

## Supplemental Material

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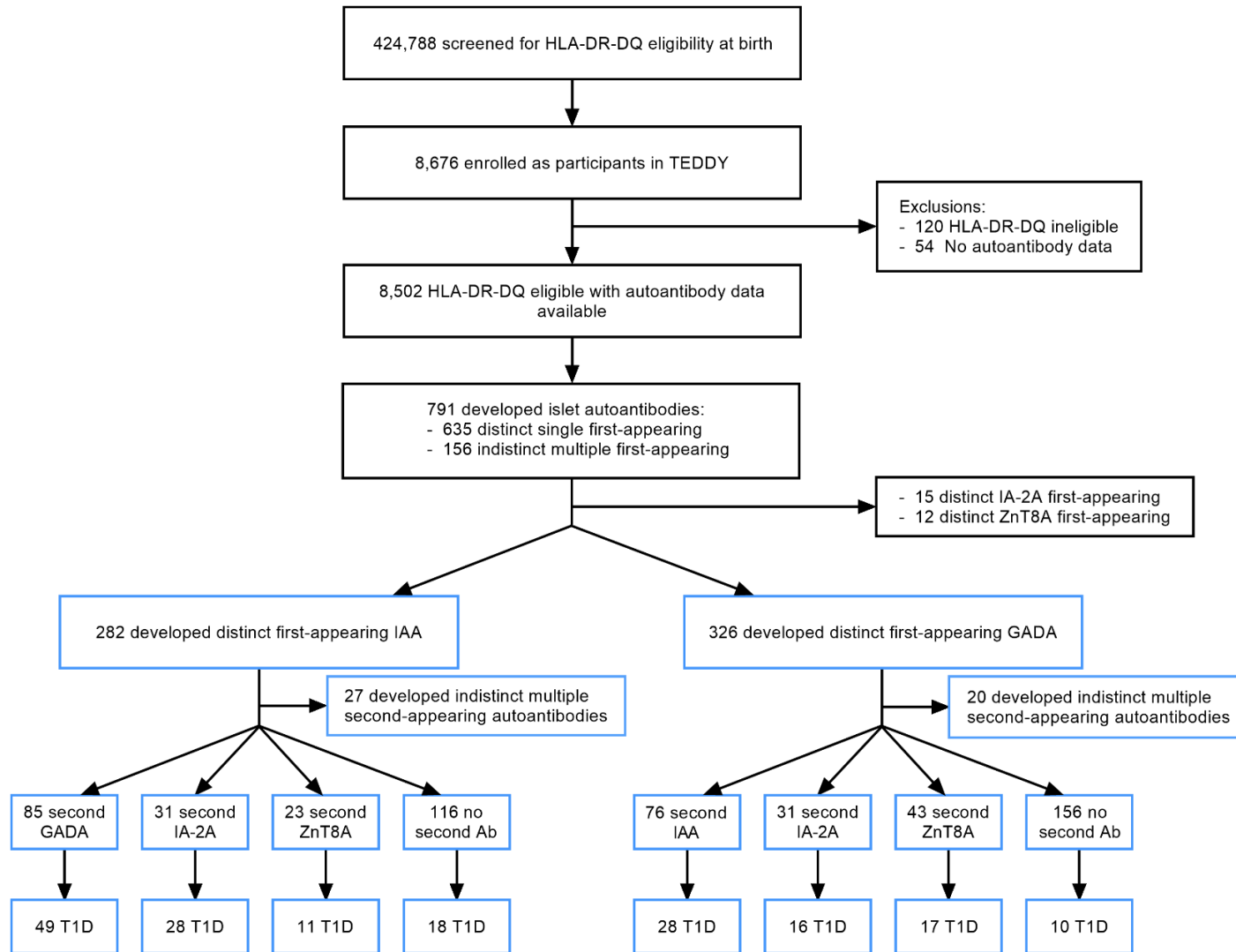
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