Genomic variants associated with age at diagnosis of childhood type 1 diabetes

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ONLINE SUPPLEMENTARY MATERIAL

Supplementary methods M1

Genome wide genotyping

The 1956 patients provided genome-wide data results by January 2015: 525 patients were genotyped with Illumina HumanCNV370v1_C (370,000 SNPs) microarrays, 680 patients with Illumina Human610-Quadv1_B (610,000 SNPs) microarrays, and 751 patients with Illumina Human Omni 5 Exome microarrays (4,500,000 SNPs).

Genome-wide genotyping was performed on bar-coded LIMS (Laboratory Information Management System) tracked samples using three different Illumina microarrays (HumanCNV370v1_C, Human610-Quadv1_B and HumanOMNI5-4v1_B). BeadChips were processed within an automated BeadLab at the Centre National de Genotypage (https://www.cnrgh.fr) as per the manufacturer's instructions. Samples were subject to strict quality control criteria including assessment of concentration, fragmentation and response to PCR. A total of 20 µl of DNA aliquoted to a concentration of 50 ng/µl was used for each array.

In the discovery phase, genome-wide genotypes were used for controlling the quality of the samples. First individuals with call rates <95% or duplicates and individuals who were possibly non-European were removed. By using this filtered sample set, we calculated quality control statistics, and SNPs with call rates <98% or SNPs with a Hardy–Weinberg equilibrium test P–value $<1.0 \times 10^{-6}$ or SNPs with a minor allele frequency <1% were excluded. Finally, 273,835 experimentally genotyped SNPs (HumanCNV370v1_C), 517,864 SNPs (Human610-Quadv1_B) and 3,309,261 SNPs (HumanOMNI5-4v1_B) were used for imputation analysis.

Imputation. Imputation was done using IMPUTE v2 (http://mathgen.stats.ox.ac.uk/impute_v2.html), following the instructions provided by the author. Full sequence data from chromosome 22 from the phase I 1000 Genomes Project was used, and the imputed genetic dosage with R-squared statistics >0.5 was used for the association analysis. As a result, ~30 million SNPs of three Illumina microarray were imputed, and association tests were performed for ~17 million SNPs with an imputation quality metric R-squared value of >0.5 and a minor allele frequency of >0.01.

To validate our imputation quality, rs4900384 and rs169560936 SNPs were genotyped by TaqMan® pre-designed SNP genotyping assay technology (TaqMan probes and primers and TaqMan Universal

Master Mix) (Appliedbiosystems, Thermo Fisher Scientific, Les Ulis, France). TaqMan assay were performed on LightCycler® 480 instrument (Roche Applied Science): PCR reactions were carried out with a total volume of 5 µl/well and consisted of 0.25 µl of 20X TaqMan® assay and 2.55 µl of 2X genotyping master mix with 10 ng of genomic DNA. Amplification was performed using one cycle of denaturation for 10 min at 95°C followed by amplification for 45 cycles (denaturation 95°C for 15 s and annealing/extension 60°C for 1 min). The genotype was determined by Endpoint Genotyping Analysis using the Roche Applied Science Software version 1.5.1.62.

SNP selection

We imputed the HLA haplotypes for 1609 individuals in our cohort using SNPs selected from [1,2]. Each of the participants who had been analyzed for their HLA genotypes has been categorized into one of six risk groups based on the summary effect of their HLA-DR/DQ haplotypes. Thus, we used six groups in the analyses.

Outside of the HLA region, 133 SNPs known to be associated with T1D were retrieved from the literature. Eight of these SNPs were not available in our imputation data. To identify a non-redundant set of associated variants, we LD pruned (keeping the most strongly associated SNP and removing those with $R^2<0.4$) the 125 remaining SNPs, which resulted in 94 SNPs and this was used for all subsequent analyses. Genotypes of these 94 SNPs were extracted for the genome-wide genotyping described above and crossed with age at diagnosis of T1D (Table S2).

