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A single-nucleotide polymorphism in the sterol-regulatory element-binding protein 1c gene is predictive of HIV-related hyperlipoproteinaemia

A single-nucleotide polymorphism (3′322C/G) was identified in the gene encoding a key cholesterol/triglyceride regulator, sterol-regulatory element-binding protein 1c (SREBP-1c). Although it did not alter the amino acid sequence, SREBP-1c-3′322C/G was predictive of highly active antiretroviral therapy-related hyperlipoproteinaemia. Increases in cholesterol were less frequently associated with homozygous SREBP-1c-3′322G (genotype 22) than with heterozygous/homozygous SREBP-1c-3′322C (genotypes 11/12) and correlated with leptin and insulin increases, particularly in genotype 11/12 carriers. A functional mutation linked to SREBP-1c-3′322C/G or messenger RNA conformation differences may explain our findings.

Highly active antiretroviral therapy (HAART) including protease inhibitors (PIs) drastically lowers HIV-1 mortality rates [1], but is frequently associated with hyperlipoproteinaemia, peripheral lipodystrophy, and insulin resistance [2]. Sterol-regulatory element-binding protein 1c (SREBP-1c; also called adipocyte determination and differentiation factor 1; ADD-1) [3–5] is important in cholesterol [5], triglyceride [5,6], and fatty acid metabolism [7,8], peripheral adipocyte determination and differentiation [4], and insulin resistance [7]. As PIs inhibit SREBP-1c/ADD-1 activation [9,10], SREBP-1c/ADD-1 might have an impact on HAART-related hyperlipoproteinaemia. On the basis of the observation that hyperlipoproteinaemia affects only a part of the treated individuals [2], we investigated associations between hyperlipoproteinaemia and particular single-nucleotide polymorphisms (SNPs) predicting this adverse event.

Inclusion criteria for HIV-1-infected individuals were participation in the Swiss HIV Cohort Study [11], total cholesterol, CD4 cell count, and HIV-1 mRNA measurements before/after HAART treatment of 6 months or more. Exclusion criteria were a body mass index of less than 15 kg/m^2 and elevated baseline total cholesterol concentration (> 75th percentile). Plasma total cholesterol (age- and gender-adjusted) and triglyceride levels were prospectively determined [11], plasma leptin and insulin from frozen plasma samples. Of 71 asymptomatic HIV-1-infected subjects one was excluded because of a body mass index of less than 15 kg/m^2, and three because of elevated baseline total cholesterol. Controls (N = 2′727) were from large-scale population studies (SPREAD [12], SIBSHIP [13], BASEL [14]). HIV-1-infected and control subjects were screened for apolipoprotein E SNPs (C112R = apolipoprotein E4, R158C = apolipoprotein E2) known to modify plasma total cholesterol and for the previously undescribed SREBP-1c/ADD-1-3′322C/G SNP, which had not previously been described (see Fig. 1).

The apolipoprotein E and SREBP-1c/ADD-1 SNP allele frequencies showed no population or subgroup-specific selection bias: neither departures from the Hardy–Weinberg equilibrium, nor differences between control and HIV-1-infected subjects (χ^2 test).

In the controls, the frequency of SREBP-1c/ADD-1-3′322C homozygosity (genotype 11) was 40.3%, SREBP-1c/ADD-1-3′322C/SREBP-1c/ADD-1-3′322G heterozygosity (genotype 12) 45.6%, and SREBP-1c/ADD-1-3′322G homozygosity (genotype 22) 14.1%, resulting in a high polymorphism information content value of 0.37.

