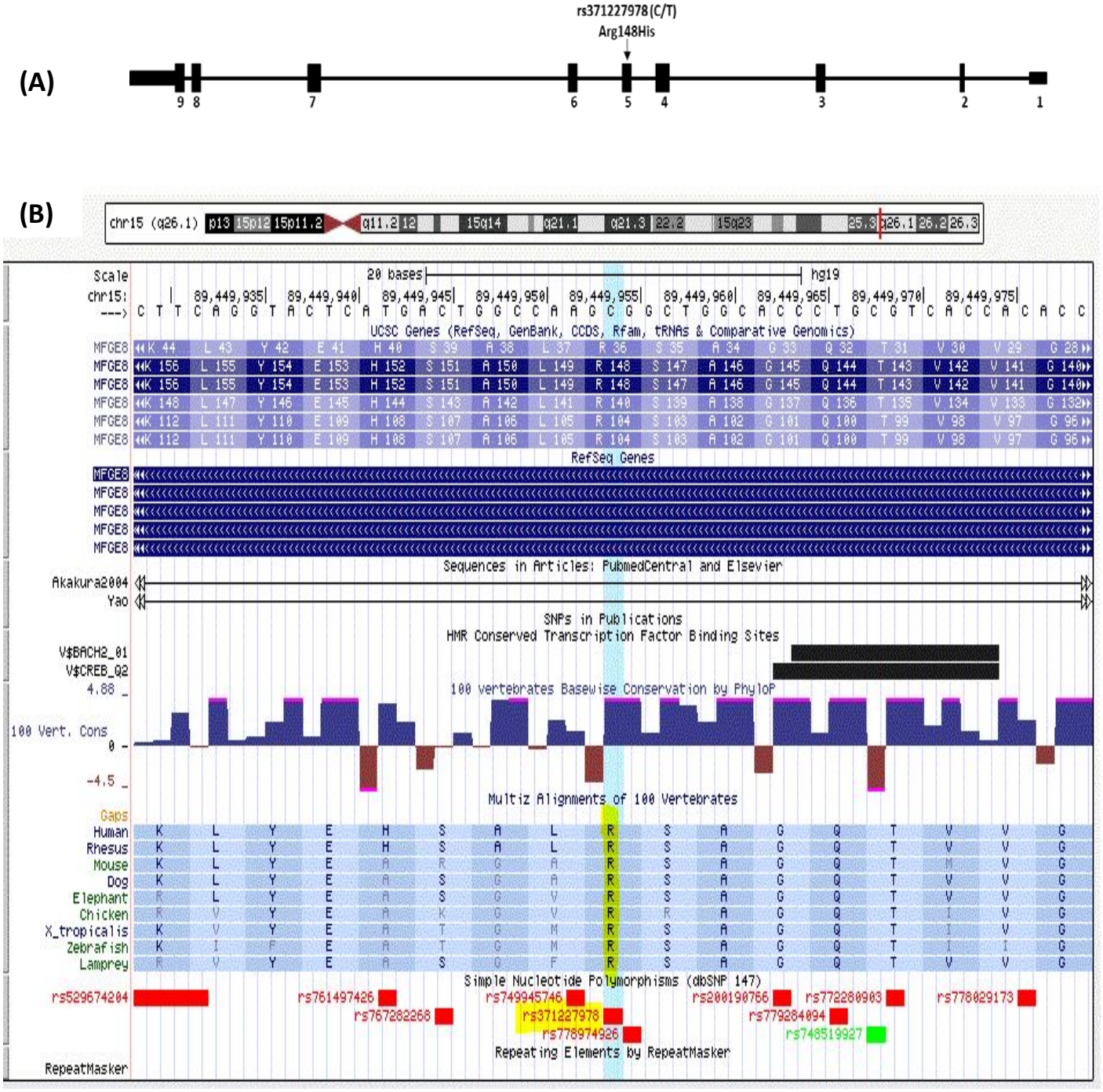
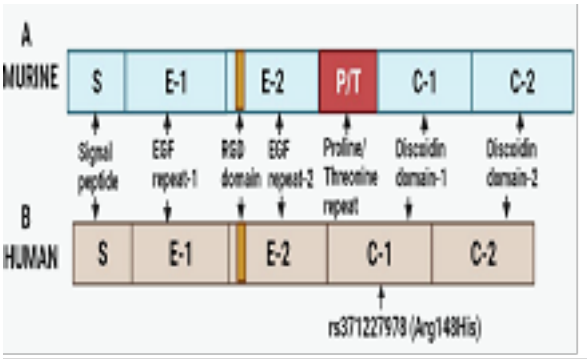


