IGF2 mRNA-binding protein 2: biological function and putative role in type 2 diabetes

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Abstract

Recent genome-wide association (GWA) studies of type 2 diabetes (T2D) have implicated IGF2 mRNA-binding protein 2 (IMP2/IGF2BP2) as one of the several factors in the etiology of late onset diabetes. IMP2 belongs to a family of oncofetal mRNA-binding proteins implicated in RNA localization, stability, and translation that are essential for normal embryonic growth and development. This review provides a background to the IMP protein family with an emphasis on human IMP2, followed by a closer look at the GWA studies to evaluate the significance, if any, of the proposed correlation between IMP2 and T2D.

Introduction

Insulin-like growth factor 2 (IGF2) mRNA-binding protein 2 (IMP2/IGF2BP2) belongs to a family of mRNA-binding proteins (IMP1, IMP2, and IMP3) involved in RNA localization, stability, and translation. IMPs are mainly expressed during development and are essential for normal embryonic growth and development. Based on a series of genome-wide association (GWA) studies, IMP2 was recently implicated in type 2 diabetes (T2D). Here, we review the molecular properties of the IMP family and IMP2, as well as the possible connection between IMP2 and T2D.

Nomenclature

The nomenclature of the IMP family is not straightforward, mainly because the members of the family were identified and ascribed different functions in different biological systems. Attempts to reach a unifying acronym (VICKZ; Yisraeli 2005), based on the first letter of the initially described members have not caught on, so until a clearer picture in terms of molecular mechanism has emerged, the awkward nomenclature is likely to persist. The human members received their acronym IMP from the original observation of a high-affinity binding site in one of the IGF2 mRNAs (Nielsen et al. 1999) and from the anticipated dwarf phenotype of the knock-out mouse (IMP noun: small devil or demon). To add to the general confusion, the public databases unfortunately annotate these RNA-binding proteins as IGF2BP. Figure 1A provides a phylogenetic overview of experimentally described members of this RNA-binding protein family, including their original abbreviation.

Evolutionary history of IMPs

Genes encoding paralogous factors within an individual species is a typical vertebrate feature, originating from two gene duplications allowing subsequent non-, sub- or neo-functionalization. Inspection of the exon–intron architecture of the mammalian members reveals a considerable level of conservation, since IMP1 and IMP3 are encoded by 15 exons, whereas the slightly larger IMP2 protein is encoded by 16 exons (Fig. 1B). In addition, the human IMP2 gene encodes a splice variant where exon 10 is skipped, generating an IMP2 isoform originally named p62 (Zhang et al. 1999a). Among the mammalian species, intron 2 is by far the largest intron, and the single nucleotide polymorphism (SNP) reported to be associated with T2D in the GWA studies described below is situated within the 125 kbp intron 2 in the IMP2 gene at chromosome 3 q27.2 position 186994381 (Fig. 1B). An intriguing feature of the chromosomal locations of the IMP genes is
In a phylogenetic and experimental standpoint, it also seems clear that the four KH domains constitute a functional entity in terms of high-affinity RNA-binding, granular RNP assembly, and RNA localization (Nielsen et al. 2002), although invertebrate homologs may exhibit rudimentary features of the two RRMs.

We are lacking high-resolution structural information for both the IMPs alone and, more urgently, their complexes with target RNAs. So the present picture is based on biochemical experiments and inference from structural data derived from RRMs and KH domains in other RNA-binding proteins. Whereas ample biochemical evidence has accumulated regarding the RNA-binding potential of KH domains in IMPs, the significance of the two RRMs is far more elusive, since there are no data pointing to a direct role in RNA-binding (Git & Standart 2002, Nielsen et al. 2002, 2004). Inspection of the characteristic RNP2 and RNP1 consensus sequences in the two RRMs in IMP2 reveals that RRM1 exhibits the characteristic consensus, whereas RRM2 does not. Nevertheless, a comparison of vertebrate IMP2 orthologs shows that the conservation pressure on both RRMs is similar to the conservation of the KH domains, so whatever the function of the two RRMs, it must be advantageous in chordates (the sea squirt Ciona intestinalis exhibits one member with the modular 2+4 architecture).