To test interaction with non-HLA SNPs, we simplified the analysis by pooling patients in two groups as in [3], using SNPs selected from [1,4]: high-risk HLA genotype (DR3/DR4-DQ8 heterozygotes) and non-DR3/DR4-DQ8 genotypes. We observed no evidence of deviation from multiplicative interaction.

Supplementary Table S1. Main characteristics of the studied children. (IQR: interquartile range)

	N	Age at T1D diagnosis (yrs)		
		Mean ± sd	**Median**	**IQR**
Total	1956	7.9 ± 3.0	7.8	4.5
Born 1980-1995	980	9.0 ± 2.9	9.1	4.4
Born 1996-2008	976	6.9 ± 2.6	6.4	3.9
T1D diagnosis <7 yrs	812	5.1 ± 1.1	5.1	2.0
T1D diagnosis 7-13 yrs	1036	9.6 ± 1.6	9.5	2.7
T1D diagnosis >13 yrs	108	13.8 ± 0.6	13.7	0.8

Supplementary Table S2. Age at diagnosis in the HLA groups. **(IQR: interquartile range)**

HLA	N	Age at T1D diagnosis (yrs)		
		Mean ± sd	**Median**	**IQR**
DR3/4	589	8.0 ± 2.9	7.8	4.4
DR3/3	146	8.2 ± 3.0	8.0	4.9
DR4/4	92	8.8 ± 3.1	9.0	5.1
DR3/X	262	7.9 ± 3.1	7.8	4.5
DR4/X	378	8.2 ± 3.0	8.1	4.7
DRX/X	142	8.1 ± 3.2	8.1	5.6

Supplementary Table S3. List of the 94 studied susceptibility variants and degree of significance for their association with age at diagnosis. P-values were calculated using point wise unadjusted statistics (first column), following FDR correction for multiple tests. The last column shows the P-values for those SNPs that associated with age at T1D onset under a dominant pattern (**Fig. 1** and **Fig. S2**).

SNP	Reported or mapped gene(s)	Chr	Unadjusted P-value	BH FDR adjusted P-value	Dominant test P-value
rs2476601	PTPN22	1p13.2	0.18	0.46	
rs1983853	LPAR3	1p22.3	0.15	0.44	
rs2269241	PGM1	1p31.3	0.02	0.12	
rs7528684	**FCRL3**	**1q23.1**	**3.9×10^{-5}**	**4.5×10^{-4}**	**6.4×10^{-6}**
rs2816316	RGS1	1q31.2	0.05	0.23	
rs3024505	**IL10**	**1q32.1**	**6.3×10^{-4}**	**0.005**	**NA**
rs2639703	ENAH	1q42.12	0.08	0.33	
rs6547853	FOSL2	2p23.2	0.43	0.69	
rs2165738	NCOA1	2p23.3	0.23	0.48	
rs478222	EFR3B	2p23.3	0.34	0.59	
rs1534422	MIR3681HG	2p25.1	0.09	0.33	
rs1160542	AFF3	2q11.2	0.93	0.98	
rs917997	IL18RAP	2q12.1	0.89	0.94	
rs1990760	IFIH1	2q24.2	0.56	0.81	
rs7574865	STAT4	2q32.3	0.08	0.33	
rs6752770	STAT4	2q32.3	0.59	0.82	
rs3087243	CTLA4	2q33.2	0.61	0.82	
rs11711054	CCR5	3p21.31	0.64	0.82	
rs3772534	CBLB	3q13.11	0.32	0.58	
rs10517086	RBPJ	4p15.2	0.86	0.93	
rs2069763	**IL2**	**4q27**	**2.0×10^{-7}**	**6.1×10^{-6}**	**9.8×10^{-8}**
rs2069762	**IL2**	**4q27**	**7.1×10^{-4}**	**0.005**	**NA**
rs6897932	IL7R	5p13.2	0.23	0.48	
rs249240	CTNND2	5p15.2	0.41	0.68	
rs2544677	MIR4280	5q14.3	0.78	0.89	
rs380607	LOC728342	5q23.1	0.75	0.89	
rs17166496	FSTL4	5q31.1	0.97	0.99	
rs2296336	ITPR3	6p21.31	0.49	0.76	
rs9273363	HLA-DQB1	6p21.32	0.01	0.07	
rs9272346	HLA-DQA1	6p21.32	0.12	0.40	
rs11755527	BACH2	6q15	0.34	0.59	
rs9388489	CENPW	6q22.3	0.10	0.35	
rs6920220	**TNFAIP3**	**6q23.3**	**2.4×10^{-5}**	**3.2×10^{-4}**	**3.1×10^{-6}**
rs10499194	**TNFAIP3**	**6q23.3**	**4.3×10^{-5}**	**4.5×10^{-4}**	**NA**
rs1738074	TAGAP	6q25.3	0.62	0.82	
rs924043	LOC10272475	6q27	0.50	0.76	
rs4948088	COBL	7p12.1	0.30	0.56	
rs10272724	IKZF1	7p12.2	0.79	0.89	
rs550448	LOC100128081	7p15.1	0.23	0.48	