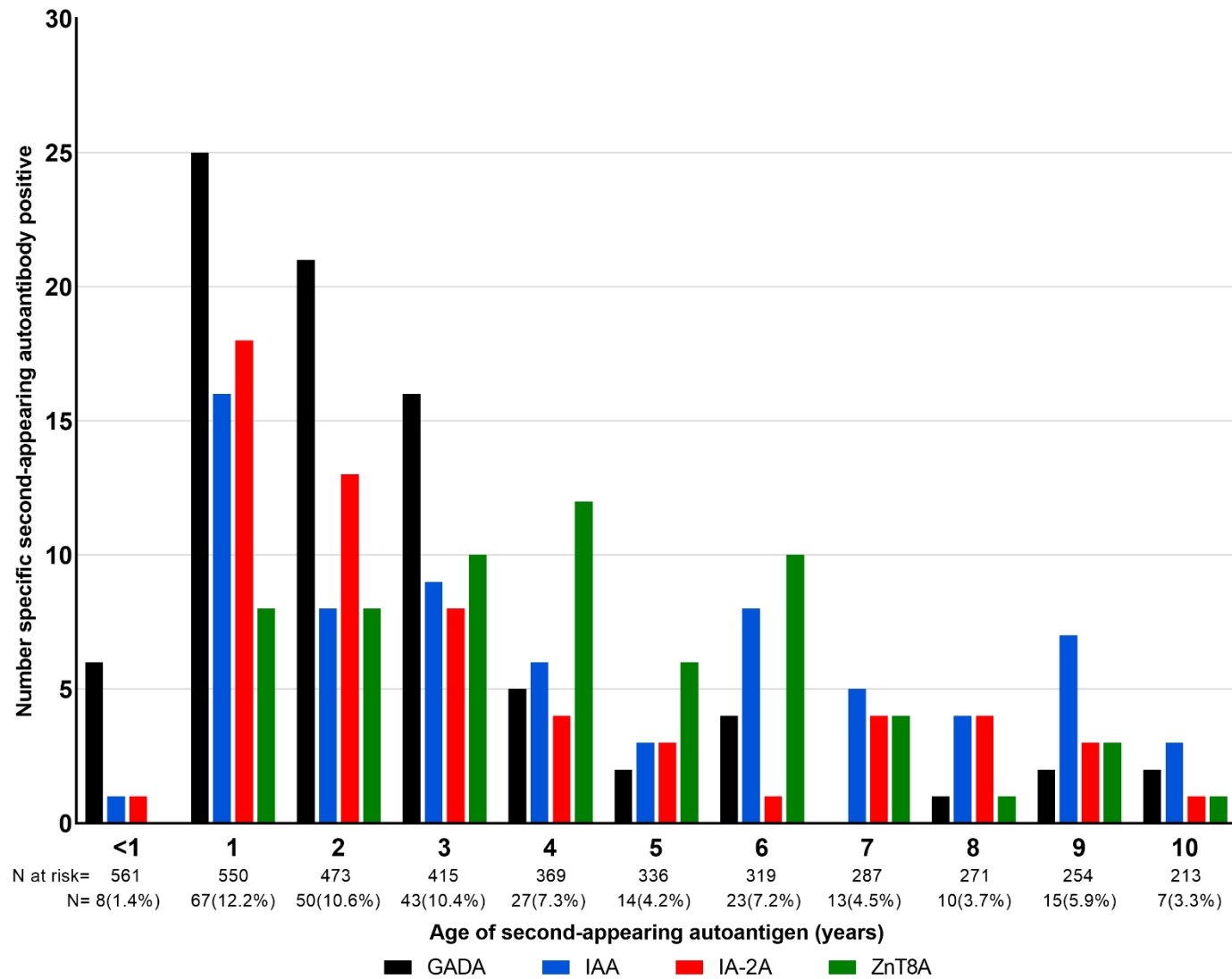
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### Listing of members of the TEDDY Study Group