There is no evidence that the different human IMP isoforms should target different RNA molecules. The contribution of each KH domain to the RNA-binding platform is unclear, but if comparisons with structural studies of Nova KH domains (Jensen et al. 2000) are carried out, the probable scenario is that each KH domain binds to a 4-nucleotide motif, and that high affinity and specificity are provided by the multiple KH domains. The multiplicity of putative contacts is further enhanced by the dimerization of IMPs via a sequential mechanism on its RNA target, and both homo- and heterodimerization among the paralogs seem feasible (Nielsen et al. 2004). KH3 and KH4 domains, at least from IMP1, encompass an ability to dimerize both in a homo- and heteromorphic manner, and it is also the same part of the protein that is able to associate with HuD (Atlas et al. 2004) and PABP (Patel & Bag 2006). A direct interaction with fragile X mental retardation protein (FMRP) in an RNA-independent manner has also been reported to be mediated via KH3 and KH4 (Rackham & Brown 2004), but the latter interaction is more controversial, since FMRP and IMP1 do not seem to colocalize in the same RNP granules (Jonson et al. 2007). Both IMP2, the splice variant p62 (that lacks 43 amino acids between KH2 and KH3), and IMP3 are also able to form homodimers (Nielsen et al. 2004). Moreover, IMP2 was previously found to interact with the AU-rich element-binding factor AUFI (Moraes et al. 2003) indicating that IMP2 could be involved in the regulation of mRNA stability.

Figure 1 (A) Phylogeny of the IMP family of RNA-binding proteins represented by an unrooted dendogram of IMPs and their orthologs. IMP1 is almost identical to mouse coding region determinant-binding protein (CRD-BP) and closely related to chicken zip-code binding protein 1 (ZBP1), and IMP3 is orthologous to Xenopus Vg1RBP/Vera and mouse K-homology (KH1–4) domains (Fig. 1B; Nielsen et al. 2009). Whereas two RRMs or four KH domains (RRM1 and 2) and four C-terminal hnRNP K-homology (KH1–4) domains (Fig. 1B; Nielsen et al. 1999). Whereas two RRMs or four KH domains can be found in other RNA-binding proteins such as hnRNP A1 and KSRP respectively, the 2+4 modular architecture seen in IMPs is unique. A similarity of sequence and spacing in regions between the two RRMs and between KH domains 1 and 2 and domains 3 and 4, combined with the considerable divergence of regions between RRM2 and KH1 and between KH2 and KH3, has led to the notion that the RNA-binding modules cooperate pairwise (Git & Standart 2002). From both a phylogenetic and experimental standpoint, it also

Protein structure

The human IMP1–3 family members, with expected molecular masses of 63, 66, and 64 kDa and an overall sequence identity of 59%, exhibit six characteristic RNA-binding modules, namely two N-terminal RNA recognition motifs (RRM1 and 2) and four C-terminal hnRNP K-homology (KH1–4) domains (Fig. 1B; Nielsen et al. 1999). Whereas two RRMs or four KH domains can be found in other RNA-binding proteins such as hnRNP A1 and KSRP respectively, the 2+4 modular architecture seen in IMPs is unique. A similarity of sequence and spacing in regions between the two RRMs and between KH domains 1 and 2 and domains 3 and 4, combined with the considerable divergence of regions between RRM2 and KH1 and between KH2 and KH3, has led to the notion that the RNA-binding modules cooperate pairwise (Git & Standart 2002). From both a phylogenetic and experimental standpoint, it also
**Cellular functions**

Different RNA-binding proteins are attached to eukaryotic mRNAs during their life cycle. Major transitions include the exchange of nuclear RNA-binding proteins with cytoplasmic factors. Moreover, the exon-junction complex that is deposited during splicing is removed during the pioneering round of translation (for review see Maquat 2004, Moore 2005). The composition of RNA-binding proteins specify cytoplasmic events such as RNA localization, translation, and stability (for review see Hieronymus & Silver 2004).

