spontaneously control viral replication in the absence of cART (HIV controllers); patients who resist disease progression for at least 8–10 years, despite viremia; and those progressing to AIDS within 3 years. Investigators have hypothesized that genetic differences may partly explain this interindividual variation in risk of acquiring HIV infection and disease progression rates. In addition to these phenotypes, it has been hypothesized that genetic variation may partly underpin the risk of developing specific AIDS-defining illnesses (e.g., renal and neurologic diseases) and non-AIDS comorbidities (e.g., cardiovascular disease), as well as the variable recovery in CD4+ T cell counts observed while receiving cART.

Candidate gene approaches and genome-wide association studies (GWAS) have demonstrated associations between gene variations and the above-mentioned phenotypes. A list of some of these associations is shown in **Table 226-6**. While in vitro genome-wide functional scanning using RNA interference has identified hundreds of host factors that may be involved in the HIV life cycle, the association of these genes with HIV susceptibility and/or disease progression remains largely undefined. Below is a discussion of a few key genes with strong associations and their implications for improving clinical care.

ASSOCIATIONS WITH CCR5 AND TRANSLATION OF GENETIC FINDINGS TO THE CLINIC Possibly, the most dramatic example of the importance of genetic studies for identifying host factors that influence HIV-AIDS pathogenesis is from studies related to the gene that encodes for CC chemokine receptor 5 (CCR5). While in vitro studies established that CCR5 is the major HIV co-receptor for the cell entry of HIV-1 into the host, it was genetic studies that established the seminal in vivo role of this receptor for the initial entry of HIV and AIDS pathogenesis.

Genetic analysis revealed that the in vitro resistance to CCR5-using R5 strains of HIV is in some instances due to carriage of two defective *CCR5* alleles. This defect is a 32-bp deletion in the coding sequence (designated as the *Δ32* allele). The *CCR5 Δ32* allele encodes a truncated protein that is not expressed on the cell surface.

Approximately 1% of individuals of European ancestry are homozygous for the *CCR5 Δ32* allele. Depending on the geographic region in Europe, up to 20% of individuals are heterozygous for the *CCR5 Δ32* allele. The *CCR5 Δ32* allele is either absent or extremely rare in other populations. The evolutionary pressure that resulted in the emergence of the *CCR5 Δ32* allele in the European population remains unknown and has been speculated to be secondary to an ancestral pandemic such as the plague.

Individuals homozygous for the *CCR5 Δ32* allele *(Δ32/Δ32)* lack CCR5 surface expression and are highly resistant to acquiring HIV infection. Heterozygosity for the *CCR5 Δ32* allele is also associated with a reduced risk of acquiring HIV. Consequently, the frequency of the *CCR5 Δ32* allele is enriched in individuals of European descent who remain uninfected despite exposure to the virus. Although the *CCR5 Δ32/Δ32* genotype is associated with profound resistance to acquiring HIV, a few individuals with this genotype have become infected with the X4 HIV strain and, in some instances, experienced an accelerated disease course. In general, *CCR5 Δ32* heterozygosity is associated with a slower HIV disease course.

Subsequent studies identified single nucleotide polymorphisms (SNPs) in the promoter (regulatory region) of CCR5 that influence its expression levels. Alleles bearing specific cassettes of linked polymorphisms (haplotypes) were identified and designated as human haplogroups A to G*2 (HHA to HHG*2). The *CCR5 Δ32* is found on the HHG*2 haplotype. The *CCR5* HHE haplotype was associated with higher CCR5 expression, and genetic association studies have shown that homozygosity for the CCR5 HHE haplotype is associated with an increased risk of acquiring HIV, progressing rapidly to AIDS, and reduced immune recovery on cART. The *CCR2*-64I-bearing HHF*2 haplotype is associated with a slower HIV disease course. The *CCR5* HHA haplotype is the ancestral CCR5 haplotype and is associated with a lower CCR5 expression. The HHA haplotype was associated with slower disease progression in African populations and has been speculated to be a basis for why SIV-infected chimpanzees (who all carry the ancestral *CCR5* HHA haplotype) may resist disease progression. The *CCR5* haplotypes also influence cell-mediated immunity and immune recovery on cART.

