To the editor:

Novel childhood ALL susceptibility locus *BMI1-PIP4K2A* is specifically associated with the hyperdiploid subtype

A recent genome-wide association study of childhood acute lymphoblastic leukemia (ALL) by Xu et al[1] has identified a novel susceptibility locus encompassing *BMI1-PIP4K2A* at chr10p12.31-12.2, bringing the number of known ALL risk loci to 5 (including *ARID5B*, *IKZF1*, *CEBPE,* and *CDKN2A*).[2-4] We sought to confirm and refine the *BMI1-PIP4K2A* association using single nucleotide polymorphism (SNP) array data from 297 Hispanic children with B-cell ALL (B-ALL) and 454 Hispanic control children from the California Childhood Leukemia Study.[5]

Of 6 genome-wide significant *BMI1-PIP4K2A* SNPs reported by Xu et al,[1] their most strongly associated variant (rs7088318) was not significantly associated with B-ALL in our array data ($P = .21$). Intriguingly, the rs7088318 association approached significance when analyses were limited to hyperdiploid B-ALL ($P = .08$), the most common cytogenetic subgroup. We subsequently imputed genotypes using 1000 Genomes data (supplemental Methods) and saw a similar association pattern for their 5 remaining SNPs (supplemental Table 2), suggesting that this region may specifically confer risk for the hyperdiploid B-ALL subtype.

In total, 131 directly genotyped and 1371 imputed SNPs in the *BMI1-PIP4K2A* region were analyzed. Association tests were stratified into 3 groups: B-ALL, hyperdiploid B-ALL, and non-hyperdiploid B-ALL. No SNP was significantly associated with the risk for B-ALL in unstratified analyses ($P > .01$). A total of 8 array SNPs and 43 imputed SNPs were associated with hyperdiploid B-ALL risk ($P < .01$) (Figure 1; supplemental Table 3). The array SNP most significantly associated with hyperdiploid B-ALL risk was rs10764338 (odds ratio [OR], 2.39; 95% confidence interval [CI], 1.48-3.87; $P = 3.5 \times 10^{-4}$), but this SNP was not significantly associated with an increased risk for B-ALL in unstratified analyses (OR, 1.34; 95% CI, 0.97-1.85; $P = .078$).

One SNP (rs1750761) was associated with nonhyperdiploid ALL at $P < .01$ but had effects in opposite directions in analysis of nonhyperdiploid cases (OR, 0.55) vs analysis of hyperdiploid cases (OR, 1.62). In case-by-case comparisons, on comparison of hyperdiploid cases (N = 97) with nonhyperdiploid cases (N = 157), our top

