Diabetologia

## Author's reply

*To the Editor*: We appreciate the elegant commentary of Rieger et al. on our description of a possible relationship between the platelet PIA-SNP and the disease state of diabetes mellitus [1]. In their observational study with patients from the Vienna stroke registry they were not able to confirm a relationship of this platelet SNP with diabetes or with (cerebro-)vascular disease in comparison with apparently healthy individuals from an "official health service programme of the city of Vienna". They suggest further population-based studies to establish whether the PIA genotype is a risk factor for the development of diabetes melltius in general.

First, we explicitly agree with their conclusion, which furthers our comment that, with regard to that question, data from the population-based Kora trial are eagerly awaited. Here, we would like to mention that a preliminary release of this data set was published in abstract form at the 38th Annual Meeting of the EASD in Budapest, Hungary (2002) and in this journal [2].

Second, the available data on a possible linkage of the PIA-SNP with (vascular) disease strongly diverge, as shown by our references to the relevant literature in our Discussion section. Basically, it appears that results are greatly dependent (i) on the reference population in terms of clinical characteristics such as comorbidity, age and ethnicity, and (ii) on the circulation area for index events.

In our discussion of our results. we took into account the effect of chance by selection bias in our comparatively small cross-sectional observation. It appears that cerebrovascular outcome and cardiovascular outcome do show a differing dependence on the platelet GPIIbIIIa genotype. In support of this assumption, the Copenhagen City Heart Study, a population-based survey of 9149 individuals with a 22-year follow-up, quite recently reported a significant three- to four-fold risk of ischaemic CVD and myocardial infarction in young men homozygous for the PIA2 allele [3]. Interestingly, an increased prevalence of diabetes was noted among women homozygous for PIA2. This finding, however, did not add to the overall result of this study, which was completely negative for women, providing another hint that diabetes and (cardio-)vascular disease may be differently linked with the platelet genotype.

The data of Rieger et al. indicate a comparatively higher (non-significant) prevalence of the PIA2 allele in the diabetic group. This raises the question of power in a study with a definitely smaller fraction of diabetes patients than control subjects, and also the question of confounding by undetected (pre-)diabetic individuals in the control group, since no active diagnostic strategy was applied.

Third, in view of the diverging data on the possible association between the PIA-SNP and vascular outcome, we thought it relevant to report our data in an exploratory data analysis, which suggests that the genetic background of Type 2 diabetes could include a thrombogenetic platelet variant independent of vascular associations (common soil hypothesis).

In summary, we do not consider our data valid for PIA genotyping to predict outcome. Instead, we interpret them as a hint that the megakaryocyte-platelet system may be conditional for a genetically based prethrombotic state in Type 2 diabetes mellitus, a condition with a high risk of acute ischaemic events in the arterial circulation (under platelet control).

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## References

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