If stratified according to the PIs used, median total cholesterol changes from baseline (ΔTC) were +34% (indinavir), +36% (nelfinavir), +42% (ritonavir), +8% (saquinavir), +44% (ritonavir/saquinavir), and +38% (ritonavir/nelfinavir). As saquinavir (hard-gel capsules) induced less pronounced total cholesterol increases than the other PIs ($P = 0.0297$), we analysed whether

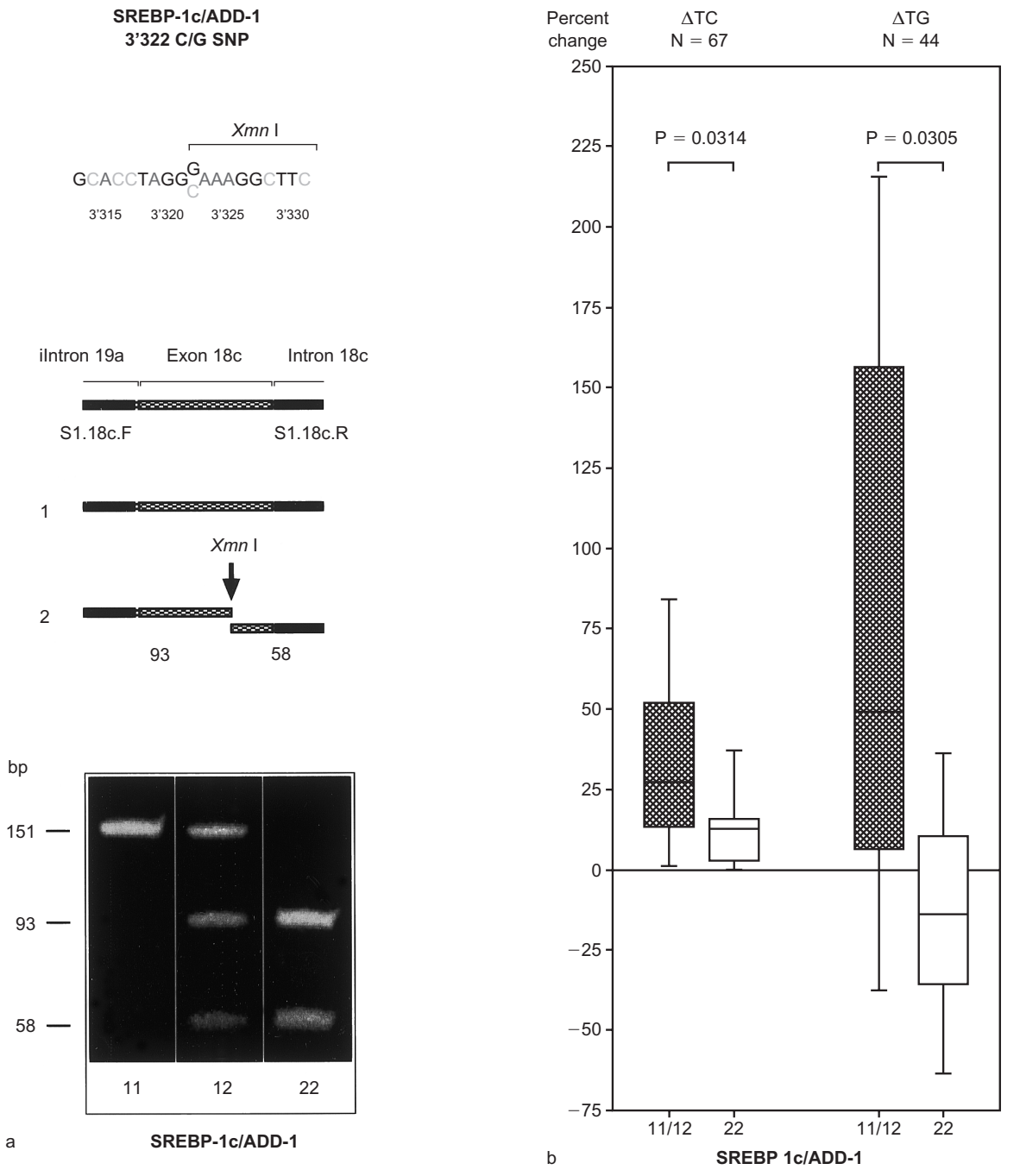

Fig. 1. (a) Single-nucleotide polymorphism of the sterol-regulatory element-binding protein 1c/adipocyte determination and differentiation factor 1 gene at nucleotide position 3'322 (exon 18c). The sterol-regulatory element-binding protein 1c (SREBP)-1c)/adipocyte determination and differentiation factor 1 (ADD-1) 3'322C/G single-nucleotide polymorphism (SNP) was identified using the single-strand conformation polymorphism technique and sequencing. As the 3'322C/G mutation is within an *Xmn* I recognition site, polymerase chain reaction amplification, restriction enzyme cleavage and identification of small fragments by electrophoresis (PRECISE) assays for high-throughput screening were developed: exon 18c was amplified by polymerase chain reaction using 5'–TGAAATTATTTATAATCTGGGTTTTGTGTCTT–3' and 5'–CATCGGGAAGAGCTAAGT TAAAAGTTGTG–3', *Xmn* I-digested, and the fragments were separated (Spreadex; Elchrom Scientific, Inc., Cham, Switzerland). The apolipoprotein E gene SNPs were identified as described [15]. To exclude alternative splicing, human complementary DNA libraries were screened using primers homologous to exon 17 and exon 19c of SREBP-1c/ADD-1 [3]. mRNA secondary structures were predicted using MFOLD 3.0 [16]. (b) Highly active antiretroviral therapy-induced changes (total cholesterol changes from baseline, total triglyceride changes from baseline) stratified according to the SREBP-1c/ADD-1 3'322C/G SNP. Box plot (10th, 25th, 50th, 75th, and 90th percentiles) of median total cholesterol changes from baseline (ΔTC) and total triglyceride changes from baseline (ΔTG) in genotypes 11/12 versus genotype 22 (Mann–Whitney U test).

