receptor on their platelets than the T/T homozygotes. Although one would expect that a higher receptor level would yield platelets that were more adhesive and hence more prone to initiate thrombosis, the higher receptor levels may also be associated with higher levels of glycocalicin (the soluble extracellular portion of GPIbα) in the plasma, which could modulate any increased adhesiveness of the platelets. Similarly, although gain-of-function mutations of GPIbα associated with platelet-type von Willebrand disease are associated with an increased affinity of the receptor for vWI, they paradoxically cause a bleeding disorder. Nevertheless, it is still possible, and perhaps even likely, that the −5C allele is associated with an increased propensity of those carrying the allele to develop thrombosis. Such an association may not be uncovered in a study such as the one of Croft et al, for several reasons. First, the study is retrospective, which precludes the analysis of an at-risk population for future events. Therefore, analysis has to rely on the identification of the proper case-controls, which are difficult to match randomly. A truly matched control population would be matched for all variables that confer risk for myocardial infarction, which these controls clearly are not. Note, for example, the differences in the percentages of smokers and diabetics in the 2 populations. Second, the study analyzed only survivors of myocardial infarction, which introduces a survival bias; ie, those with the unfavorable genotypes may have not survived the hospitalizations. Finally, those at the greatest risk for myocardial infarction are also likely to be those with the rarest genotype, the C/C homozygotes. In both the case and control populations analyzed by Croft et al the frequency of this genotype was below 2%, with a tendency for a higher frequency in the case population. Thus, it is more appropriate to analyze risk by genotype frequency rather than by allele frequency, with rare genotypes requiring very large populations for analysis.

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To the editor:

The V410I (G1228A) variant of the caspase-10 gene is a common polymorphism in the Danish population

The autoimmune lymphoproliferative syndrome (ALPS) is a rare inherited disorder associated with lymphadenopathy, accumulation of CD4/CD8 double-negative T cells, and a broad range of autoimmune phenomena.[1] The clinical phenotype can, in all cases, be ascribed to defective lymphocyte apoptosis caused by defects in the Fas signaling pathway. However, recent work has suggested that at least 3 genes may account for the inherited component of the disease. The most common form of the disease, designated ALPS type Ia, is associated with inherited mutations in the Fas receptor gene, *APT1*,[2] whereas ALPS type Ib is associated with mutations in the gene encoding the Fas ligand.[3] The remaining cases with documented lack of mutations in either of the 2 above-mentioned genes have been collectively assigned as ALPS type II.[4]

In a recent issue of *Cell*, Wang et al[5] reported on inherited missense mutations in the caspase-10 gene in two kindreds with ALPS type II. One of the probands carried a heterozygous mutation, L285F (nucleotide change C853T; nomenclature referring to the long caspase-10 isoform; Genbank accession number AF111345), that was inherited from the mother who also showed features consistent with ALPS. The other proband, an Ashkenazi Jew, was homozygous for a G to A transition at position 1228, predicted to cause the substitution of valine with isoleucine at codon 410. Both heterozygous parents were clinically normal. None of the caspase-10 variants was found on 440 normal alleles, including 200 alleles of Ashkenazi Jewish origin. The different modes of inheritance in the 2 kindreds are compatible with the investigators' in vitro expression studies, showing that the L285F mutation severely impairs caspase-10-mediated apoptosis and acts in a dominant-negative fashion, whereas the V410I mutation has a significant, albeit less severe, effect on apoptosis. The mutant caspase-10 alleles were shown to affect apoptosis induced by

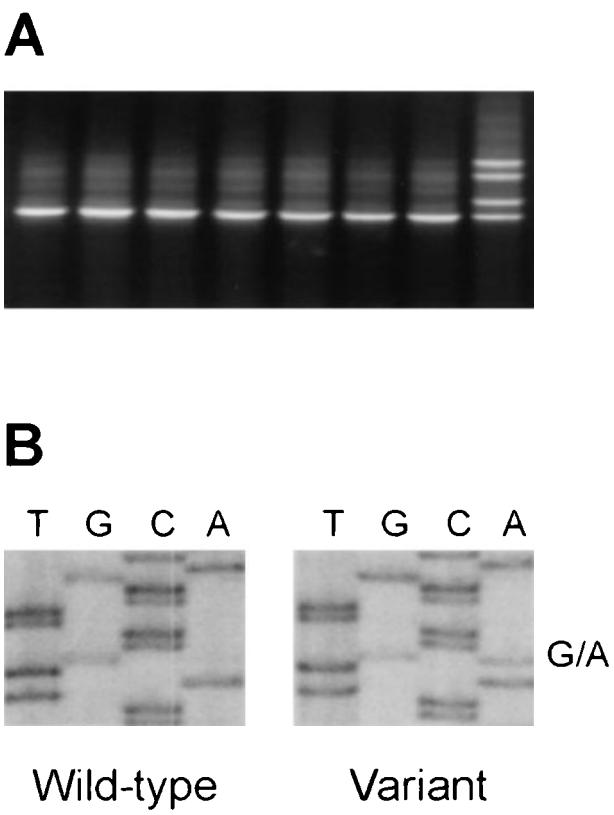

Figure 1. Detection of the V410I (G1228A) variant of the caspase-10 gene in DNA from healthy blood donors. (A) Representative denaturing gradient gel electrophoresis (DGGE) analysis of a region encompassing nucleotides 1186-1322 (codons 396-441) of the caspase-10 gene. (B) Direct sequence analysis of a sample with aberrant DGGE pattern, showing the G1228A variant.

