Letter to the Editor

Response to Comment on: Marchand and Polychronakos (2007) Evaluation of Polymorphic Splicing in the Mechanism of the Association of the Insulin Gene with Diabetes: *Diabetes* 56:709–713

Luc Marchand and Constantin Polychronakos

Rodriguez et al. (1) are right in pointing out that our findings (2) do not rule out with absolute certainty a role for rs689 in type 1 diabetes through the effects on splicing under conditions not reflected in the tissues we examined. In biological science, absolute certainty is difficult to attain.

The mid-gestation fetal pancreata, subjected to a constant influx of nutrients and responding to an intensely anabolic state, is probably a good model for maximally upregulated insulin transcription. However, it is possible that the reduced β-cell mass of type 1 pre-diabetes may represent a larger increase in transcription by individual cells, even against the inhibitory effect of cytokines in the context of insulitis. It is also possible that such increased transcription may alter the relative levels of splicing isoforms. What, in our opinion, is less plausible is that any increase in insulin production would have immunological effects in the microenvironment of the islet. T-cell receptors of infiltrating lymphocytes, regardless of avidity, are probably maximally saturated by the high local levels, and fast or slow splicing is unlikely to make a difference. In the thymus, where much lower concentrations are more likely to be within the saturation curve of T-cell receptor avidity, the splicing effect would result in higher levels of peptide derived from the predisposing allele. Such an effect would be in an opposite direction to that expected from the antigen-specific immune effects of thymic insulin expression levels that we (3) and others (4,5) have established in animal models of immune-mediated diabetes.

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