rs7804356	SKAP2	7p15.2	0.81	0.90	
rs7456390	DGKB	7p21.2	0.13	0.42	
rs17056297	ADRA1A	8p21.2	0.24	0.48	
rs2589197	SDC2	8q22.1	0.24	0.48	
rs12679857	TNFRSF11B	8q24.1	0.95	0.98	
rs7020673	GLIS3	9p24.2	0.51	0.76	
rs1953041	DAPK1	9q21.33	0.17	0.46	
rs12722495	IL2RA	10p15.1	0.14	0.43	
rs11258747	PRKCQ	10p15.1	0.60	0.82	
rs947474	DKFZ	10p15.1	0.64	0.82	
rs11594656	IL2RA	10p15.1	0.01	0.06	
rs2104286	IL2RA	10p15.1	0.14	0.43	
rs1250558	ZMIZ1	10q22.3	0.88	0.94	
rs10509540	RPL11P3	10q23.3	0.40	0.68	
rs10786436	**HPSE2**	**10q24.2**	**0.004**	**0.02**	**0.001**
rs7111341	TH - ASCL2	11p15.5	0.98	0.99	
rs3741208	INS	11p15.5	1.00	1.00	
rs689	INS	11p15.5	0.57	0.81	
rs1004446	IGF2 - INS	11p15.5	0.85	0.93	
rs4084127	**FGF4 - FGF3**	**11q13.3**	**1.4×10^{-4}**	**0.001**	**1.3×10^{-5}**
rs7126293	LOC643381	11q22.1	0.80	0.90	
rs3764021	CLEC2D	12p13.3	0.002	0.01	
rs2292239	**ERBB3**	**12q13.2**	**1.4×10^{-6}**	**2.7×10^{-5}**	**4.0×10^{-7}**
rs3184504	SH2B3	12q24.1	0.25	0.49	
rs539514	LMO7	13q22.2	0.41	0.68	
rs9585056	GPR183	13q32.3	0.20	0.48	
rs10137082	IL25	14q11.2	0.18	0.47	
rs1465788	ZFP36L1	14q24.1	0.24	0.48	
rs941576	MEG3	14q32.2	0.74	0.89	
rs4900384	C14orf64	14q32.2	0.51	0.76	
rs17574546	RASGRP1	15q14	0.16	0.44	
rs3825932	CTSH	15q25.1	0.64	0.82	
rs4788084	IL27	16p11.2	0.02	0.09	
rs12444268	UMOD-GP2	16p12.3	0.69	0.86	
rs2903692	**CLEC16A**	**16p13.1**	**1.4×10^{-10}**	**6.5×10^{-9}**	**2.9×10^{-12}**
rs149597	CLEC16A	16p13.13	0.76	0.89	
rs12928822	CLEC16A	16p13.13	0.20	0.48	
rs7202877	CTRB2 - CTRB1	16q23.1	0.72	0.89	
rs16956936	**DNAH2**	**17p13.1**	**1.3×10^{-4}**	**0.001**	**2.5×10^{-5}**
rs1008723	**GSDMB**	**17q12**	**5.2×10^{-11}**	**4.9×10^{-9}**	**4.3×10^{-11}**
rs7221109	**CCR7**	**17q21.2**	**1.7×10^{-5}**	**2.7×10^{-4}**	**NA**
rs45450798	PTPN2	18p11.21	0.17	0.46	
rs478582	PTPN2	18p11.21	0.21	0.48	
rs763361	CD226	18q22.2	0.31	0.57	
rs2304256	**TYK2**	**19p13.2**	**2.8×10^{-6}**	**6.5×10^{-6}**	**6.9×10^{-8}**

