SUPPLEMENTARY DATA

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SIFT uses sequence homology to predict whether a substitution affects protein function. SIFT scores range from 0 to 1: the amino acid substitution is predicted to be damaging if the score is <= 0.05, and tolerated if the score is > 0.05 (1).
We report the qualitative prediction estimated by POLY-PHEN2 using the 10% / 20% FPR for HumVar model (indicated for prediction of pathogenic variants in Mendelian diseases (2)). Mutations with their posterior probability scores associated with estimated false positive rates ≤10% FPR value are predicted to be probably damaging (more confident prediction). Mutations with the posterior probabilities associated with FPR comprised between 10% and 20% are predicted to be possibly damaging and mutations with estimated FPR >20% are classified as benign.
Align GVGD uses Grantham difference to predict the effect of missense variants. Missense changes are classified combining Grantham variation (GV) and Grantham deviation (GD) (3). The AGVGD output classifies amino acid changes from C0 (change unlikely to be pathogenic) to C65 (change most likely to be pathogenic).

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Supplementary Table 1. *In silico* characterization of the 9 *GATA6* missense mutations identified in patients with diabetes. The effect of each mutation on the GATA6 protein was predicted by SIFT, Polyphen2 and Align GVGD.

Mutation	**Protein**	**SIFT**	**Poly-Phen2**	**AGVGD**
c.1354A>AG	p.T452A	DAMAGING [0]	POSSIBLY DAMAGING	C55
c.1399G>GA	p.A467T	DAMAGING [0]	POSSIBLY DAMAGING	C55
c.1366C>CT	p.R456C	DAMAGING [0]	PROBABLY DAMAGING	C65
C.1396A>AG	p.N466D	DAMAGING [0]	POSSIBLY DAMAGING	C15
c.1417A>AC	p.K473Q	DAMAGING [0]	POSSIBLY DAMAGING	C45
c.1367G>GA	p.R456H	DAMAGING [0]	PROBABLY DAMAGING	C25
c.1435A>AG	p.R479G	DAMAGING [0]	PROBABLY DAMAGING	C65
c.1406G>GA	p.G469E	DAMAGING [0]	PROBABLY DAMAGING	C65
c.1339C>CT	p.C447R	DAMAGING [0]	PROBABLY DAMAGING	C65

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Supplementary Table 2. *In silico* characterization of the 7 *GATA6* intronic mutations identified in patients with diabetes. The effect of each mutation on splicing was estimated by Human Splicing Finder, NNSPLICE, SpliceSiteFinder-like, MaxEntScan and Gene Splicer.

	Human splicing finder [0-100]	**NNSPLICE [0-1]**	**SpliceSiteFinder-like [0-100]**	**MaxEntScan [0-12 for donor site, 0-16 for acceptor site]**	**GeneSplicer [0-15]**	**Comment**
1136-2A>G	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	
1303-10 C>G	Creating a new splicing acceptor site, stronger than the putative one (79.1 vs 76.7)	Creating a new splicing acceptor site, stronger than the putative one (0.4 vs 0.1)	Creating a new strong splicing acceptor site (84.3), abolishing the putative one	Creating a new splicing acceptor site, stronger than the putative one (7.1 vs 0.5)	Creating a new strong splicing acceptor site (8.8), abolishing the putative one	The mutation is predicted to create a strong cryptic acceptor site at position -9. Inclusion of 9 extra bases causes the insertion of a stop codon after 3 residues.
1303-1G>T	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	Abolishing conserved splicing acceptor site	
1429-41_1441del	Abolishing putative splicing acceptor site	Abolishing putative splicing acceptor site	Abolishing putative splicing acceptor site	Abolishing putative splicing acceptor site	Abolishing putative splicing acceptor site	The mutation abolishes the acceptor splicing site, possibly causing skipping of exon 5
1429-8T>G	Creating a new splicing acceptor site, weaker than the putative one (71.3 vs 74.4)	No prediction	Creating a new splicing acceptor site, abolishing the putative one	Creating a new splicing acceptor site, abolishing the putative one	No prediction	The mutation is predicted to create a cryptic acceptor site at position -7. Inclusion of 7 extra bases would cause frameshift and insertion of a stop codon after 9 residues
1516+1G>C	Abolishing conserved splicing donor site	Abolishing conserved splicing donor site	Abolishing conserved splicing donor site	Abolishing conserved splicing donor site	Abolishing conserved splicing donor site	
1516+4A>G	Decreasing strength of the donor site (83.1 vs 74.7), creating a cryptic strong acceptor site at +4 (79.4)	Decreasing strength of the donor site (0.9 vs 0.2), creating a cryptic acceptor site at +4 (0.03)	Abolishing the putative donor site, creating a cryptic acceptor site at +4 (74.9)	Decreasing the strength of the donor site (6.1 vs 2.9), creating a cryptic strong acceptor site at +4 (3.5)	No prediction	The mutation is predicted to affect the splicing of intron 6

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Supplementary Table 3. Clinical details of the 14 new cases with *GATA6* mutations reported.

Proband	Mutation	Protein	*De novo*	Status	Cardiac malformations	Additional endocrine abnormalities	Hepatobiliary malformations	Neurological abnormalities	Gut abnormalities
ISPAD-204	1429-8T>TG		*De Novo*	Pancreatic agenesis	Dextrocardia, aorto-pulmonary window, pulmonary hypertension, atrio-ventricular septal defects			Early cognitive and motor delay	Diaphragmatic hernia
ISPAD-205	1429-41_1441del		*De Novo*	Pancreatic agenesis	Patent ductus arteriosus				
ISPAD-206	c.1435A>AG	R479G	*De Novo*	Transient Neonatal Diabetes	Transposition of the great arteries, atrio-ventricular septal defects, pulmonary stenosis				
ISPAD-207	1136-2A>AG		Inherited	Pancreatic agenesis	Patent ductus arteriosus		Hepatic dysfunction		
ISPAD-207-02	1136-2A>AG		*De Novo*	Child-onset diabetes	Patent ductus arteriosus				
ISPAD-208	1303-1G>TG		Inherited	Permanent Neonatal Diabetes	Atrial septal defect, pulmonary stenosis	Hypothyroidism		Mild developmental delay	
ISPAD-208-02	1303-1G>TG (mosaic)		*De Novo*		Patent ductus arteriosus				
ISPAD-209	1036_1042del	p.T346PfsX44	Inherited	Pancreatic agenesis	Tetralogy of Fallot	Hypothyroidism		Mild learning difficulties	
ISPAD-209-02	1036_1042del	p.T346PfsX44	*De Novo*	Adult-onset diabetes					
ISPAD-210	c.1406G>GA	p.G469E	Inherited	Pancreatic agenesis		Hypothyroidism	Hepatomagaly	Mild to moderate developmental delay, hemiplegia	
ISPAD-210-02	c.1406G>GA	p.G469E	No parental samples available	Adult-onset diabetes					
ISPAD-211	c.1339C>CT	p.C447R	No parental samples available	Permanent Neonatal Diabetes		Hypothyroidism			
ISPAD-212	c.969C>CA	p.Y323X	Inherited	Pancreatic agenesis	Atrial septal defect, Patent ductus arteriosus				Diaphragmatic hernia
ISPAD-212-02	c.969C>CA	p.Y323X	*De Novo*	Adult-onset diabetes	Ventricular septal defect				

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