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## Questioning *INS VNTR* role in obesity and diabetes: subclasses tag *IGF2-INS-TH* haplotypes; and *-23HphI* as a STEP (splicing and translational efficiency polymorphism)

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Le Fur et al. (4) claim that *INS VNTR* subclass ID is responsible for the higher insulin secretion in children previously attributed to the whole class I group. This *VNTR* (variable number tandem repeat) is a minisatellite locus in the promoter region of *INS*. For European ancestry, there are long class III and short class I alleles, but class I is rare given African ancestry. Within both classes, there are further subclasses (IIIA, IIIB, IC, ID-, ID+) defined both by modal length; by the exact sequences of each internal repeat, the *VNTR* also being a multiple variable repeat (*MVR*); and by flanking SNP haplotypes (9). Saturation analysis of SNPs across *H19-IGF2-INS-TH* remapped the type I diabetes risk locus (*IDDM2*) to the *VNTR*, excluding adjacent genes and rejecting earlier hypothesis of differentially protective subclasses of class III, but could not exclude restriction fragment length polymorphism (RFLP) “*-23HphI*” (rs689 A/T) or +1140A/C in the 3'-untranslated region, which are in essentially perfect linkage disequilibrium (LD) with the class I/class III distinction (1). Internal sequence characterization of the *VNTR* has not identified specific repeat motifs consistent with apparent subclass-specific risk (8). The *MVR* subclasses ID/IC fully distinguished by sequencing by le Fur et al. (4) are mainly distinguishable by size, IC being smaller. We and others have previously shown that subclass IC is tagged both by allele 260 of microsatellite *TH01*, by allele A of an *ApaI* RFLP (rs680 A/G) in the 3'-untranslated region of *IGF2*, and by an 11-SNP haplotype *IGF2\*5*. In 2,743 older males, *IGF2\*5*, present in ~25% of subjects, associates with lower body mass index (BMI) ( $P < 0.00001$ ), ~1 unit per allele representing 2–2.5 kg per allele (Ref. 7, references therein, and replicated in Ref. 6) and with lower fat mass (1–1.5 kg per allele). The nonsignificant 3.2 units lower BMI of IC/IC children relative to ID/ID in Ref. 4 ( $n = 161$ ) might correspond with significantly lower weight for subclass IC in a much larger adult study (5).

However, refined subclasses or clades of a multiallelic marker, such as the *INS VNTR*, will be in strong or perfect LD with more extended flanking haplotypes (9), so causality by *VNTR* cannot be assumed without comprehensive fine mapping. Integrating multiallelic with biallelic data in interallelic LD analyses [now feasible in the program MIDAS (2)] is an important first step. *TH*, rate limiting in catecholamine synthesis and *IGF2*, an important growth factor and body composition regulator, may have causal roles. Lastly, even for *IDDM2*, causality may not, or may not only, reside in the promoter/*VNTR*. Recently, noting firstly that “*-23HphI*” is actually *INS* IVS-I -6A/T and predicting splicing efficiency effects, we examined its effects on intron-I splicing and showed that A

alleles (which perfectly tag *VNTR* class I) result in retention of this 5'-untranslated region intron and that *INS* mRNA with this retention displays sixfold greater 5'-leader-dependent proinsulin secretion (3). This represents a new type of quantitative trait locus (herewith “splicing and translational efficiency polymorphisms,” or “STEPS”). The multiallelism of the *INS MVR* makes it an excellent tag, not necessarily functional, for numerous potential functional elements distributed across several genes and metabolic pathways. Physiological genomics encapsulates the need for integrated and trait-specific remapping, for example for BMI, insulin, and glucose with dense genetic data, to understand causality for related traits and genes entwined both at the levels of haplotype blocks and of interacting metabolic pathways.

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