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Review

How twin studies help to understand inflammatory joint disease

Nathalie C. Lambert

Inserm UMRs1097, parc scientifique de Luminy, 163, avenue de Luminy, case 939, Bâtiment TPR2 Inserm, Entrée A, 1er étage, 13288 Marseille cedex 09, France

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ABSTRACT

Inflammatory joint disease (IJD) is a group of conditions that target the joints and periarticular structures. The contribution of genetic factors to these conditions is often less than 50%, suggesting a major role for environmental influences. Twin studies are the best means of assessing the role for genetic factors in IJD. Conclusive evidence has been provided by a few studies in vast samples of monozygotic and dizygotic twins, with only one twin in each pair having IJD. These studies have been most successful in ankylosing spondylitis and psoriatic arthritis. The other IJDs have proven more difficult to evaluate. This review demonstrates that genetic and environmental factors are inextricably linked and that ascribing IJDs to one or the other is misguided. Awareness of the limitations and possible sources of bias in twin studies is important when seeking to understand the development of these complex diseases.

1. Introduction

Inflammatory joint diseases (IJD) are conditions that target the joints and periarticular structures (bone, muscles, and tendons). The most common IJD is spondyloarthritis, i.e., ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Features shared by the various forms of spondyloarthritis include inflammation of the spine and pelvis, peripheral arthritis and, to variable degrees, involvement of other organs. The second in frequency is rheumatoid arthritis (RA), which is the most common autoimmune joint disease. Polymyalgia rheumatica (PMR) is less common and chiefly affects individuals older than 60 years of age. The IJD family also includes crystal-deposition and autoinflammatory arthritides such as gout and articular chondrocalcinosis, which are relatively common. Finally, some arthritides related to microorganisms lie in the gray zone between infection and inflammation: a viral or bacterial agent can trigger an inflammatory response, as occurs in reactive arthritis. The immune response is often disproportionate, similar to that seen in rheumatic fever. Finally, the joints are sometimes involved in various systemic autoimmune disorders such as scleroderma, dermatomyositis, and systemic lupus erythematosus (SLE).

Many genetic factors are involved in these diseases. The human leukocyte antigen (HLA) genes have long been identified as the main risk factors for most IJDs. For instance, HLA-B*27 is associated with AS [1,2] and some of the HLA-DRB1 alleles (e.g., *0101, *0401, *0404, *0405, and *1001) that carry an amino acid motif known as the shared epitope are associated with RA [3]. Genome-wide association studies indicate that numerous other genes are risk factors; however, they convey far lower levels of risk, and some polymorphisms are associated with more than one IJD. Thus, *PTPN22*, which encodes the protein tyrosine phosphatase non-receptor type 22, is associated with many autoimmune diseases [4]. Recent research indicates an association linking PsA to variants in *RUNX3*, a previously identified AS-susceptibility gene [5].

In most IJDs, concordance between monozygotic twins is lower than 50%. This fact supports a strong role for environmental factors. Twin studies are the best means of assessing the contribution of genetic factors to the development of a disease.

2. Twins: identical versus fraternal

Dizygotic or fraternal twins are produced when two ova are independently fertilized by two sperm cells. Each twin develops in its own amniotic sac and has its own placenta: the pregnancy is dichorionic and diamniotic (Fig. 1). Very rarely, dizygotic twins are produced during different ovulations and therefore have different gestational ages. About three-quarters of all twin pairs are dizygotic.

Monozygotic twins are formed from a single ovum fertilized by a single sperm cell and account for about one-quarter of all twins. Depending on the stage at which the zygote divides into two embryos, there may be two placentas and amniotic sacs (dichorionic diamniotic, 29%), a single placenta but two amniotic sacs (monochorionic diamniotic, 70%), or a single placenta and a single