various death receptors including Fas, TNFR1, DR3, DR4 (TRAIL-R1) and DR5 (TRAIL-R2), presumably by interaction with caspase-8/FADD in the death-inducing signaling complexes (DISCs).

We have recently demonstrated somatic *APT1* mutations in a subset of non-Hodgkin's lymphomas (NHL) associated with extranodal disease and autoimmune features.[6] Because of the proposed association between ALPS and caspase-10, an obvious extension of our work would be to examine whether somatic caspase-10 mutations might also be involved in the pathogenesis of NHL. We initially established a mutation detection assay based on polymerase chain reaction (PCR) and denaturing gradient gel electrophoresis (DGGE) to analyze a 137-bp genomic region of caspase-10 encompassing nucleotides 1186-1322 (codons 396-441). During the establishment of this assay, we observed an altered DGGE pattern in 1 of 10 normal control DNA samples (Figure 1A). Surprisingly, direct sequence analysis of this sample demonstrated the G1228A substitution in the heterozygous constellation (Figure 1B). Subsequent analysis of DNA samples from 85 healthy Danish blood donors (170 alleles) identified 12 additional heterozygotes, corresponding to allele frequencies of 93.2% (for the G1228 allele) and 6.8% (for the A1228 allele). Our preliminary analysis of 96 NHL cases shows a similar allele distribution in NHL.

Because we did not identify V410I homozygotes among our panel of normal controls, we cannot formally exclude that this variant is associated with severe impairment of Fas-mediated apoptosis *in vivo*. Nevertheless, the predicted homozygosity frequency of approximately 1 in 200 in the Danish population strongly argues against a major contribution to the ALPS phenotype. Further documentation is required to solidify the association between caspase-10 mutations and ALPS type II, and to establish whether the V410I variant is a benign polymorphism or may contribute to the ALPS phenotype together with other yet undefined factors involved in the control of apoptosis and lymphoproliferation.

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To the editor:

HIV-associated dysfunction of in vitro IL-12 production depends on the nature of the stimulus and on the CD4 T-cell count of the patient

A recent paper by Marshall et al suggests that decreased production of interleukin-12 (IL-12) is crucial in human immunodeficiency virus (HIV)-associated immune deficiency.[1] According to these authors, peripheral blood mononuclear cells (PBMC) from HIV-positive subjects produce lower levels of IL-12 in response to a wide range of stimuli, irrespective of the disease stage. Interferon-gamma (IFN-γ) production was decreased in response to IL-12, and upregulation of the IL-12 receptor β2 chain, critical for signal transmission, was impaired. The latter defect could be reversed by rIL-12 pretreatment. The authors logically conclude: ''A primary IL-12 defect may lead to secondary deficiencies in expression of the genes for IL-12Rβ2 and IFN-γ, thus amplifying immune deficiency during HIV infection.'' These data are in line with the ''type-1 to type-2 shift'' paradigm of HIV pathogenesis.[2-4] Because addition of IL-12 to PBMC cultures from HIV-positive subjects was shown to partly restore responses to antigen stimulation,[5] rIL-12 seems a good candidate for immunotherapy in acquired immunodeficiency syndrome (AIDS).

Other authors, including our group, observed HIV-associated cytokine imbalances, which are partly inconsistent with a type-1 to -2 shift.[6-8] Increased levels of various cytokines, including IFN-γ and IL-12, were measured in serum of HIV-positive subjects, even in advanced disease.[9-11] PBMC stimulation resulted in increased IFN-γ production in early HIV stages and lower IFN-γ levels in AIDS patients, as compared to controls.[12,13] Marshall's claim about a stimulus- and stage-independent impaired IL-12 production has also been challenged. One group demonstrated that IL-12 p40 production, induced by *Staphylococcus aureus* (SAC), inversely correlated with the patients' CD4 T count, and 2 studies indicated that IL-12 induced by lipopolysaccharide (LPS) and *Candida*, was not consistently decreased in HIV-positive subjects.[14,15] Moreover, in Marshall's study, induction by stimuli other than SAC, resulted in lowered production of IL-12 p40, but not of IL-12 p70 (bioactive), in HIV-positive PBMC cultures. We recently studied the physiological pathway of IL-12 production through interaction