saquinavir-treated subjects had a higher genotype 22 frequency, potentially accentuating the observed genotype-specific effect. However, all saquinavir-treated subjects were genotype 11/12 carriers.

ΔTCs, stratified according to SNP alleles, were not different in the apolipoprotein E genotype subgroups. However, ΔTC was +26.4% in SREBP-1c/ADD-1 genotypes 11/12, but only +10.6% in genotype 22 ($P = 0.0314$).

An increase if defined as ΔTC greater than 10% was observed in 76% (51/67 HIV-1-infected subjects), if defined as ΔTC greater than 15%, in 69% (46/67), if defined as ΔTC greater than 20%, in 60% (40/67). An increase if defined as exceeding the total cholesterol reference range (> 5.2 mmol/l) was present in 55% (37/67). A particular apolipoprotein E genotype was not associated with HAART-related hyperlipoproteinaemia. In contrast, the SREBP-1c/ADD-1 genotype 22 was negatively associated with hyperlipoproteinaemia. Genotype 22 was less and genotypes 11/12 were more frequent in subjects developing hyperlipoproteinaemia (ΔTC > 20%, $P = 0.0096$, χ^2 test).

As the above definitions of HAART-related hyperlipoproteinaemia are arbitrary, receiver operating characteristics analyses were performed, allowing us to change the cut-off continuously while calculating the respective sensitivities and specificities. A genetic test, however, has no cut-off that can be continuously changed; its positivity or negativity depends on the presence or absence of a particular SNP allele. Therefore, we examined the reverse case, whether ΔTC can predict the SREBP-1c/ADD-1 genotype. Using a cut-off of ΔTC greater than 43%, the positive predictive value of ΔTC to predict the SREBP-1c/ADD-1 genotypes 11/12 was 100% (specificity 100%, sensitivity 35%). Likewise, using a cut-off of ΔTC greater than 18%, the positive predictive value was 98% (specificity 86%, sensitivity 68%). On the other hand, the negative predictive value of genotype 22 to predict ΔTC greater than 18% was 86% and the positive predictive value of genotypes 11/12 to predict ΔTC greater than 18% was 68%.

