Genetic screening for metabolic and age-related complications in HIV-infected persons
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Abstract
Genetic screening for HIV-related complications is emerging as a clinically relevant prediction tool. A number of single nucleotide polymorphisms associated with conditions such as dyslipidemia and type 2 diabetes have been identified in both the general population and in HIV-infected individuals. Additionally, genome-wide association studies have looked at hepatitis C susceptibility in HIV-infected people, and genetic studies are ongoing for coronary artery disease, osteoporosis, and neurocognitive dysfunction. To date, understanding the contribution of genetic variation to the pathogenesis of lipoatrophy and kidney disease in HIV-infection is limited.

Introduction and context
Diabetes, osteoporosis, chronic liver disease, and coronary artery disease are just some of the common ‘metabolic’ conditions that affect millions of people, especially later in life. Unfortunately, for those infected with HIV, these conditions tend to occur more frequently and at an earlier age compared with the general population. One theory is that the activation of the immune system and subsequent inflammatory reactions to HIV infection might cause premature aging [1], accelerating the onset of these metabolic complications, despite the use of effective antiretroviral therapy. Alternatively, antiretroviral drugs themselves have been linked to metabolic complications, particularly the class of drugs called protease inhibitors. However, these metabolic complications are at least partly genetically determined; in fact, disease heritability rates range from approximately 30 to 90%, depending on the condition. This highlights why it is important to gain a deeper understanding of how genetic factors contribute to metabolic complications in HIV-infected people. Figure 1 summarizes genetic studies of common metabolic complications in the general population and in the setting of HIV-infection.

Recent advances
The genetic factors contributing to these major metabolic disorders are typically complex and no single gene mutation or variant is likely to explain a large proportion of the differences in clinical presentation between individuals. Rather, genome-wide association studies (GWAS), which look for genetic variations associated with a disease across the entire human genome in the general population, have identified dozens of common (i.e., present in at least 5% of the general population) single nucleotide polymorphisms (SNPs) – single base substitutions of one nucleotide for another – associated with specific metabolic disorders. Identification of these genetic differences may help to predict an individual’s likelihood of developing a disease as well as their response to treatment [2]. A catalogue of published GWAS is available online [3].

In the case of type 2 diabetes, GWAS of the general population have identified at least 22 SNPs associated with the disease [4]. This is significant because insulin resistance and type 2 diabetes are considered serious complications in HIV-infected patients, given the
Figure 1. Current status of genetic studies of metabolic complications in HIV-infected individuals

**Dyslipidemia**
- GWAS (33 SNPs)
- Confirmed in HIV+

**Neurocognitive Disorders**
- GWAS ongoing in HIV+

**Chronic Liver Disease**
- Association with hepatitis C clearance and response to peg-Interferon+Ribavirin:
  - GWAS (IL-28B)
  - Confirmed in HIV+

**Coronary Artery Disease**
- GWAS (45 SNPs)
- Confirmation study ongoing in HIV+

**Osteoporosis**
- GWAS (30 SNPs)
- Unconfirmed in HIV+

**Lipoatrophy**
- ? Genetic predisposition

**Diabetes Mellitus**
- GWAS (24 SNPs)
- Confirmed in HIV+

**Obesity, Metabolic Syndrome**
- GWAS (37 SNPs)
- Unconfirmed in HIV+

**Kidney disease**
- ? Genetic predisposition

Summary of the genome-wide association studies (GWAS) performed in the general population to discover genetic variations associated with various metabolic disorders, including the number of single nucleotide polymorphisms (SNPs) identified and whether there have been genetic studies conducted in HIV-infected individuals.
increased risk for premature cardiovascular disease. The importance of identifying these SNPs was confirmed very recently in a long-term study of 644 white HIV-infected patients [5]. In the study, 20% of the patients had an unfavorable ‘genetic risk score’ (i.e., those patients who carried multiple diabetes-associated SNPs), associated with a threefold increase in the risk of developing diabetes compared with patients who had a favorable genetic score. For comparison, this increased risk is similar to the effect of established risk factors such as advancing age but greater than the effect of antiretroviral therapy. Interestingly, the effect of the SNPs was still less than the effect of having an increased body mass index.

The situation is similar for people affected by dyslipidemia, a condition where patients suffer from abnormal levels of lipids (such as cholesterol and triglycerides) in the blood, predisposing them to heart disease. All SNPs consistently associated with serum lipid levels were validated in a recent paper analyzing 745 HIV-infected patients [6]. A patient’s genetic background and use of antiretroviral therapy contributed to similar proportions of lipid variation. A favorable genetic score (based on the patient's number of dyslipidemia-associated SNPs) was associated with high levels of ‘bad’ cholesterol in 32% of patients taking antiretroviral drugs; in patients with an unfavorable genetic score, this figure rose to 53%. Similarly, low levels of ‘good’ HDL cholesterol during protease inhibitor-based antiretroviral therapy were seen in 17% of patients with a favorable genetic score versus 42% with an unfavorable genetic score.