IMPs are mainly cytoplasmic, but the presence of two nuclear export signals imply that they attach to their target mRNAs in the nucleus and facilitate nuclear export of the transcripts (Nielsen et al. 2003, Oleynikov & Singer 2003). In the cytoplasm, they form large RNP granules dispersed around the nucleus and in cellular protrusions (Fig. 2A). Granules travel at a speed of 0.2 μm/s, and during migration cells are able to switch from a delocalized to a localized pattern (Nielsen et al. 2002). In neuronal cells, granules localize to dendrites and growth cones (Zhang et al. 2001, Tiruchinapalli et al. 2003), and in *Xenopus* oocytes the IMP3 ortholog Vg1RBP/Vera anchors at the vegetal pole (Deshler et al. 1998, Havin et al. 1998).

IMP1 granules represent a unique RNP entity, distinct from neuronal hStaufen and/or FMRP granules, P-bodies and stress-granules (Jønson et al. 2007). Granules are 100–300 nm in diameter and consist of IMPs, 40S ribosomal subunits, shuttling hnRNPs, poly(A)-binding proteins, and mRNAs. Moreover, granules contain CBP80 and factors belonging to the exon-junction complex. They lack eIF4E, eIF4G and 60S ribosomal subunits, indicating that constituent mRNAs have never been translated. Embodied mRNAs correspond to about 3% of the transcriptome, so the individual granules are likely to be heterogeneous. Messenger RNAs encoding proteins participating in the secretory pathway and ER-associated quality control, as well as ubiquitin-dependent metabolism, are enriched in IMP1 granules (Jønson et al. 2007), providing support to the concept of RNP granules as post-transcriptional operons (Keene & Tenenbaum 2002).

Target mRNAs for IMPs frequently exhibit multiple binding sites that are located in either the 5′ untranslated region (UTR), the 3′UTR or even in the coding region. Therefore, it could be anticipated that the proteins affect several different post-transcriptional events. Based on studies of *Xenopus* Vg1RBP/Vera (IMP3 ortholog), it was recognized early that this RNA-binding protein was important for RNA localization (Deshler et al. 1998, Havin et al. 1998). This view gained support from other early studies indicating that the chicken IMP1 ortholog ZBP1 was implicated in localization of β-actin mRNA to the leading edge of motile fibroblasts (Farina et al. 2003). In the same vein, neuronal ZBP1 is required for the localization of β-actin mRNA to dendrites and growth cones (Zhang et al. 2001, Tiruchinapalli et al. 2003). Finally, IMPs also play a role in *H19* and *Tau*-mRNA transport (Runge et al. 2000, Atlas et al. 2004). RNA localization is important in the establishment of cellular asymmetries – for instance during migration. The salient feature behind the mechanism is the ability to transport mRNAs in a repressed form, and at a given signal, unload the RNA enabling protein synthesis at the final destination. Although not necessarily mutually exclusive with regard to RNA localization, IMPs also control both the translatability and stability of particular mRNAs. IMPs impair translation of leader 3′ *IGF2* mRNA that exhibits at least six binding elements in the 5′UTR (Nielsen et al. 1999), and the mouse IMP1 ortholog CRD-BP was at an early stage found to stabilize the *c-myc* transcript by preventing the access of an endonuclease to the coding
region (Doyle et al. 1998). Moreover, IMPs prolong the half-life of CD44 mRNA and stimulate invadopodia formation (Vikesaa et al. 2006).