rs425105	PRKD2	19q13.3	0.01	0.06
rs602662	FUT2	19q13.33	0.27	0.53
rs601338	FUT2	19q13.33	0.45	0.72
rs12463137	ZNF773	19q13.43	0.04	0.17
rs2253815	SIRPB1	20p13	0.74	0.89
rs2281808	SIRPG	20p13	0.61	0.82
rs11203203	UBASH3A	21q22.3	0.79	0.89
rs5753037	LIF	22q12.2	0.10	0.35
rs743777	IL2RB	22q12.3	0.54	0.79
rs229541	C1QTNF6	22q12.3	0.23	0.48

Supplementary Table S4. Prevalence of the alleles of the 14 SNPs associated with age at T1D diagnosis according to sex.

Chr	Gene locus	SNP	SNP alleles*	Frequency of allele associated with early diagnosis		
				Total	**M**	**F**
1q23.1	*FCRL3*	rs7528684	**A**/G	0.617	0.616	0.618
1q32.1	*IL10***	rs3024505	**A**/G	0.112	0.108	0.116
4q27	*IL2***	rs2069763	**C**/A	0.693	0.697	0.688
4q27	*IL2***	rs2069762	**A**/C	0.736	0.721	0.753
6q23.3	*TNFAIP3***	rs6920220	**G**/A	0.813	0.812	0.815
6q23.3	*TNFAIP3***	rs10499194	**C**/T	0.746	0.747	0.744
10q24.2	*HPSE2*	rs10786436	**C**/T	0.730	0.729	0.731
11q13.3	*FGF3/4*	rs4084127	**G**/A	0.667	0.681	0.653
12q13.2	*ERBB3*	rs2292239	**T**/G	0.460	0.456	0.464
16p13.13	*CLEC16A*	rs2903692	**A**/G	0.403	0.409	0.398
17p13.1	*DNAH2*	rs16956936	**C**/T	0.914	0.915	0.912
17q12	*GSDMB***	rs1008723	**G**/T	0.563	0.589	0.535
17q21.2	*CCR7*	rs7221109	**T**/C	0.440	0.442	0.438
19p13.2	*TYK2*	rs2304256	**C**/A	0.793	0.795	0.791

* In bold, allele associated with earlier age at diagnosis of T1D.
** Previously associated with age at diagnosis in [17–19].

Supplementary Table S5. Association of the 12 loci with other autoimmune diseases.
SLE, systemic lupus erythematosus; RA, Rheumatoid arthritis; MS, multiple sclerosis; IBD, inflammatory bowel diseases; CD, Celiac disease; AITD, autoimmune thyroid diseases