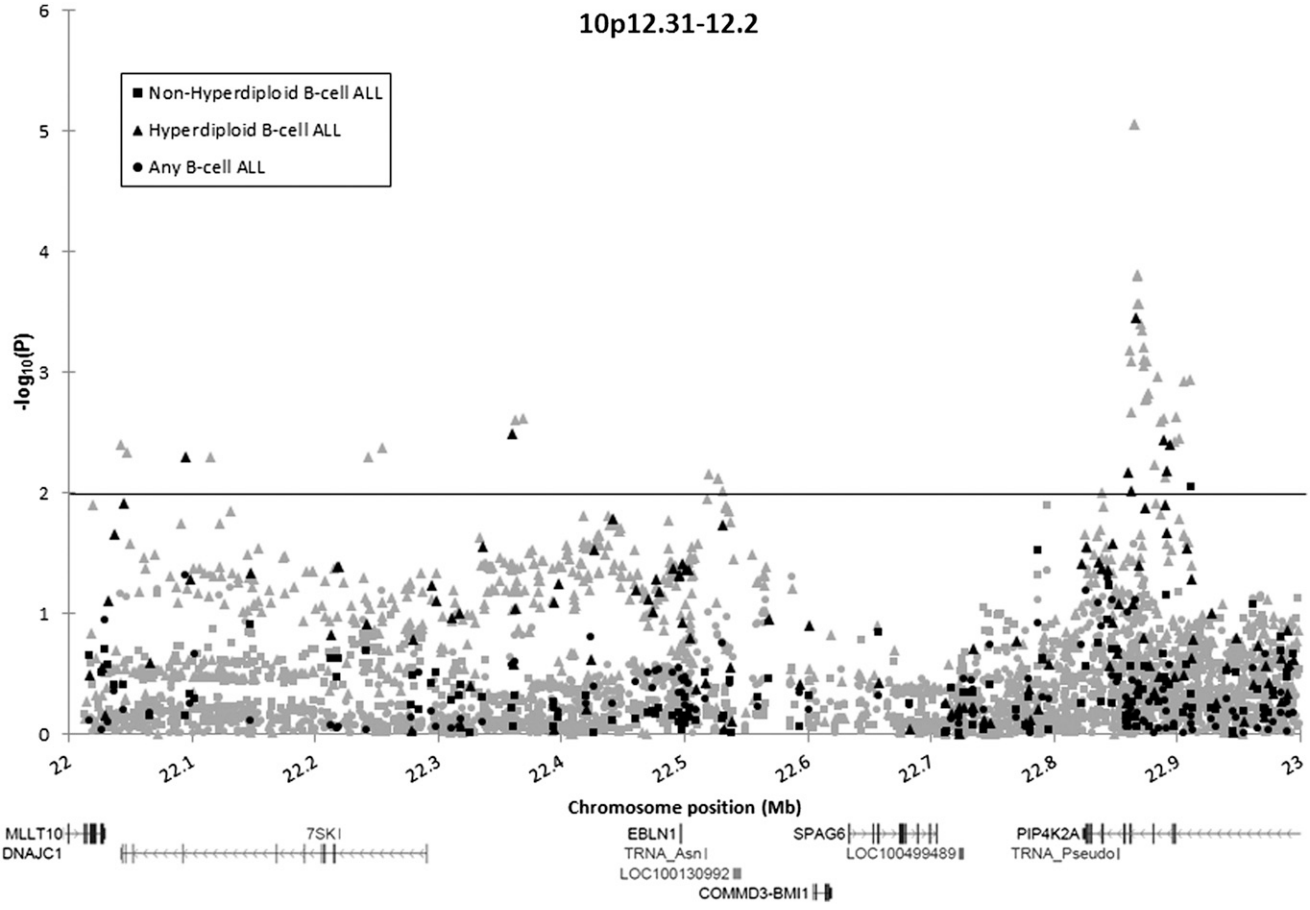

Figure 1. Association of SNPs in the *BMI1-PIP4K2A* locus with B-ALL among Hispanic children, by ploidy. Association of 131 directly genotyped SNPs (black) and 1371 imputed SNPs (gray) with the risk for B-ALL, adjusted for sex, age, and the first 5 principal components. Circles denote associations for children with B-ALL compared with control children. Squares denote associations for children with nonhyperdiploid B-ALL compared with control children. Triangles denote associations for children with hyperdiploid B-ALL compared with control children.

directly genotyped SNP from case-control analyses (rs10764338) was again significantly associated with an increased risk for hyperdiploid B-ALL (OR, 2.47; 95% CI, 1.42-4.29; $P = 9.8 \times 10^{-4}$).

Although risk loci in *ARID5B* have been shown to confer a greater risk for hyperdiploid B-ALL vs other subtypes,[2,4] the risk loci in *BMI1-PIP4K2A* reported here are the first to be exclusively associated with this ALL subtype. Our results confirm that variation at chr10p12.31-12.2 confers a risk for childhood ALL and further indicates that these variants distinguish hyperdiploid B-ALL from other subtypes. Fine-mapping via SNP imputation refined the association peak to a ~35kb region in *PIP4K2A*, which includes a rare variant (rs142846483; minor allele frequency in controls = 0.011) conferring an exceptionally high risk for hyperdiploid B-ALL among Hispanic children (OR, 15.15; 95% CI, 4.57-50.21 $P = 8.8 \times 10^{-6}$).

The risk variants identified by Xu et al do not affect protein coding, although they found that the rs7088318 risk allele was associated with increased *PIP4K2A* messenger RNA expression.[1] Our most strongly associated SNPs were also intronic, suggesting that variants in *PIP4K2A* that confer risk for hyperdiploid B-ALL may be regulatory in nature, as has been observed in fine-mapping studies of other neoplastic diseases.[6,7]

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To the editor:

Gender influences the birth order effect in HLA-identical stem cell transplantation

An earlier report by Bucher et al[1] indicated a better stem cell transplant (SCT) outcome with younger sibling donors (YSD). Transmaternal cell flow during pregnancy[2] might explain this observation. Notably, cord blood comprises minor H antigen experienced T cells that are not only directed against maternal foreign minor H antigens.[3,4] This observation prompted us to investigate the role of minor H antigens in the birth order effect in HLA identical SCT.

Hereto, we made use of a large database of 10/10 HLA allele-matched and minor H antigen–typed SCT donor/recipient pairs (Spierings et al, submitted), collected under the auspices of the International Histocompatibility and Immunogenetics Workshop and Conference. Additional relevant family information was included for 311 10/10 HLA allele–matched sibling donor/recipient pairs.