**Supplemental Figure S1.** Flow diagram of number of study participants, eligibility, distinct single appearing islet autoantibody (first and second) and progression to type 1 diabetes. Distinct denotes the specific autoantibody can be discerned; whereas, indistinct denotes the specific autoantibody cannot be determined given timing of another autoantibody(s) in same visit time window. Blue outlined boxes indicate children included in this analysis (n=608).



**Supplemental Figure S2.** The age distribution for the number of specific second-appearing autoantibody in children autoantibody positive for first-appearing IAA or GADA (n=561, black bar represents GADA, blue bar represents IAA, red bar represents IA-2A and green bar represents ZnT8A). Those who developed multiple second-appearing autoantibodies (n=47) no included in figure.

**Supplemental Table S1. Characteristics of first-appearing autoantibody profile and development of second-appearing autoantibody and type 1 diabetes (n=791)**

<b>First-Appearing Autoantibody Profile</b>	<b>N</b>	<b>Median (IQR) Age at Seroconversion (months)</b>	<b>Second Appearing Autoantibody, n, (% yes)</b>	<b>Diagnosed with type 1 diabetes, n (% yes)</b>	<b>Median (IQR) age diagnosis with type 1 diabetes (months)</b>	<b>Median (IQR) age of follow-up (months)</b>
GADA only	326	51.4(27.2-90.1)	163(50.0)	70(21.5)	82.8(52.8-111.1)	126.3(107.5-144.4)
IAA only	282	22.0(12.0-45.8)	165(58.5)	113(40.1)	54.0(32.4-97.4)	114.3(69.2-136.8)
IA-2A only	15	67.0(38.8-92.3)	10(66.7)	7(46.7)	94.3(92.3-112.6)	112.6(94.3-135.3)
ZnT8A only	12	82.2(38.3-100.2)	12(100)	5(41.7)	103.1(72.7-112.8)	119.6(106.7-149.2)
GADA, IAA	85	27.9(14.6-49.1)	64(75.3)	60(70.6)	58.9(27.7)	84.5(35.2-116.9)
GADA, IA-2A	5	86.4(24.7-95.2)	3(60.0)	3(60.0)	89.8(21.0-115.7)	115.7(89.8-119.4)
GADA, ZnT8A	15	60.2(50.8-97.1)	8(53.3)	3(20.0)	127.3(103.3-168.8)	133.5(121.0-159.1)
IAA, IA-2A	5	28.3(23.3-80.6)	4(80.0)	3(60.0)	94.5(19.4-153.1)	133.6(94.5-147.7)
IAA, ZnT8A	9	26.5(18.3-46.5)	7(77.8)	5(55.6)	76.6(61.2-98.1)	98.1(68.1-119.6)
IA-2A, ZnT8A	3	80.9(48.0-95.6)	2(66.7)	1(33.3)	84.1	156.3(84.1-165.11)
GADA, IAA, IA-2A	15	36.3(16.5-85.8)	5(33.3)	12(80.0)	49.8(21.7-90.8)	58.3(31.6-135.3)
GADA, IAA, ZnT8A	8	37.7(20.9-77.8)	5(62.5)	6(75.0)	89.7(82.0-102.4)	89.7(74.6-105.3)
GADA, IA-2A, ZnT8A	4	92.4(82.7-104.7)	2(50.0)	2(50.0)	113.7(87.7-139.8)	115.2(98.0-130.9)
IAA, IA-2A, ZnT8A	2	90.4(60.3-120.4)	1(50.0)	0	na	116.2(67.5-164.8)
GADA, IAA, IA-2A, ZnT8A	5	43.8(38.4-109.2)	0	4(80.0)	73.4(47.4-114.1)	97.6(49.1-130.6)

**Supplemental Table S2. Characteristics of TEDDY children who developed a distinct second-appearing autoantibody by first-appearing IAA or GADA (n=608).**