Physiological roles

The IMP proteins have previously been regarded as oncofetal, since they originally were discovered in developing embryos and in transformed cells (Nielsen et al. 1999). Clearly, the fetal expression is most prominent, but data demonstrating postnatal expression of IMPs are accumulating (Mori et al. 1999, Wang et al. 2003, Hansen et al. 2004). Mammalian IMPs are expressed in a biphasic fashion – with an early expression in the oocyte and in the zygote (for review see Nielsen et al. 2001, Yaniv & Yisraeli 2002), followed by an increase in the expression of all three IMPs from mouse embryonic day 10.5–12.5 (Nielsen et al. 1999, Runge et al. 2000).

At midgestation IMPs are expressed in most developing cells, and particularly high concentrations are found in neuronal and epithelial cells. Imp1 and Imp3 mRNAs are mainly expressed in fore- and hindbrain, in the snout, the branchial arches, the gut, the tail, the vertebrae, and in skin (Mueller-Pillasch et al. 1999, Mori et al. 2001, Hansen et al. 2004). A similar pattern is also observed in Xenopus, zebrafish, and Drosophila (Mueller-Pillasch et al. 1999, Zhang et al. 1999b, Nielsen et al. 2000, Adolph et al. 2009). Towards the end of embryogenesis, Imp3 mRNA expression has essentially disappeared, whereas sustained IMP1 expression is observed in small and large intestine, kidney, and liver.

During embryogenesis, the expression of IMP2 resembles that of IMP1 and IMP3 (Hansen, Hammer, Christiansen & Nielsen, 2005, unpublished; Fig. 2B). At E17.5, IMP2 staining remains significant in the brain – including the neopallial cortex, ventricular zone, and the striatum – in the nasal cavity, lung, liver, intestine, and in the kidney. Moreover, IMP2 mRNA has been detected in several organs during the perinatal period and in adult tissues, such as brain, gut, bone marrow, kidney, lung, muscle, liver, testis, and pancreas, in mouse or human (Gu et al. 2004, Hammer et al. 2005, Hansen et al. unpublished). Taken together, it may be concluded that IMP2 expression is largely overlapping with the previously described IMP1 and IMP3 expression during development (Mueller-Pillasch et al. 1999, Mori et al. 2001, Hansen et al. 2004). However, in contrast to its paralogs – IMP2 is also found in a variety of adult organs.

The physiological role of IMPs has been addressed by reverse genetics in different loss- and gain-of-function models. In Drosophila, aberrant expression of neuronal dIMP is followed by compromised synaptogenesis both centrally and peripherally, indicating that dIMP is required for proper axon guidance (Boylan et al. 2008). In Xenopus, knockdown of Vg1RBP/Vera (the IMP3 ortholog) showed that it was necessary for migration of cells from the roof plate of the neural tube and for neural crest migration (Yaniv et al. 2003). Consistent with a possible role of Vg1RBP/Vera in cell movement, the cells were correctly determined but simply remained at their site of origin. IMP1 deficient mice are on average 40% smaller than normal sex-matched littermates and exhibit a significant perinatal mortality and imperfect development of the gut. Global expression profiling of the postnatal intestine showed a reduced expression of transcripts encoding extracellular matrix components (Hansen et al. 2004). Mice overexpressing IMP1 in mammary epithelial cells develop mammary tumors (Tessier et al. 2004), showing that IMPs may play a causal role in cancer. Of interest to the putative role of IMP2 in diabetes, overexpression of IMP5/K homology domain containing protein overexpressed in cancer (KOC) using the metallothionin promoter was found to induce acinar-ductal metaplasia (Wagner et al. 2003). Moreover, loss-of-function analysis indicates that Vg1RBP/Vera is required for the establishment of pancreatic fate within the endoderm (Spagnoli & Brivanlou 2006).