Assuming that genotypes 11/12 lead to more pronounced HAART-related total cholesterol increases than genotype 22, we expected an increase in plasma leptin (ΔLP) and insulin (ΔIN) parallel to ΔTC, in particular in genotypes 11/12. In fact, if all genotype carriers were considered, ΔTC was positively correlated with ΔLP ($P = 0.001$) and ΔIN ($P = 0.01$). If genotype 11/12 carriers alone were considered, this effect was more significant (ΔTC/ΔIN, $P = 0.0049$; ΔTC/ΔLP, $P = 0.0004$).

To further investigate the molecular basis of these SNP-associated differences, we first excluded the possibility that SREBP-1c/ADD-1-3′322G causes alternative splicing and used computer-based analyses to predict differences in the putative mRNA secondary structure (SREBP-1c/ADD-1-3′322C versus SREBP-1c/ADD-1-3′322G).

The findings of our study were that: (i) differential PI-related effects on total cholesterol were associated with SREBP-1c/ADD-1 genotypes; (ii) ΔTC correlated with ΔLP and ΔIN in genotypes 11/12; and (iii) predicted mRNA secondary structures were different.

We recently characterized the SREBP-1a, SREBP-1c/ADD-1, and SREBP-2 gene promoters [17]. In the splice variant SREBP-1c/ADD-1, exons 1, 18, and 19 are different from SREBP-1a [3], leading to dramatically different biological properties of SREBP-1c/ADD-1 versus SREBP-1a [18]. Exon 18c is one of only three exons responsible for these functional differences. Exon 18c harbours the SREBP-1c/ADD-1-3′322C/G SNP, thus acting as a reliable marker for SREBP-1c/ADD-1-specific biological functions: if another mutation in the SREBP-1c/ADD-1 gene was responsible for HAART-related effects, it might be expected to be linked to SREBP-1c/ADD-1-3′322C/G (linkage disequilibrium).

Furthermore, synonymous mutations, such as SREBP-1c/ADD-1-3′322C/G, cannot *a priori* be considered as neutral or non-pathogenic, because they may directly affect mRNA structure and/or stability [19]. Computer-based analyses revealed conformational differences of SREBP-1c/ADD-1-3′322C/G at the mRNA level. This finding is particularly important because the SREBP-1c/ADD-1 pathway is probably regulated at the mRNA level [20]. Differences in genotype-specific mRNA stability may therefore cause differences in the susceptibility to triggers (i.e. HAART) [20,21]. Insulin regulates SREBP-1c/ADD-1 [7]; SREBP-1c/ADD-1 controls the genes encoding lipoprotein lipase (LPL) [6], fatty acid synthase (FAS) [8,22], peroxisome proliferator-activated receptor (PPAR)γ [21–23], glucokinase [7], and other insulin-dependent enzymes (insulin-mimicking SREBP-1c/ADD-1 effect) [7]. Furthermore, SREBP-1c/ADD-1 controls the adipocyte determination and differentiation effect [4,21].

PIs inhibit:

SREBP-1c/ADD-1 [9,10]. Because SREBP-1c/ADD-1 controls the LPL-mediated lipoprotein uptake [6], inhibition of SREBP-1c/ADD-1 and thus of LPL results in hyperlipoproteinaemia (increase in total cholesterol, triglyceride concentrations), as observed in the LPL deficiency syndrome [24].

FAS [22,23]. Because SREBP-1c/ADD-1 controls the

gene encoding FAS [7,8], HAART-related inhibition of FAS may be mediated by SREBP-1c/ADD-1.

Adipocyte determination and differentiation [22,23]. Because SREBP-1c/ADD-1 controls adipocyte determination and differentiation [4,21], HAART-related inhibition of adipocyte determination and differentiation may be mediated by SREBP-1c/ADD-1.