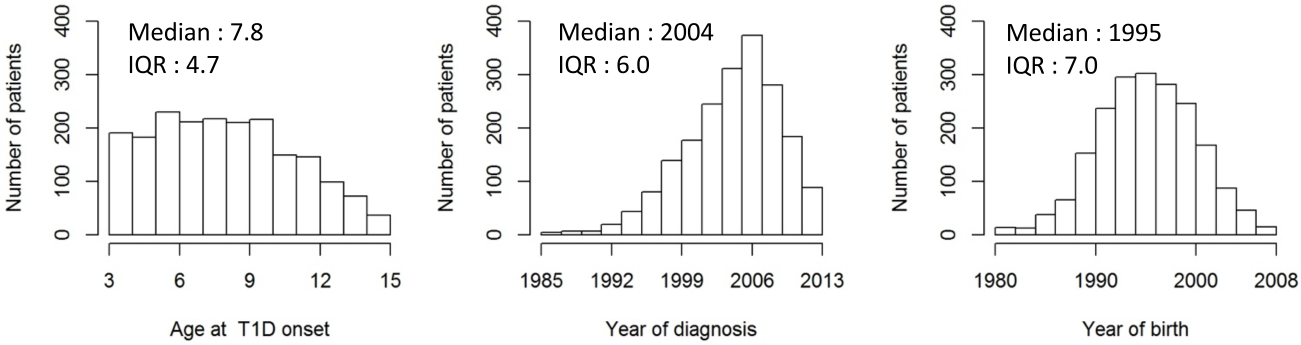
Chr	Gene locus	SLE	RA	MS	IBD	CD	AITD
1q23.1	FCRL3	[7]	[7–11]	[12]			[7,13]
1q32.1	IL10	[14,15]	[16–18]	[19]	[20–24]		
4q27	IL2	[25]	[26]		[27]	[28–30]	
6q23.3	TNFAIP3	[15,31–34]	[35–42]	[43]	[20,23]	[37,44,45]	
10q24.2	HPSE2				[20,22–24,46–51]		
11q13.3	FGF3/4						
12q13.2	ERBB3	[52]	[40]	[53]			
16p13.13	CLEC16A	[52]	[40]	[53]			
17p13.1	DNAH2	[15,33]	[40,54,55]	[43,53,55–58]	[23,24,59,60]	[45]	
17q12	GSDMB						
17q21.2	CCR7	[32]	[36,61,62]		[20,22–24,49,61]		
19p13.2	TYK2	[63]					

Supplementary Table S6. List of all the diabetes centers by alphabetic order (according to city) participating to the Isis-Diab Network.