Second appearing autoantibody	IAA-First appearing children at risk for second-appearing (n=282§)				GADA-First appearing children at risk for second-appearing (n=326‡)			
	GADA	IA-2A	ZnT8A	None	IAA	IA-2A	ZnT8A	None
n (%)	85 (30.1)	31 (11.0)	23 (8.2)	116 (41.1)	76 (23.1)	31 (9.5)	43 (13.2)	156 (47.9)
Sex, n (% female)	35 (41.2)	14 (45.2)	7 (30.4)	59 (50.9)	34 (44.7)	17 (54.2)	17 (39.5)	78 (50.0)
Family History with T1D, n (% yes)	21 (24.7)	7 (22.6)	5 (21.7)	12 (10.3)	12 (17.1)	8 (25.0)	10 (23.8)	19 (12.2)
Sibling with T1D	9 (10.6)	1 (3.2)	0	4 (3.5)	1 (1.3)	0	3 (7.1)	2 (1.3)
Father with T1D	10 (11.8)	4 (12.9)	5 (21.7)	5 (4.3)	9 (11.8)	5 (15.6)	4 (9.5)	11 (7.1)
Mother with T1D	2 (2.4)	2 (6.5)	0	3 (3.0)	3 (4.0)	3 (9.4)	3 (7.1)	6 (3.9)
HLA-DR-DQ genotype, n (%)								
DR3/4	53 (62.4)	12 (38.7)	14 (60.9)	46 (39.7)	47 (61.8)	16 (51.6)	19 (44.2)	69 (44.2)
DR4/4	18 (21.2)	6 (19.4)	3 (13.0)	16 (13.8)	11 (14.5)	4 (12.9)	6 (14.0)	25 (16.0)
DR4/8	8 (9.4)	12 (38.7)	5 (21.7)	29 (25.0)	9 (11.8)	4 (12.9)	5 (11.6)	21 (13.5)
DR3/3	2 (2.4)	0	1 (4.4)	20 (17.2)	8 (10.5)	7 (22.6)	13 (30.2)	39 (25.0)
First Degree Relative (FDR) Specific*	4 (4.7)	1 (3.2)	0	5 (4.3)	1 (1.3)	0	0	2 (1.3)
HLA A*24:X, n (%)	11 (12.9)	9 (29.0)	11 (47.8)	19 (16.4)	11 (14.5)	5 (16.1)	4 (9.3)	29 (18.6)
HLA B*18:X, n (%)	13 (15.3)	5 (16.1)	1 (4.4)	20 (17.2)	7 (9.2)	4 (12.9)	8 (18.6)	13 (8.3)
HLA B*39:X, n (%)	5 (5.9)	5 (16.1)	2 (8.7)	7 (6.0)	3 (4.0)	1 (3.2)	4 (9.3)	5 (3.2)
Maternal islet autoimmunity, n (% yes)	3 (3.5)	1 (3.2)	0	2 (1.7)	1 (1.3)	1 (3.2)	0	5 (2.1)
Probiotics started by 28 days, n (% yes)	4 (4.7)	1 (3.2)	3 (13.0)	5 (4.3)	3 (4.0)	3 (9.7)	3 (7.0)	8 (5.1)
Weight at 12 months, median z score (IQR)	-0.13(-1.00-0.67)	-0.35(-0.91-0.45)	-0.10(-0.77-0.57)	-0.06(-0.75-0.71)	0.23(-0.72-0.76)	0.16(-0.32-0.81)	0.37(-0.55-0.86)	-0.005(-0.63-0.66)
Child conditions before first clinical visit at age 3 months, n (%)								
Upper respiratory infection	20 (23.5)	6 (19.4)	6 (26.1)	27 (23.3)	12 (15.8)	8 (25.8)	8 (19.1)	34 (21.8)
Lower respiratory infection	14 (16.5)	3 (9.7)	0	11 (9.5)	11 (14.5)	5 (16.1)	7 (16.2)	10 (6.4)
Diarrhea	7 (8.2)	1 (3.2)	3 (13.0)	14 (12.1)	4 (5.2)	2 (6.5)	2 (4.7)	13 (8.3)

