homozygous N370S mutations tend to show a milder phenotype; they may even be asymptomatic and not diagnosed until much later in life [3,4]. In contrast, heterozygous patients with N370S/other present earlier and show predominantly visceral disease and more severe skeletal involvement [4].

Our patient has heterozygous mutation N370S/G377S. Unlike N370S, the G377S mutation is rare and usually seen in patients of Portuguese and Spanish descent [1] and is also seen in type 3 GD (neuropathic GD) [5]. The N370S (c.1226A>G) and G377S (c.1246G>A) mutations are known mutations [3], but to our knowledge, G377S (c.1246G>T) has not been previously described. The predicted replacement of a nonpolar amino acid glycine for polar amino acid cysteine would have deleterious effects, leading to a GD type 1 phenotype. We describe the contribution of a novel G377S mutation in a patient with adult-onset GD. The patient's significant thrombocytopenia, monoclonal gammopathy, and osteopenia illustrate the importance of evaluating and monitoring GD patients for associated bone disease and potential hematologic cancers.

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***IRB=HIPAA**: Our institutional policy stipulates IRB approval is not required for case reports of 3 or fewer patients. We notified our institution privacy officer, and as this case study utilizes no PHI data elements, HIPAA is also not applicable.*

***Note:** The bone marrow biopsy results from the case will be presented in poster form at the College of American Pathologists 2013 Annual Meeting (CAP '13), Gaylord Palms, Orlando, Florida, October 13-16, 2013.*

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Genetic modulation of HbF in Brazilians with HbSC disease and sickle cell anemia

To the Editor: Sickle cell anemia (homozygosity for HbS) and HbSC disease (compound heterozygosity for HbS and HbC) are the most common genotypes of sickle cell disease (SCD). Fetal hemoglobin (HbF), the major genetic modulator of SCD, interferes with deoxyHbS polymerization [1]. Patients with HbSC disease have about half the number of complications as do HbS homozygotes [1]; however, their mean HbF levels were 2.4% compared with about 6% in patients with sickle cell anemia [2]. Single nucleotide polymorphisms (SNPs) in quantitative trait loci cis and trans to the β-globin gene cluster are associated with HbF. We analyzed the association of SNPs in *BCL11A*, (chromosome 2p), in the *HBS1L-MYB* intergenic region (*HMIP*) (chromosome 6q), and in the 5′ olfactory receptor (*OR*) gene cluster of chromosome 11p with HbF in Brazilian patients with SCD.

Six hundred twenty-two patients were studied. They were not treated with hydroxyurea and were aged ≥6 years. Hemoglobin was analyzed by HPLC. SNPs rs766432 and rs6732518 in *BCL11A*; rs35959442 and rs11759553 in *HMIP*; and rs4910755 and 7483122 located in *OR51B5-OR51B6* were genotyped by ABI TaqMan Assays. The β^S and β^C globin haplotypes were investigated with PCR and restriction fragment length polymorphism techniques. Mean HbF was compared according to genotype using the additive genetic model adjusting for age, gender, and HbS homozygotes versus HbSC. A dominant genetic model adjusting for age, gender, and SCD genotype was used to test the association of SNPs with HbF. We tested to see whether there was an association between HbF and SNPs in the *OR* gene cluster region after adjusting for age, gender, SCD genotype, and the *HBB* gene cluster haplotype (Central African Republic [CAR] or Bantu versus absence of a CAR haplotype). To determine whether there was a synergistic effect between the SNPs or if the effect exerted on HbF was independent, we developed multivariable linear regression models adjusting for age, gender, and SCD disease status and ran stepwise linear regression analyses where we added the most significant SNPs from *BCL11A*, *HMIP* one-at-a-time. Data analysis was performed using R version 2.14.1 and the cubic root transformation of HbF [3].

Three hundred ninety-two patients were HbS homozygotes (HbF 7.4 ± 4.4%) and 230 had HbSC disease (HbF 2.5 ± 2.3%). The association between HbF and SNPs in the *BCL11A, HMIP*, and the *OR* gene cluster for all patients combined and for HbS homozygotes and HbSC patients separately are shown in Supporting Information Table Ia–c. In the combined group, there is a statistically significant association between HbF levels and both *BCL11A* SNPs and with *HMIP* SNP rs11759553 after adjusting for age, gender, and the SCD genotype. As the number of minor alleles increase, so does HbF level; in HbS homozygotes a similar result was found; in HbSC disease both SNPs in *BCL11A* and *HMIP* were associated with HbF. The association between HbF levels and SNPs in the *OR* genes, after adjusting for *HBB* haplotype was not significant (Supporting Information Table II). In a stepwise linear regression analysis adding the SNPs to a multivariable linear regression model as described, after adjusting for age, gender, and SCD genotype rs35959442 is still significantly associated with HbF indicating that its effect on HbF is independent of rs766432 (Supporting Information Table III).

We dichotomized the patients according to the *HBB* gene cluster haplotype. Brazilians with SCD have a higher prevalence of the CAR haplotype compared with African Americans. This haplotype is associated with lower levels of HbF than other haplotypes [4,5]. Patients with sickle cell anemia were heterozygous or homozygous for the CAR haplotype chromosome or lacked a CAR haplotype chromosome; HbSC disease patients had or did not have a CAR haplotype chromosome. Most patients with a CAR haplotype had the minor allele for rs4910755 and rs7483122, both of which are located in the 5′ *OR* gene cluster of chromosome 11p and could be in linkage disequilibrium with SNPs characterizing this haplotype.

HbSC disease patients usually have low HbF levels. Nevertheless, it is a milder condition than sickle cell anemia even though patients are more susceptible to clinical events related to high blood viscosity. Although HbF in HbSC disease is lower than in HbS homozygotes, *BCL11A* and *HMIP* modulate HbF in both genotypes.

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Additional Supporting Information may be found in the online version of this article.

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