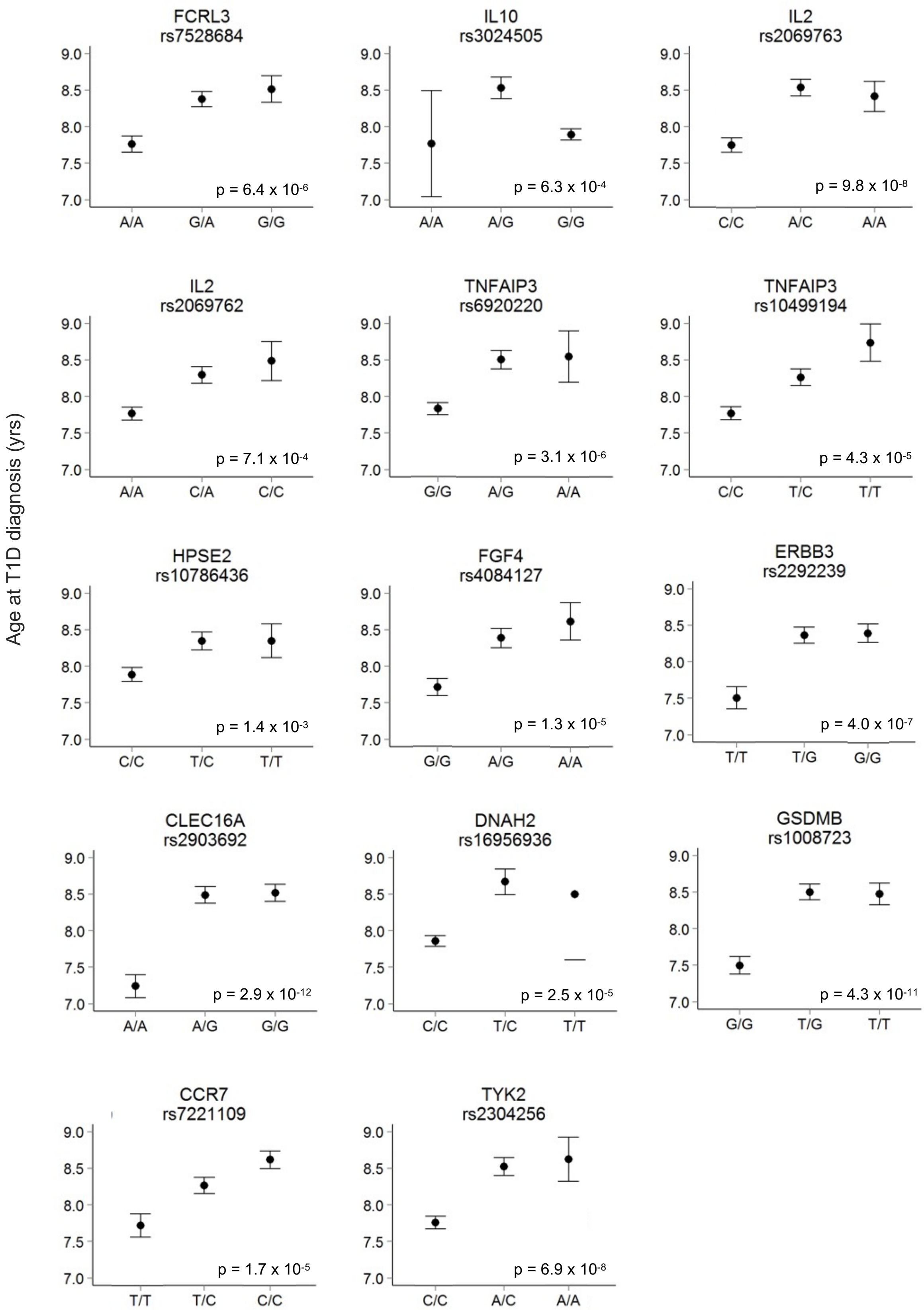
Center (City (Department))	Principal investigator
Aix-en-Provence (Pediatrics)	Dr Dominique Thevenieau
Alençon (Diabetology)	Dr Corinne Fourmy Chatel
Amiens (Diabetology)	Dr Rachel Desailloud
Amiens (Pediatrics)	Dr Hélène Bony-Trifunovic
Angers (Diabetology)	Dr Pierre-Henri Ducluzeau
Angers (Pediatrics)	Prof Régis Coutant
Armentières (Pediatrics)	Dr Sophie Caudrelier
Arras (Pediatrics)	Dr Armelle Pambou
Aurillac (Diabetology)	Dr Emmanuelle Dubosclard
Avignon (Pediatrics)	Dr Florence Joubert
Bar-le-Duc (Pediatrics / Diabetology)	Dr Philippe Jan
Belfort-Montbéliard (Pediatrics)	Dr Estelle Marcoux
Besançon (Pediatrics)	Dr Anne-Marie Bertrand/Dr Brigitte Mignot
Besançon (Diabetology)	Prof Alfred Penformis
Béthune (Pediatrics)	Dr Chantal Stuckens
Blois (Diabetology)	Dr Régis Piquemal
Bordeaux (Pediatrics)	Prof Pascal Barat
Bordeaux (Diabetology)	Prof Vincent Rigalleau
Boulogne-Billancourt (Pediatrics)	Dr Chantal Stheneur
Boulogne-sur-Mer (Pediatrics)	Dr Sylviane Fournier
Brest (Diabetology)	Prof Véronique Kerlan
Brest (Pediatrics)	Dr Chantal Metz
Brive (Pediatrics)	Dr Anne Fargeot-Espaliat
Caen (Diabetology)	Prof Yves Reznic
Cahors (Diabetology)	Dr Frédérique Olivier
Cambrai (Pediatrics)	Dr Iva Gueorguieva
Chartres (Diabetology)	Dr Arnaud Monier
Cholet (Pediatrics)	Dr Catherine Radet
Clamart (Pediatrics)	Dr Vincent Gajdos
Clermont-Ferrand (Pediatrics)	Dr Daniel Terral
Compiègne (Pediatrics)	Dr Christine Vervel
Contamine (Pediatrics)	Dr Djamel Bendifallah
Dijon (Pediatrics)	Dr Candace Ben Signor
Douai (Pediatrics)	Dr Daniel Dervaux
Draguignan (Pediatrics)	Dr Abdelkader Benmahammed
Dunkerque (Pediatrics)	Dr Guy-André Loeuille
Epinal (Pediatrics)	Dr Françoise Popelard
Gap (Diabetology)	Dr Agnès Guillou
Grenoble (Diabetology)	Prof Pierre-Yves Benhamou
Hyères (Pediatrics)	Dr Jamil Khoury
La Roche-sur-Yon (Pediatrics)	Dr Jean-Pierre Brossier
Laval (Pediatrics)	Dr Joachim Bassil
Le Creusot (Diabetology)	Dr Sylvaine Clavel
Le Havre (Pediatrics)	Dr Bernard Le Luyer
Le Kremlin-Bicêtre (Pediatrics)	Prof Pierre Bougnères
Le Mans (Pediatrics)	Dr Françoise Labay
Lens (Pediatrics)	Dr Isabelle Guemas
Lille (Pediatrics)	Prof Jacques Weill