Rash	16 (18.9)	3 (9.7)	7 (22.6)	24 (20.7)	10 (13.2)	7 (22.6)	8 (18.6)	35 (22.4)
SNPs (minor allele frequency)								
rs2476601_A ( <i>PTPN22</i> )	0.16	0.21	0.17	0.15	0.19	0.15	0.14	0.10
rs1534422_G	0.41	0.44	0.48	0.47	0.47	0.45	0.42	0.44
rs10517086_A	0.30	0.29	0.26	0.31	0.33	0.29	0.27	0.26
rs2327832_G ( <i>TNFAIP3</i> )	0.18	0.16	0.22	0.19	0.24	0.15	0.17	0.21
rs1004446_A ( <i>INS</i> )	0.30	0.24	0.35	0.34	0.30	0.42	0.36	0.35
rs2292239_T ( <i>ERBB3</i> )	0.36	0.47	0.35	0.34	0.38	0.40	0.37	0.34
rs3184504_C ( <i>SH2B3</i> )	0.48	0.56	0.48	0.46	0.48	0.44	0.42	0.51
rs13266634_T ( <i>SLC30A8</i> )	0.32	0.31	0.39	0.34	0.36	0.27	0.29	0.32
Median (IQR) Age at Second Appearing Autoantibody (months)	29.9(18.5-45.0)	19.4(17.8-29.2)	37.2(21.1-59.8)	na	57.8(29.4-102.8)	65.6(35.9-105.9)	60.9(48.7-85.5)	na
Median (IQR) duration of time from First to Second-Appearing Autoantibody (months)	3.7(3.0-9.7)	5.9(3.2-9.3)	9.6(3.3-24.1)	na	5.9(3.0-25.9)	12.4(6.2-23.7)	15.2(8.7-23.7)	na
Progression to type 1 diabetes from time of second appearing autoantibody, n (%)	49 (57.7)	28 (90.3)	11 (47.8)	18 (15.5)	28 (36.8)	16 (51.6)	17 (39.5)	10 (6.4)
Median (IQR) time from Second Appearing Autoantibody to type 1 diabetes (months)	51.0(20.1-76.8)	27.2(9.2-43.2)	75.9(38.2-92.1)	6.7(1.7-23.9)**	44.9(18.9-68.6)	31.9(16.4-61.1)	75.8(42.6-86.7)	27.9(4.5-40.8)**
Developed a third or fourth autoantibody, n (% yes)	68 (80.0)	17 (54.8)	17 (73.9)	na	50 (65.8)	19 (61.3)	30 (69.8)	na
Median (IQR) age of follow-up (months) from initial seroconversion	82.3(42.8-114.5)	34.9(15.4-63.1)	109.6(67.1-138.8)	71.3(38.3-111.1)	65.4(45.2-102.9)	65.0(33.4-87.0)	91.9(59.6-107.4)	63.3(36.4-93.7)

§ 27 children developed two autoantibodies within the same 3-month interval as second appearing autoantibodies. Data not presented due to difficulty in determining order of appearance.

‡ 20 children developed two autoantibodies within the same 3-month interval as second appearing autoantibodies. Data not presented due to difficulty in determining order of appearance.

\* FDR specific includes: DR4/1, DR4/9, DR4/13, DR3/9, DR4/4-DQB1\*20X, DR4/4-DQB1\*304.

\*\* From time of first appearing autoantibody.

**Supplemental Table S3. Univariate cause-specific hazards ratios (HR) in children with a single first-appearing IAA or GADA positivity (n=608) for progression to second autoantibody positivity (n=336†)**