IMP2 in T2D

An association between IMP2 and T2D was recently inferred from a series of GWA studies (Saxena et al. 2007, Scott et al. 2007, The Welcome Trust Control Consortium 2007; Table 1), demonstrating that SNPs mainly located in the second intron of IMP2 provided a moderately increased risk of developing T2D. Subsequent replication studies in different populations

<table>
<thead>
<tr>
<th>Genome-wide association studies with association to IMP2</th>
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<tbody>
<tr>
<td>Welcome Trust Case Control Consortium (2007)</td>
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<tr>
<td>Saxena et al. (2007)</td>
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<td>Scott et al. (2007)</td>
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Table 1 Primary type 2 diabetes genome-wide associations (GWAs) where an association to insulin-like growth factor 2 mRNA-binding protein 2 (IMP2) was found.
and meta-analyses have further supported the finding (Grarup et al. 2007, Scott et al. 2007, Zeggini et al. 2007, Groenewoud et al. 2008, Herder et al. 2008, Hertel et al. 2008, van Hoek et al. 2008, Horikawa et al. 2008, Kirchhoff et al. 2008, Lyssenko et al. 2008, Ng et al. 2008, Omori et al. 2008, Palmer et al. 2008, Sanghera et al. 2008, Tabara et al. 2008, Wu et al. 2008; Table 2). The reported association with the IMP2 locus based on all studies (OR 1.14 (95% CI 1.10–1.17)), represents a 3% difference in allele frequency between the case and control groups in over 34 000 subjects (Duesing et al. 2008). It should be recalled that all 10 GWA-identified risk genes only explain 5% of the inherited risk of T2D (Altshuler et al. 2008).

We also need to consider if the reported SNP association is causally related to IMP2 and which role IMP2 plays in T2D. Intron 2 harboring the majority of the significant SNPs spans about 125 kb, and it is not obvious how the variants should affect splicing or otherwise regulate expression. Fine mapping and re-sequencing are necessary to uncover additional causal IMP2 variants. SNPs could also directly affect or be linked to nearby variants affecting microRNAs, larger non-coding transcripts, or even antisense mRNAs transcribed in the large intron 2. Moreover, as it has been pointed out, other genes such as the protein phosphatase 1 regulatory subunit 2 (PPPIR2), mitogen-activated protein kinase (MAP3K13), lipase H (LIPH), diacylglycerol kinase γ-1 (DGKG), α-2-HS-glycoprotein (AHSG), and the insulin-sensitizing adipokine adiponectin (ADIPQ), which have been implicated in metabolism and regulation of insulin activity, are located in proximity to IMP2 (Doria et al. 2008).

Replication studies have indicated that IMP2 variants are more likely associated with reduced β-cell function (Grarup et al. 2007, Horikoshi et al. 2007, Groenewoud et al. 2008, Lyssenko et al. 2008, Palmer et al. 2008) than with reduced insulin sensitivity or fasting glucose levels (Ruchat et al. 2008), but we are still awaiting a detailed analysis of the expression of IMP2 protein in adult human pancreas. Microarray data from the

### Table 2

<table>
<thead>
<tr>
<th>Replication studies with association to IMP2</th>
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<th>Controls (n)</th>
<th>Population</th>
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<td>14 586</td>
<td>17 968</td>
<td>WTCC, DGI, FUSION, UKT2DGC, EFSoCH</td>
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<td>Kirchhoff et al. (2008)</td>
<td>1630</td>
<td>1065</td>
<td>Germany&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Omori et al. (2008)</td>
<td></td>
<td>1064</td>
<td>Japan</td>
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<tr>
<td>Palmer et al. (2008)</td>
<td>126&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1268 + 581</td>
<td>Hispanic + African–American&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Groenewoud et al. (2008)</td>
<td>424&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1908&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Wu et al. (2008)</td>
<td>878&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Chinese Han</td>
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<td>6544&lt;sup&gt;b&lt;/sup&gt;</td>
<td>The Netherlands</td>
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<td>van Hoek et al. (2008)</td>
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<td>Herder et al. (2008)</td>
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<td>16 630</td>
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<td>1638</td>
<td>1858</td>
<td>Norway</td>
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</table>

