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.

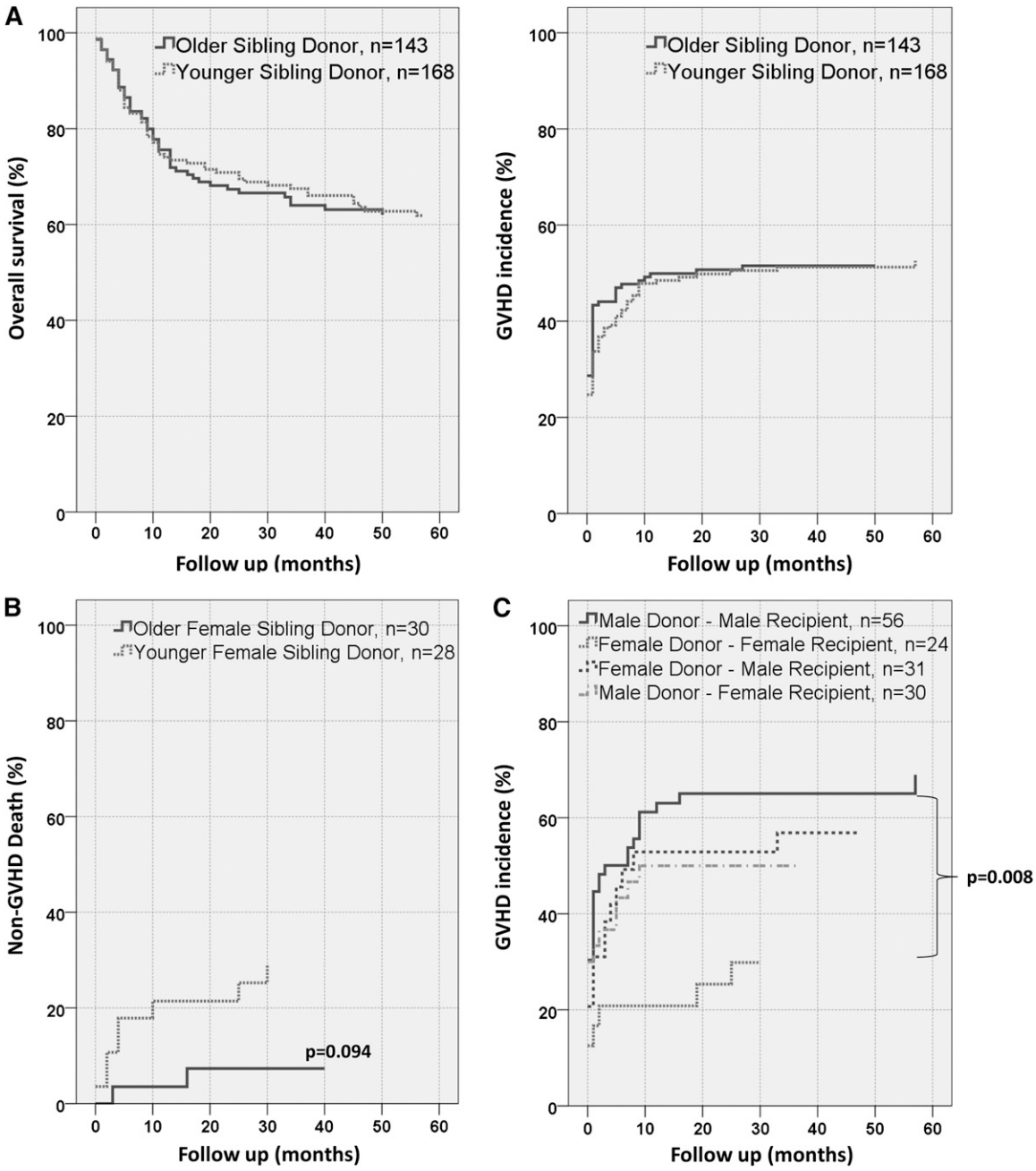

Figure 1. Influence of birth order on overall survival and GVHD incidence. (A) Overall survival and GVHD incidence in recipients with a YSD (n = 168) compared with recipients with an OSD (n = 143) are not statistically significantly different. (B) Female donors with female recipients have a higher non-GVHD death incidence (ie, relapse) in YSD compared with OSD (hazard ratio = 3.76, $P = .094$). (C) Adult YSD are subdivided by gender. Female donors in female recipients have a significantly ($P = .008$) reduced GVHD incidence compared with M→M.

In the whole cohort of 311 pairs, overall survival, graft versus host disease (GVHD) incidence, GVHD-related mortality, and GVHD-free survival were not statistically significantly different in SCT with older sibling donors (OSD, n = 143) compared with SCT with YSD (n = 168; Figure 1A).

The sample size of 311 appeared too small to analyze the effect of either single or multiple autosomally or of single Y chromosome–encoded minor H antigen(s). However, the effect of gender mismatch[5] on the birth order effect appeared feasible to investigate. Interaction analyses of birth order and gender mismatch showed a statistically significant interaction for non-GVHD, which is merely relapse-related, death ($P < .05$; data not shown). Subsequent analysis in female recipients of female donors (F→F; Figure 1B) showed lower, nonsignificant non–GVHD-related death in the YSD group (hazard ratio = 3.76, $P = .094$).

The study cohort comprised pediatric and adult SCT pairs. The number of pediatric pairs (n = 40) was too small to analyze separately. Analysis of the adult SCT pairs revealed a significant reduced GVHD incidence in the YSD group as opposed to the OSD group by comparing F→F transplantation with male donors to male recipients (M→M) transplantation (hazard ratio = 0.337, $P = .008$; Figure 1C). Furthermore, GVHD-free survival

was significantly better in F→F compared with M→M SCT (hazard ratio = 0.547, $P = .043$; data not shown).

In summary, we support the existence of a birth order effect as reported before.[1,6] Additionally, we show that gender might be one of the causal factors. Interestingly, the birth order effect was significant in the adult female donor/female recipient SCT pairs. Our current plausible explanation is the intrauterine exposure to sibling antigens occurring during pregnancy, leading to minor H antigen experienced T-cell responses in women.[4] These responses might lead to immune regulation.[7] Subsequent (re-)exposure to fetal antigens during pregnancy of the donor herself explains the favorable younger female SCT donor in combination with the female recipient.

To get a clearer picture of the influence of minor H antigens on the birth order effect, we suggest a much larger cohort of HLA-identical sibling SCT with detailed information regarding family and obstetric history of both patient and donor.

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