E-mail address: nathalie.lambert@inserm.fr

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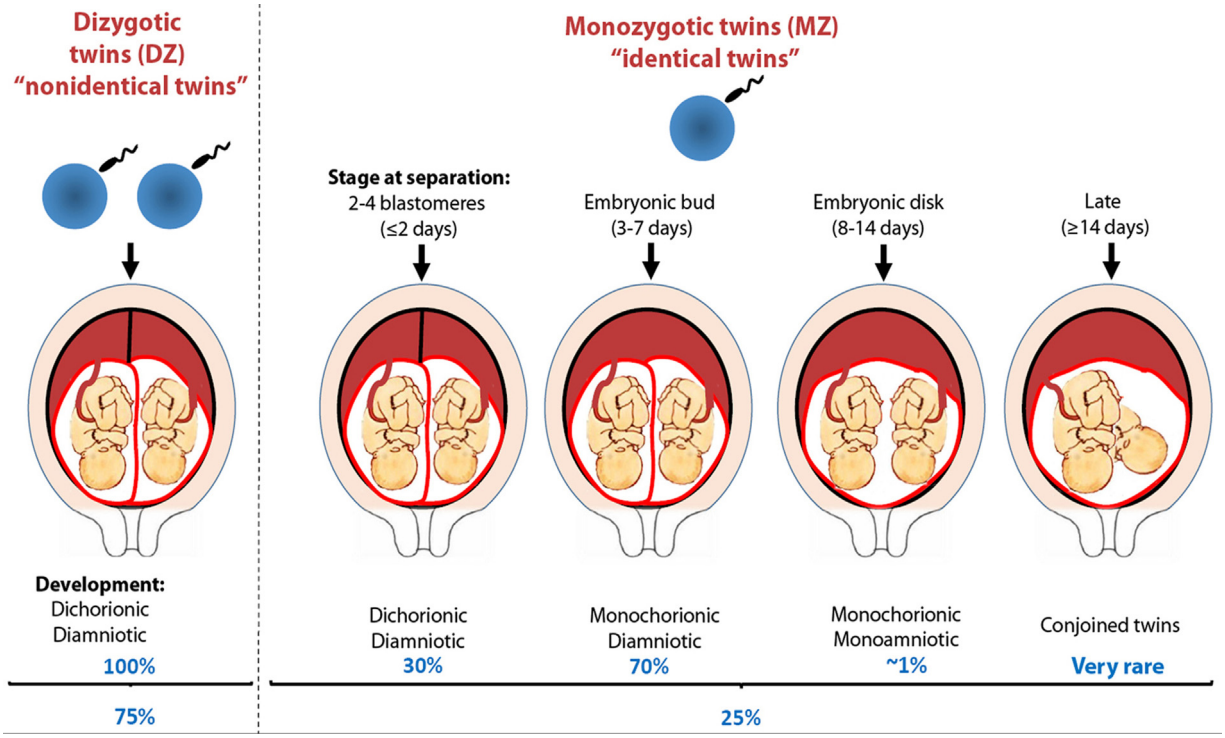

Fig. 1. Development of monozygotic and dizygotic twins.

amniotic sac (monochorionic monoamniotic, 1%) (Fig. 1). Late separation of the zygote is an exceedingly rare event that results in conjoined twins. Twins may differ in their development, with one weighing more than the other. In vanishing twin syndrome, one twin fails to develop and disintegrates [6]. Twinning occurs in about 13/1000 pregnancies overall. However, the frequency of twinning varies with several maternal characteristics including age, ethnicity, nutrition, and fertility [7,8]. The frequency of twinning is highest in Benin (28/1000) and lowest in Asia (<9/1000) [8]. Differences across ethnic groups occur chiefly for dizygotic twins. The frequency of monozygotic twinning is almost identical throughout the world, at about 4/1000 pregnancies [7]. Fertility treatments also tend to increase the frequency of twinning.

3. Determining the zygosity of twins

Determining whether two same-sex twins are dizygotic or monozygotic relies to a variable degree on an empirical approach. Some studies used questionnaires to collect information from twins about their physical resemblance and instances of one having been mistaken for the other. This similarity-based method is practical in vast studies of several thousand-twin pairs. However, in 5% to 10% of cases, the responses are not assessable or not interpretable. Among assessable data, most are fairly reliable: comparisons with genetic testing for zygosity showed less than 5% of classification errors [9]. Nevertheless, the most reliable method is genetic analysis of polymorphisms or short tandem repeats [10].

4. Evaluation of the genetic and environmental contributions to a disease

The development of a disease is multifactorial. Some diseases are characterized by strong heritability, which indicates a major role for genetic factors. Nevertheless, environmental factors may contribute to the development of a disease to a similar extent as genetic factors. Such environmental factors include occupation-related exposures to chemicals, the living environment, and lifestyle factors (e.g., alcohol use, smoking, diet, and birth control methods). Environmental factors may act via epigenetic mechanisms to modify the susceptibility of an individual to the development of a disease. Epigenetic factors are molecular mechanisms that induce reversible changes in gene expression levels, in the absence of alterations in the DNA sequence. They include DNA methylation, histone deacetylation, and the expression of small noncoding RNA fragments known as micro-RNAs [11]. Epigenetic factors allow changes in the expression of certain genes depending on the individual's environment. The influence of genetic factors can be assessed by computing the concordance rate for the disease between monozygotic twins and comparing this value to that in dizygotic twins.

5. Computing concordance rates

Two main types of concordance rate are used, the pairwise concordance rate and the probandwise concordance rate. The pairwise concordance rate is the proportion of twin pairs with at least one affected twin in which the other twin is also affected. This statistical parameter is thus the proportion of affected pairs in which both twins are affected (Fig. 2A). The probandwise concordance rate (or rate per affected individuals) is the proportion of affected individuals among co-twins of previously identified affected twins. This parameter measures the risk of having the disease among individuals who have an affected twin (Fig. 2B).

A higher concordance rate for a disease among monozygotic twins than among dizygotic twins supports a major role for genetic factors in the development of the disease. Higher concordance among dizygotic twins suggests a strong role for environmental factors.

A disease caused solely by genetic factors would consistently affect both members of pairs of monozygotic twins. In reality, concordance rates among monozygotic twins are only about 50%, indicating a strong influence of nongenetic factors (Fig. 2).