There are also some preliminary studies suggesting that there is a genetic component to the mitochondrial dysfunction widely implicated in lipoatrophy, a physically disfiguring condition that results in localized loss of fat tissue and that has been linked to the use of certain antiretroviral drugs in HIV-infected patients. Some evidence for this comes from a recent report involving 536 white Multicenter AIDS Cohort Study participants, which demonstrated that having one of a group of SNPs in mitochondrial DNA (haplogroup H), is a risk factor for lipoatrophy [7]. Additionally, a recent study of 103 Thai patients showed that the human leukocyte antigen gene HLA-B*4001 was associated with lipoatrophy, implicating the immune system in this disorder [8]. However, these findings await confirmation in other populations and, as yet, no unifying hypothesis of the genetic predisposition to lipoatrophy has emerged.

Even less is understood about a direct genetic contribution to coronary artery disease risk in HIV-infected individuals, but the international MAGNIFICENT consortium is intending to report the results of a study on this by Summer 2011. It features more than 600 HIV-infected patients with coronary artery disease and more than 1200 HIV-infected patients without this complication [9]. The SNPs evaluated in MAGNIFICENT will include SNPs associated with coronary artery disease that have already been identified in GWAS of the general population. Recently, a step towards identifying a genetic predisposition to cardiovascular problems in HIV-infected persons was made through a small GWAS (177 white male subjects genotyped) in which a SNP involved in the development of atherosclerosis of the carotid arteries was reported [10].

Chronic liver disease, often following infection with hepatitis C virus, is another significant cause of death in HIV-infected patients. Considerable enthusiasm was generated by the description of variation in IL-28B (the gene for interleukin 28B, which is responsible for the production of the antiviral cytokine known as interferon-λ3) that accounts for a large proportion of the variation in the spontaneous clearance of hepatitis C, as well as the response to treatment with pegylated interferon and ribavirin [12-15]. In addition, higher frequencies of the unfavorable IL-28B gene variants appear to be responsible for the lower response rate to hepatitis C treatment seen in individuals of African or Hispanic origin. IL-28B genetic screening is already being advocated and is becoming a key element in the stratification of patients enrolled in clinical trials of new anti-hepatitis C compounds. IL-28B plays a similarly important role in people infected with both HIV and hepatitis C [16], as having the favorable IL-28B gene variants improved spontaneous hepatitis C viral clearance rates and treatment response compared with patients carrying the unfavorable form of the gene.

On a similar note, a genetic analysis of osteoporosis risk in HIV-infected individuals is overdue, given the aging HIV-infected population, the remarkably increased rates of this complication in the setting of HIV-infection, and the large degree of heritability of osteoporosis (estimated at 60-90%). Several GWAS in the general population (reviewed in [11]) have identified around 30 osteoporosis-associated SNPs.

Unfortunately, there are also several chronic complications of HIV infection where there are no clear insights into the genetics involved in pathogenesis, such as kidney disease and HIV-associated neurocognitive disorders, although a GWAS to evaluate a potential genetic predisposition in the latter is ongoing. In addition, no new reports have been published since the identification of a possible genetic association of a SNP in resistin (a gene previously implicated in obesity and insulin resistance)
Implications for clinical practice

Despite the current gaps in our knowledge, genetic screening for HIV-related metabolic complications is emerging as a clinically relevant prediction tool. In fact, genetic prediction is already used in routine HIV care to identify individuals at risk of developing a hypersensitivity reaction to the antiretroviral drug abacavir [18]. However, the nearly 100% accuracy of this test is because only a single locus (HLA-B*5701) is involved. This is in distinct contrast to the multiple SNPs implicated in common metabolic disorders. Thus, the best guess based on current knowledge is that a panel of SNPs will need to be screened to produce a ‘risk score’ for metabolic complications in HIV-infected individuals, and that this will need to be combined with clinical variables to give an accurate prediction.

An additional, consistent lesson learned from GWAS is that the known common SNPs for a disorder account for less than 10% of the variability in disease seen between individuals. This applies to all metabolic and non-metabolic disorders assessed in GWAS [2,19]. In the next few years, the genetic basis of an increased fraction of the variability between individuals is likely to be uncovered. This will be achieved by re-sequencing the risk genes documented in GWAS (in order to identify rare variants causally implicated in the phenotype), large scale genome sequencing projects (see [20]) and whole genome sequencing of people with extreme versions of the disorders. However, all these approaches are costly [21]. Costs per patient are, as of June 2010, 400 US dollars (USD) for a single GWAS and around 10,000 USD for whole genome sequencing. Until these tests become cheaper, re-assessing the SNPs associated with metabolic disorders in the general population and screening HIV-infected patients for them (at a cost of 0.5-1 USD per SNP, per patient) remains a reasonable approach.

Abbreviations

GWAS, genome wide association study; SNP, single nucleotide polymorphism; USD, US dollars.

Competing interests

The authors declare that they have no competing interests.

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