quality of life and healthcare costs [1,2]. Despite the growing knowledge of the disease pathogenesis and the continuous development of new therapies, the causes of autoimmune diseases remain enigmatic [3]. It is now widely accepted that genetic factors are necessary but insufficient for the development of an autoimmune phenotype and environmental triggers concur to disease onset. Among non-genetic factors, candidates proposed for specific autoimmune diseases is continuously growing as new evidence is reported for infectious agents and chemicals/xenobiotics (Table 1), with various mechanisms are implied (Table 2) [4]. The resulting multi-hit model has been proposed for various multifactorial diseases, including autoimmune diseases and the limited applicability of the most robust genomic associations from genome-wide association studies (GWAS) have supported it [5]. Furthermore, similarities between autoimmune diseases outnumber differences, as well represented by the shared autoantibody profiles (i.e. antinuclear antibody), by the striking female predominance in nearly all conditions, or the common treatment approaches, as for TNFα inhibitors. Twin studies are powerful tools to discriminate whether a complex disease is dominated by genetic or environmental factors as twins represent naturally occurring models to weigh the role of individual hereditary factors. In particular, monozygotic (MZ) twins share an identical genetic background, therefore diseases with high concordance rates between MZ twins suggest a genetic predisposition, while low concordance rates will support an environmental factor [5]. This is of particular importance when concordance rates in MZ twins are compared to those in dizygotic (DZ) twins, which share 50% of their genes, as in regular siblings, but also young-age environmental factors. A major advantage of twin studies is the possibility to calculate the genetic heritability of each condition, i.e. the proportion of total variance in disease liability that is explained by genetic variance. Since heritability is a proportion, its value will range from 0 (when genes do not contribute to phenotypic differences) to 1 (when the environment does not contribute to phenotypic differences). This estimate depends on numerous variables, including the prevalence of the trait in the general population and does not reflect the risk of getting a disease but the variance between twins. We may identify sources of individual variation into additive and dominant genetic effects (A, D), common environmental effects (C) and random environmental effects (E) with “heritability” defined as the proportion of the phenotypic variance attributable to genetic variance (A + D). From a semantic standpoint, the term “environmentability” represents the proportion of phenotypic variance attributable to environmental variance (or 1-heritability). Of particular importance in the discussion of environmental factors is the fact that environmentability includes environmental influences that are sum of the common/shared environmental factors and individual environmental variance while also including the variance due to measurement errors or observation bias [6].

We will herein focus on the most recent findings in twin studies for selected autoimmune and chronic inflammatory diseases, discuss the utilized methodology, and stress the importance of rigorous methods in case ascertainment with adequate observation periods to warrant the identification of incident cases.

Table 1
Environmental factors associated with autoimmune disease development.

Factors
• Infectious agents (bacteria, viruses)
• Chemical/xenobiotics
• Adjuvants
• Physical elements (ultraviolet radiation

2. Methods used in twin studies

Twin studies can be subdivided in classical and case-control studies. In the former type, the classical twin study exploits the identical genetic background of MZ twin pairs compared to DZ twins sharing 50% of their genetic background [7]. The degree of phenotypic similarity is evaluated by means of twin concordance rates or correlation coefficients. Concordance can be expressed as either pairwise or probandwise rates. The pairwise concordance rate illustrates the proportion of affected pairs concordant for the disease, while the probandwise rate provides an estimation of the risk that one twin will develop the disease if her/his twin has been already diagnosed [5]. Concordance rates of diseases with a substantial genetic component are expected to be significantly different in MZ compared to DZ twins [8]. Different from classical twin studies, the co-twin control method is best suited to study the impact of specific genes or environmental risk factors on the development of disease [9]. Twin pairs who are discordant for a given phenotype are considered as matched pairs and the healthy co-twin serves as a control for the affected twin [4]. Additional gains to be considered using a twin study design and analysis include the evaluation of gender effect and the estimation of the shared genetic and environmental components in comorbidity, using a cross-twin cross- trait approach. Finally, twin registries are databases including both MZ and DZ twins used for clinical, epidemiological and genetic studies. There are various twin registries generally referring to a specific geographical area or Country, including Italy, Sweden, Denmark, Norway, Finland, Australia, Japan, China, Brasil and the United Kingdom [10–12], necessarily with different twin identification and case ascertainment methods specific for each registry or study.

While twin studies are considered both robust and valid [8], their interpretation must take into account several important issues. First, we cannot assume that the phenotype is not influenced by gene-gene or by gene-environment interaction. MZ twin pairs, while inheriting identical DNA, might have changes in their genetic setup, converting MZ twin pairs into genetically non-identical pairs, as the epigenetic drift during ageing independent of the DNA sequence [13]. Ageing MZ twins exhibit growing differences in global and locus-specific DNA methylation and histone-modification differences, which are associated with phenotypic discordance attributed to environmental factors appearing later in life and thus not shared by older twins [13,14]. Second, a recent comprehensive investigation on over 100 healthy twin pairs, comparing a large panel of serum cytokines, chemokines and growth factors, immune cell subsets, and cellular responses to cytokine stimulations and vaccines, reported that these functional