	Second-appearing autoantibody		
	GADA or IAA	IA-2A Cause-specific HR* (95% CI), P	ZnT8A
Female vs. Male	0.85(0.62-1.16), p=0.31	1.11(0.67-1.84), p=0.68	0.62(0.37-1.02), p=0.06
Family History with type 1 diabetes (reference= no family history)			
Sibling with type 1 diabetes	<b>2.22(1.15-4.30), p=0.018</b>	0.78(0.11-5.72), p=0.80	2.06(0.63-6.67), p=0.23
Father with type 1 diabetes	1.39(0.85-2.28), p=0.19	1.54(0.71-3.31), p=0.27	<b>2.12(1.03-4.36), p=0.041</b>
Mother with type 1 diabetes	0.86(0.35-2.11), p=0.74	2.18(0.84-5.64), p=0.11	1.60(0.49-5.22), p=0.43
HLA-DR-DQ genotype (reference=DR4/4)			
DR3/4	1.35(0.89-2.04), p=0.16	1.20(0.58-2.47), p=0.63	1.38(0.66-2.90), p=0.39
DR4/8	<b>0.53(0.29-0.97), p=0.039</b>	1.59(0.70-3.59), p=0.27	0.92(0.37-2.30), p=0.86
DR3/3	<b>0.36(0.17-0.75), p=0.006</b>	0.74(0.28-1.97), p=0.55	1.15(0.49-2.36), p=0.75
First Degree Relative (FDR) Specific**	1.12(0.42-2.93), p=0.83	0.75(0.09-6.02), p=0.79	NA, p=0.98
HLA A*24:X (yes vs. no)	0.83(0.53-1.31), p=0.43	1.52(0.83-2.76), p=0.17	0.75(0.36-1.57), p=0.44
HLA B*18:X (yes vs. no)	1.02(0.63-1.64), p=0.95	1.16(0.56-2.38), p=0.70	1.24(0.61-2.52), p=0.55
HLA B*39:X (yes vs. No)	0.81(0.39-1.66), p=0.56	2.06(0.86-4.93), p=0.11	1.42(0.60-3.35), p=0.43
Maternal islet autoimmunity (yes vs. no)	0.91(0.33-2.54), p=0.85	1.16(0.27-5.04), p=0.84	NA p=0.98
Probiotics started by 28 days (yes vs. no)	0.78(0.36-1.72), p=0.54	1.16(0.40-3.37), p=0.78	2.12(0.84-5.34), p=0.11
Weight at 12 months z score	0.96(0.84-1.10)p=0.55	0.98(0.79-1.25), p=0.93	1.08(0.86-1.36), p=0.49
Child conditions before first clinical visit at age 3 months (yes vs. no)			
Upper respiratory infection	0.86(0.58-1.27), p=0.45	0.91(0.50-1.68), p=0.77	1.00(0.55-1.83), p=0.99
Lower respiratory infection	1.46(0.95-2.24), p=0.09	1.19(0.56-2.53), p=0.64	0.98(0.45-2.15), p=0.96
Diarrhea	0.71(0.38-1.33), p=0.29	0.61(0.19-1.98), p=0.41	0.80(0.31-2.04), p=0.64
Rash	0.67(0.44-1.03), p=0.07	0.63(0.32-1.26), p=0.19	1.11(0.62-2.00), p=0.73
SNPs (reference= no minor allele)			
rs1534422_G	1.14(0.79-1.63), p=0.49	0.77(0.45-1.32), p=0.34	0.86(0.51-1.45), p=0.58

rs10517086_A	1.31(0.95-1.80), p=0.11	0.98(0.59-1.63), p=0.94	1.19(0.72-1.96), p=0.50
rs2327832_G ( <i>TNFAIP3</i> )	1.30(0.94-1.79), p=0.11	0.79(0.45-1.38), p=0.41	0.89(0.53-1.49), p=0.65
rs1004446_A ( <i>INS</i> )	<b>0.72(0.53-0.98), p=0.037</b>	0.95(0.57-1.57), p=0.84	1.07(0.64-1.77), p=0.81
rs2292239_T ( <i>ERBB3</i> )	1.05(0.76-1.45), p=0.78	1.17(0.68-2.02), p=0.57	0.88(0.54-1.45), p=0.62
rs3184504_C ( <i>SH2B3</i> )	0.91(0.65-1.28), p=0.58	1.14(0.64-2.02), p=0.66	0.97(0.56-1.66), p=0.90
rs2476601_A ( <i>PTPN22</i> )	1.25(0.89-1.75), p=0.20	1.25(0.73-2.15), p=0.42	1.30(0.76-2.23), p=0.34
rs13266634_T ( <i>SLC30A8</i> )	1.02(0.74-1.39), p=0.93	0.78(0.47-1.29), p=0.33	0.66(0.41-1.08), p=0.10
First Appearing Ab (GADA vs. IAA)	0.85(0.61-1.19), p=0.34	1.06(0.62-1.81), p=0.83	1.65(0.97-2.81), p=0.07
Age at First Appearing Autoantibody	<b>0.99(0.98-0.99), p&lt;0.0001</b>	<b>0.98(0.97-0.99), p=0.0003</b>	<b>0.99(0.98-99), p=0.004</b>

\*Univariate models adjusted for first appearing autoantibody (GADA vs. IAA) and age at first appearing Ab. Stratified Cox Regression with country of residence.

\*\* FDR specific includes: DR4/1, DR4/9, DR4/13, DR3/9, DR4/4-DQB1\*20X, DR4/4-DQB1\*304.

‡ 47 children developed two autoantibodies within the same 3-month interval as second appearing autoantibodies and were censored at time of second appearing autoantibody positivity. Data not presented due to difficulty in determining order of appearance.



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