PIs do not inhibit:

PPARγ [23]. Both SREBP-1c/ADD-1 and leptin induce PPARγ [7,21,25]. HAART-related inhibition of SREBP-1c/ADD-1 and of PPARγ might be reversed by increased leptin levels: the net result would be no HAART-related inhibition of PPARγ.

The inhibition of LPL and other insulin-dependent genes leads to hyperglycaemia, hyperinsulinaemia, and insulin resistance. Therefore, an increase in total cholesterol, insulin, and to compensate [26], a parallel increase in leptin are expected when SREBP-1c/ADD-1 is inhibited. In line with this hypothesis, we found a correlation between ΔTC/ΔLP and ΔTC/ΔIN in HAART-treated individuals. Genotype 11/12 carriers were particularly susceptible to this effect. This further supports our hypothesis of a SREBP-1c/ADD-1 genotype-specific susceptibility.

In summary, we discovered a pharmacogenetic association of hyperlipoproteinaemia with a novel SNP in SREBP-1c/ADD-1 that predicts the risk of HAART-related adverse events.

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Short-term exercise training improves body composition and hyperlipidaemia in HIV-positive individuals with lipodystrophy

Exercise/physical activity is increasingly being advocated as a positive addition to the treatment regimen of HIV-positive individuals. We investigated the effects of 10 weeks' aerobic and resistance training on individuals with HIV-related lipodystrophy. These individuals demonstrated an improvement in exercise tolerance, body composition and blood lipid profiles. Potentially, such changes may contribute to an amelioration of some of the adverse metabolic effects associated with highly active antiretroviral therapy.

Metabolic and body compositional disorders are increasingly apparent in patients prescribed highly active antiretroviral therapy (HAART) for HIV infection [1]. Patients typically present with a combination of hyperlipidaemia, peripheral muscle fat wasting, adipose tissue redistribution, and insulin resistance [1]. Classified under the collective term 'lipodystrophy' [1], many of these abnormalities may act as risk factors for coronary artery disease (CAD) [2]. As therapeutic interventions are increasingly prolonging the life expectancy of HIV-infected individuals, a possible increase in the risk of the development of CAD gives cause for considerable concern [2]. Although discontinuation or switching of HAART may be effective in attenuating the features of lipodystrophy, such an approach may not always be clinically feasible. Exercise has been shown to be efficacious in ameliorating hyperlipidaemia, central adiposity, and other co-morbidities associated with CAD in non-HIV-infected populations. In men with AIDS wasting, combined resistance training and testosterone supplementation resulted in positive functional and body compositional adaptations [3]. However, this protocol was associated with a negative impact on HDL concentrations, primarily attributable to testosterone supplementation. Consequently, this regimen may not be suitable for patients with HIV-related lipodystrophy. We hypothesized that in HIV-infected patients with lipodystrophy, exercise training without testosterone supplementation would improve blood lipid profiles while attenuating the adverse body compositional changes.

In order to test this hypothesis, we undertook a prospective 10 week study, combining aerobic and resistance training exercise as an adjunct to HAART. Six HIV-infected individuals with lipodystrophy (five men, one woman, mean age 40.7 ± 13.9 years; height 175.1 ± 6.36 cm; body mass 69.4 ± 17.4 kg, body fat 21%, body mass index 22.4 ± 4.66 kg/m^2; CD4 cell count 456 ± 175/mm^3) gave informed consent to participate in the study. Lipodystrophy was diagnosed on the basis of a doctor's confirmation of patient self-report of fat wasting in the face, arms or legs [1]. Inclusion criteria were defined as: (i) no history of exercise during the preceding 12 weeks; (ii) currently following a HAART regimen (four were prescribed a nucleoside reverse transcriptase inhibitor (NRTI)/protease inhibitor regime, one was prescribed a non-NRTI/protease inhibitor combination and the final patient was on a triple NRTI regimen); (iii) not