<sup>a</sup>Persons with increased T2D risk.  
<sup>b</sup>rs4402960 is only associated to decreased disposition index in Hispanics.  
<sup>c</sup>Impaired glucose tolerance.  
<sup>d</sup>Normal glucose tolerance.  
<sup>e</sup>T2D.  
<sup>f</sup>Increased fasting glucose.  
<sup>g</sup>Normal fasting glucose.  
<sup>h</sup>Population-based study.  
<sup>i</sup>Non-significant after Bonferroni correction.  
<sup>j</sup>Borderline significant.
The Diabetes Genome Anatomy Project (DGAP; http://www.diabetesgenome.org), recently presented by Doria et al. showed that IMP2 mRNA is expressed in islets, and islet IMP2 mRNA expression was not significantly different among diabetics and normal subjects, so additional studies are needed to define the role of IMP2 in islet function and T2D. Support for a role of IMP2 in pancreatic function, as a whole, mainly comes from mouse studies of fetal and adult pancreas (Mueller-Pillasch et al. 1999, Gu et al. 2004, Hansen et al. unpublished), and the function of IMP2 in β-cell function has not been directly addressed. Several of the T2D association studies mention that the IMP3 orthologs Vg1RBP/Vera and IMP3/KOC have been implicated in Xenopus pancreatic development and mouse pancreatic metaplasia respectively (Wagner et al. 2003, Spagnoli & Brivanlou 2006), but it should be noted that all IMPs are expressed in the developing pancreas, and none of the GWAs provide evidence for an association with either IMP1 or IMP3. Perhaps, this simply reflects that IMP1 and IMP3 do not contain similar causal variants as IMP2, but further studies are needed to confirm this.

T2D is frequently described as a complex disease characterized by reduced insulin sensitivity in muscle, fat, and liver, combined with a perturbed pancreatic glucose response and insulin secretion. Both processes are influenced by a series of different pathways under control of both environmental and genetic factors (for review see Kahn 1994). Among these, physical inactivity, obesity, the gut microbiome and food uptake, and even the intrauterine environment, are believed to play a role for the development of T2D. There is presently no evidence of major differences in RNA-binding ability among the IMPs and the functional significance of particular protein interactions needs further characterization. However, in contrast to IMP1 and IMP3, IMP2 is widely expressed in many adult tissues including the gut, muscle, and the brain. In these organs, small quantitative differences in IMP2 expression could have a subtle impact on, e.g., food uptake, metabolism, feeding behavior, or even more complex behavioral features, which could affect physical activity or the risk of obesity and thus life-time risk of developing T2D.

### Concluding remarks

Although there is compelling evidence for the association between SNPs in IMP2 and T2D, we have presently no molecular mechanism that explains the involvement in T2D. Future studies defining the expression, RNA targets and protein interactions of IMP2 in relevant tissues, as well as a characterization of the metabolism in the IMP2 knock-out mouse may provide additional clues. Moreover, resequencing may be necessary to identify causal variants in IMP2 and support the direct involvement of IMP2 in T2D. If these analyses are accomplished with a positive outcome, they may force us to change our general picture of T2D and further emphasize the enormous potential of GWA studies in providing new and fundamental understanding of common diseases.

### Table 3  Genome-wide associations (GWAs) and replication studies of type 2 diabetes (T2D) where no association to insulin-like growth factor 2 mRNA-binding protein 2 (IMP2) is found

<table>
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<tr>
<th>Study type</th>
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<th>Controls (n)</th>
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<td>GWAs</td>
<td>661</td>
<td>614</td>
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<td>1399</td>
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<td>3819(^b)</td>
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<td>1940</td>
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<td>Lewis et al. (2008)</td>
<td>Replication</td>
<td>993</td>
<td>1054</td>
</tr>
</tbody>
</table>

\(^a\)Healthy individuals from the RISC cohort.
\(^b\)Individuals at high risk for T2D.
Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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