Response: CIC-Kb Mutation Revisited

We appreciate the contribution of Milton et al confirming the allele frequency of the CIC-KbT481S polymorphism in a South Australian population.

The discrepant definition of the affected nucleotide position affected by the thymine for adenine replacement is caused by different ways of counting. Milton et al start counting the nucleotides with the first base of exon 1, whereas we \(^1\) started counting with the first base of the annotated ATG Start Codon, which is 34 bases downstream from the first base of exon 1. Counting from the first nucleotide of translated sequence appears more useful for the functional approach on protein level used in our study. The position of the affected nucleotide is also clearly defined by the subsequent amino acid substitution (T481S) and by our respective TaqMan/Light Cycler probes used for genotyping.\(^1\) In Table 1 of our publication\(^1\) the calculation of allele frequency did indeed not include all wild-type individuals of group 3. Nevertheless, the result was virtually identical to that of the complete subgroup, was similar to that of the other white populations, and significantly different from the African population.

More importantly, 2 other articles failed to demonstrate an association between the CIC-KbT481S polymorphism and blood pressure.\(^2,3\) In our population, however, mean arterial blood pressure was significantly (\(P<0.001\)) higher in CIC-KbT481S carriers than in wild-type individuals. As the genetic analysis in our study has been strictly blinded and performed in separate laboratories as blood pressure measurements, the results could not have been biased by the study design. On the other hand, the studied population was small (47 carriers and 173 wild-type), thus leaving some uncertainty. We presently attempt to explore the prerequisites for an impact of CIC-Kb on blood pressure.

In a previous study, we had identified a polymorphism of the serum and glucocorticoid inducible kinase SGK1, which in our hands was associated with increased blood pressure.\(^4\) Besides ENaC, SGK1 stimulates CIC-Ka\(^5\) and CIC-Kb (G. Seebohm, F. Lang, unpublished observation, 2005). A subsequent study on a similarly small group failed to observe an association of the same gene variant with blood pressure.\(^6\) A most recent study in a very large group of individuals, however, clearly confirmed the association of the SGK1 gene variant with blood pressure and at the same time disclosed that the association was particularly prominent in individuals with hyperinsulinism.\(^7\) This latter observation is in perfect agreement with recent observations in SGK1 knockout mice.\(^8\) We do hope that future research will similarly define the mechanisms affecting the influence of CIC-KbT481S on blood pressure.

In view of the analysis of Milton et al it would further be interesting to learn whether the authors have found any difference of the allele frequency between the autochthonic Australian population and successors of European immigration. Compelling evidence points to interethnic differences in genotypes between Australian Aborigines and, for example, Caucasians. For instance, we have recently shown such differences for the clinically most relevant cytochrome P450 drug metabolizing enzymes 2D6 and 2C19.\(^9\)

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Nikola Jeck, Siegfried Waldegger, Bernd Wissinger, Matthias Schwab and Florian Lang

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