Supplementary Figure 1. (A) Identification of the rare missense variant rs371227978 (C/T: Arg148His) located on codon 148 of the fifth exon of the *MFGE8* gene by exome sequencing of AIDHS families with T2DM. Black rectangles represent the exons, and the horizontal line indicates non-coding sequence.

(B) Physical map of the Chromosome 15 region showing *MFGE8* gene location at chromosome position 15q25. Lower light blue rectangle is the data from BLAST showing sequence alignment of the portion of the *MFGE8* gene across different species surrounding Arg148His variant (rs371227978) highlighted in yellow. The yellow highlighted vertical bar indicates amino acid Arginine to be highly conserved among species (https://genome.ucsc.edu/cgi/MFGE8).



Supplementary Figure 2. Structural comparison of the functional domains of murine (A) human (B) Mfge8. The N-terminal site of Mfge8 has two EGF like domains, while the C-terminal site has two discoidin like domains (C1 and C2) with sequence similarity to blood coagulation factor V/VIII. The murine Mfge8 has additional Proline/Threonine repeat domain and has 57.7% similarity with human Mfge8. The variant rs371227978(Arg148His) resides on the C1 domain.

Supplementary Tables

Table1S: Exome sequencing identified 293 of 469 key genes in four major T2D-related pathways showing excess of rare variants among T2D patients

Pathways	*P*-value	Genes with mutations	Genes in the pathway
Insulin signaling	5.50E-15	100	161
Glucose Transport	4.30E-14	41	48
G-protein signaling	1.10E-10	60	92
MAPK signaling	1.90E-09	92	168

Table 2S: Correlations between Cardiometabolic traits, *MFGE8* genotypes and serum Mfge8 concentrations

		T2DM	FBG	TG	BMI	*MFGE8* Genotype	Serum Mfge8 Conc.
T2DM	Pearson Correlation	1	.637**	.146**	.126**	.040	.381**
	Sig. (2-tailed)		**<.001**	**2.91×10^{-18}**	**2.87×10^{-16}**	**.010**	**.001**
FBG (mg/dL)	Pearson Correlation		1	.207**	.094**	.014	.364**
	Sig. (2-tailed)			**1.99×10^{-30}**	**1.73×10^{-8}**	.396	**.002**
TG (mg/dL)	Pearson Correlation			1	.146**	.016	.331**
	Sig. (2-tailed)				**4.64×10^{-18}**	.346	**.005**
BMI	Pearson Correlation				1	-.015	-.098
	Sig. (2-tailed)					.345	.398
MFGE8 Genotype	Pearson Correlation					1	.215
	Sig. (2-tailed)						.058
Serum Mfge8 Conc.	Pearson Correlation						1
	Sig. (2-tailed)						

**Correlation is significant at the 0.01 level (2-tailed);serum Mfge8 measures were available in a subset of samples including 39 T2DM cases and age- and gender matched 39 controls; Bivariate Pearson's correlation was calculated using SPSS Vs. 19.

Table 3S. Distribution of *MFGE8* variant (rs371227978) in major global populations in Exome Aggregation Consortium

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
South Asian	175	16512	3	0.0106
European (Non-Finnish)	2	66722	0	2.998e-05
African	0	10406	0	0
East Asian	0	8652	0	0
European (Finnish)	0	6614	0	0
Latino	0	11574	0	0
Other	0	906	0	0
Total	**177**	**121386**	**3**	**0.001458**