Lille (Diabetology)	Dr Jean-Pierre Cappoen
Limoges (Diabetology)	Dr Sylvie Nadalon
Limoges (Pediatrics)	Dr Anne Lienhardt-Roussie
Lisieux (Diabetology)	Dr Anne Paoli
Lisieux (Pediatrics)	Dr Claudie Kerouedan
Lorient (Diabetology)	Dr Edwige Yollin
Lyon (Pediatrics)	Prof Marc Nicolino
Marseille (Pediatrics)	Prof Gilbert Simonin
Marseille Saint-Joseph (Diabetology)	Dr Jacques Cohen
Marseille CHU Nord (Diabetology)	Dr Catherine Atlan
Maubeuge (Pediatrics)	Dr Agnès Tamboura
Mérignac (Pediatrics)	Dr Hervé Dubourg
Mont-de-Marsan (Pediatrics)	Dr Marie-Laure Pignol
Montfermeil (Pediatrics)	Dr Philippe Talon
Nancy (Pediatrics)	Dr Stéphanie Jellimann
Nantes (Diabetology)	Dr Lucy Chaillous
Nantes (Pediatrics)	Dr Sabine Baron
Nice (Pediatrics)	Dr Marie-Noëlle Bortoluzzi
Nice Lenval (Pediatrics)	Dr Elisabeth Baechler
Nîmes (Pediatrics)	Dr Randa Salet
Niort (Pediatrics)	Dr Ariane Zelinsky-Gurung
Palavas Les Flots (Pediatrics)	Dr Fabienne Dallavale
Paris Hôtel-Dieu (Diabetology)	Dr Etienne Larger
Paris Lariboisière (Pediatrics)	Dr Marie Laloi-Michelin
Paris Saint-Louis (Diabetology)	Dr Jean-François Gautier
Pau (Pediatrics)	Dr Bénédicte Guérin/Dr Laure Oilleau
Pontoise (Pediatrics)	Dr Laetitia Pantalone
Reims (Diabetology)	Dr Céline Lukas
Rennes (Diabetology)	Dr Isabelle Guilhem
Rennes (Pediatrics)	Dr Marc De Kerdanet
Rouen (Pediatrics)	Dr Marie-Claire Wielickzo
Saint-Brieuc (Diabetology)	Dr Mélanie Priou-Guesdon
Saint-Etienne (Pediatrics)	Dr Odile Richard
Saint-Avold (Pediatrics)	Dr François Kurtz
Saint-Lo (Pediatrics)	Dr Norbert Laisney
Saint-Lo (Diabetology)	Dr Déborah Ancelle
Saint-Nazaire (Pediatrics)	Dr Guilhem Parlier
Saintes (Pediatrics)	Dr Catherine Boniface
Strasbourg (Diabetology)	Dr Dominique Paris Bockel
Tarbes (Pediatrics)	Dr Denis Dufillot
Toulon (Pediatrics)	Dr Berthe Razafimahefa
Toulouse (Diabetology)	Dr Pierre Gourdy
Toulouse (Pediatrics)	Dr Pierre Gourdy
Tours (Diabetology)	Prof Pierre Lecomte
Tours (Pediatrics)	Dr Myriam Pepin-Donat
Tremblay-en-France (Diabetology)	Dr Marie-Emmanuelle Combes-Moukhovsky
Troyes (Pediatrics)	Dr Brigitte Zymmermann
Valence (Pediatrics)	Dr Marina Raoulx
Valenciennes (Pediatrics)	Dr Anne Gourdin
Vienne (Pediatrics)	Dr Catherine Dumont
Villefranche-sur-Saône (Pediatrics)	Dr Michèle Chambon