The association of variations in the *CCR5* gene with HIV-AIDS phenotypes is also an example of how discoveries made in the laboratory (bench) have been translated to improve health outcomes (bedside). The discovery that the *CCR5 Δ32/Δ32* genotype is associated with strong resistance to HIV infection, and that uninfected Caucasians bearing this genotype did not appear to have impaired immunity, led to the development of two kinds of therapies. First, it spurred the development of a new class of FDA-approved therapies, entry inhibitors (e.g., maraviroc), that block the interaction of CCR5 with the HIV envelope. Second, it led to the development of novel experimental cellular therapies. An HIV-infected patient with acute myelogenous leukemia was given an allogeneic stem-cell transplantation from an HLA-compatible person whose cells lacked expression of CCR5 due to the *Δ32/Δ32* genotype. There has been no evidence of HIV-1 infection in the transplanted patient thus far (6 years). This observation spurred the hope of an HIV cure and led to the development of additional novel cellular therapies involving autologous transplantation of CD4+ T-cells in which the *CCR5* gene is inactivated ex vivo using new gene editing procedures.

DISCOVERY OF HLA CLASS I ALLELES THAT ASSOCIATE WITH VIROLOGIC CONTROL OF HIV INFECTION There is a strong association between variations within the *HLA-B* gene with protective (e.g., HLA-B*57 and -B*27 alleles) or detrimental (e.g., HLA-B*35 allele) outcomes during HIV infection. Carriage of the HLA-B*57 and/or HLA-B*27 alleles is associated with slower disease progression. The beneficial effects of these alleles may relate in part to their consistent associations with a lower virologic setpoint as well as to higher cell-mediated immunity. The protective effect of the HLA-B*57 and -B*27 alleles on HIV disease course is underscored by the finding that the prevalence of these alleles is higher among long-term nonprogressors and HIV elite controllers (see above). On the other hand, the HLA-B*35 allele has been associated with faster progression to AIDS and higher viral load. The prevalence of the *HLA-B* alleles differs between populations. HLA-B*57:01 in Europeans and HLA-B*57:03 in African Americans are the protective alleles. In some populations (e.g., Japanese) where the HLA-B*57/-B*27 alleles are absent, HLA-B*51 is associated with a protective phenotype.

Possession of the protective *HLA-B* alleles is associated with broader and stronger CD8+ T cell responses to HIV epitopes. The mechanisms underlying the differential effects of the *HLA-B* alleles on HIV disease course may relate to differences in the ability of antigen-presenting cells to present immunodominant HIV epitopes to T helper or cytotoxic T lymphocytes in the context of MHC-encoded molecules. This may result in differential immune responses that influence viral replication. In this regard, the *HLA-B* alleles that impact HIV disease course differ in their amino acid residues in the HLA-B peptide-binding groove—and this may play a critical role in virologic control.

Investigators have also examined the influence of extended *HLA* haplotypes (linked alleles) on HIV disease course. The extended *HLA* ancestral haplotype (AH) 8.1 is defined by the presence of HLA-A1, HLA-B8, and HLA-DR3 alleles. AH 8.1 is the most common ancestral haplotype in Caucasians (present in 10%) and is associated with multiple autoimmune diseases in HIV-uninfected persons. These associations of AH 8.1 are thought to be due to a genetically determined hyperresponsiveness characterized by high TNF-α production and lack of complement C4A. Strong epidemiologic data indicate that carriage of AH 8.1 in HIV-infected persons is associated with a rapid decline in CD4+ T cells and faster progression to AIDS development. Gene–gene interactions between HLA alleles and other genes (e.g., killer cell immunoglobulin-like receptors) also may influence HIV disease progression rates.

POLYMORPHISMS IDENTIFIED BY GWAS THAT ASSOCIATE WITH VIROLOGIC CONTROL Large-scale GWASs have been conducted for the phenotype of viral load, including in a large group of HIV controllers. GWAS in HIV-infected persons of European ancestry identified four SNPs in genes in the HLA class I loci that associated with virologic control.