Hypoandrogenism Men and postmenopausal women with RA have lower mean serum testosterone, luteinizing hormone (LH), and dehydroepiandrosterone (DHEA) levels than control populations. It has thus been hypothesized that hypoandrogenism may play a role in the pathogenesis of RA or arise as a consequence of the chronic inflammatory response. It is also important to realize that patients receiving chronic glucocorticoid therapy may develop hypoandrogenism owing to inhibition of LH and follicle-stimulating hormone (FSH) secretion from the pituitary gland. Because low testosterone levels may lead to osteoporosis, men with hypoandrogenism should be considered for androgen replacement therapy.

EPIDEMIOLOGY

RA affects approximately 0.5–1% of the adult population worldwide. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. The incidence and prevalence of RA varies based on geographic location, both globally and among certain ethnic groups within a country (Fig. 380-3). For example, the Native American Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates in some studies of nearly 7%. In contrast, many population studies from Africa and Asia show lower prevalence rates for RA in the range of 0.2–0.4%.

Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2–3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1. Given this preponderance of females, various theories have been proposed to explain the possible role of estrogen in disease pathogenesis. Most of the theories center on the role of estrogens in enhancing the immune response. For example, some experimental studies have shown that estrogen can stimulate production of tumor necrosis factor a (TNF-α), a major cytokine in the pathogenesis of RA.

GENETIC CONSIDERATIONS

It has been recognized for over 30 years that genetic factors contribute to the occurrence of RA as well as to its severity. The likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2–10 times greater than in the general population. There remains, however, some uncertainty in the extent to which genetics plays a role in the causative mechanisms of RA. Although twin studies imply that genetic factors may explain up to 60% of the occurrence of RA, the more commonly stated estimate falls in the range of 10–25%. The estimate of genetic influence may vary across studies due to gene–environment interactions.

The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC). It has been estimated that one-third of the genetic risk for RA resides within this locus. Most, but probably not all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β-chain molecule. The disease-associated HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β-chain, termed the *shared epitope (SE)*. Carriership of the SE alleles is associated with production of anti-CCP antibodies and worse disease outcomes. Some of these HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, *0404, *1001, and *0901). Additionally, there is regional variation. In Greece, for example, where RA tends to be milder than in western European countries, RA susceptibility has been associated with the *0101 SE allele. By comparison, the *0401 or *0404 alleles are found in approximately 50–70% of northern Europeans and are the predominant risk alleles in this group. The most common disease susceptibility SE alleles in Asians, namely the Japanese, Koreans, and Chinese, are *0405 and *0901. Lastly, disease susceptibility of Native American populations such as the Pima and Tlingit Indians, where the prevalence of RA can be as high as 7%, is associated with the SE allele *1042. The risk of RA conferred by these SE alleles is less in African and Hispanic Americans than in individuals of European ancestry.

Genome-wide association studies (GWAS) have made possible the identification of several non-MHC-related genes that contribute to RA susceptibility. GWAS are based on the detection of single-nucleotide polymorphisms (SNPs), which allow for examination of the genetic architecture of complex diseases such as RA. There are approximately 10 million common SNPs within a human genome consisting of 3 billion base pairs. As a rule, GWAS identify only common variants, namely, those with a frequency of more than 5% in the general population.

Overall, several themes have emerged from GWAS in RA. First, the non-MHC loci identified as risk alleles for RA have only a modest

European ancestry:
HLA-DRB1:
*0401
*0404
*0301
***0101**

PTPN22: European
STAT4: North American
TNFAIP3: North American
TRAFI/CF: North American
CTLA4: European

Asian ancestry:
HLA-DRB1:
*0401 (East Asian)
*0405
*0901 (Japanese, Malaysian, Korean)

PADI4
CD244

Other:
CD40

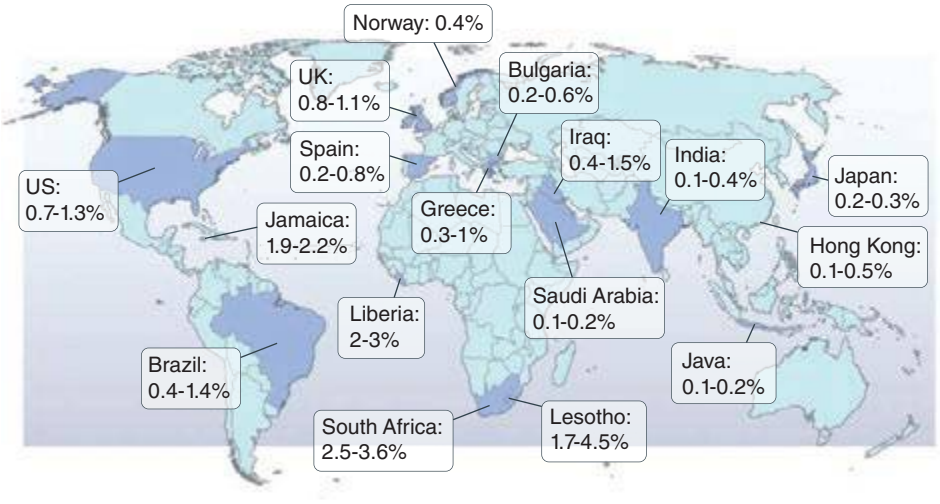

FIGURE 380-3 Global prevalence rates of rheumatoid arthritis (RA) with genetic associations. Listed are the major genetic alleles associated with RA. Although human leukocyte antigen (HLA)-DRB1 mutations are found globally, some alleles have been associated with RA in only certain ethnic groups.