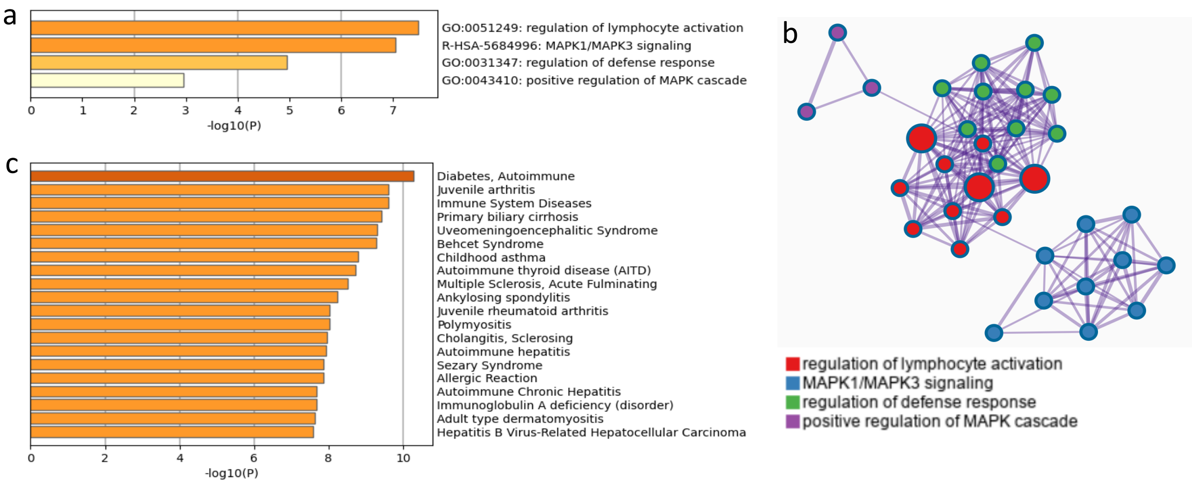
Supplementary Figure S1. Distribution of the age at diagnosis of T1D, date of birth and date of clinical diagnosis in the studied 1956 children. **(IQR: interquartile range)**



Supplementary Figure S2. Age at diagnosis in the genotypic groups for the 14 SNPs that were associated with age at T1D diagnosis. A recessive pattern appears for rs3024504, rs2069762, rs10499194, rs3764021, rs7221109, and a dominant pattern for the 9 other SNPs. P-values are shown for each SNP depending on this pattern.



Supplementary Figure S3. Functional enrichment analysis for the T1D age at diagnosis associated genes. (a) Pathway and process enriched terms for the associated genes, colored by p-values. (b) Network visualization of the enriched terms in (a), colored by different cluster IDs (enriched terms). (c) DisGeNET enrichment analysis for the associated genes, colored by p-values. The top 20 enriched terms are shown in (c).



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