

An Interferon-Induced Helicase (*IFIH1*) Gene Polymorphism Associates With Different Rates of Progression From Autoimmunity to Type 1 Diabetes

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OBJECTIVE—Genome-wide association studies have identified gene regions associated with the development of type 1 diabetes. The aim of this study was to determine whether these associations are with the development of autoimmunity and/or progression to diabetes.

RESEARCH DESIGN AND METHODS—Children ($n = 1,650$) of parents with type 1 diabetes were prospectively followed from birth (median follow-up 10.20 years) for the development of islet autoantibodies, thyroid peroxidase antibodies, tissue transglutaminase antibodies, and diabetes. Genotyping for single-nucleotide polymorphisms of the *PTPN22*, *ERBB3*, *PTPN2*, *KIAA0350*, *CD25*, and *IFIH1* genes was performed using the MassARRAY system with iPLEX chemistry.

RESULTS—Islet autoantibodies developed in 137 children and diabetes developed in 47 children. Type 1 diabetes risk was associated with the *IFIH1* *rs2111485* single-nucleotide polymorphism (hazard ratio 2.08; 95% CI 1.16–3.74; $P = 0.014$). None of the other genes were significantly associated with diabetes development in this cohort. *IFIH1* genotypes did not associate with the development of islet autoantibodies ($P = 0.80$) or autoantibodies against thyroid peroxidase ($P = 0.55$) and tissue transglutaminase ($P = 0.66$). Islet autoantibody-positive children with the *IFIH1* *rs2111485* GG genotype had a faster progression to diabetes (31% within 5 years) than children with the type 1 diabetes protective GA or AA genotypes (11% within 5 years; $P = 0.006$).

CONCLUSIONS—The findings indicate that *IFIH1* genotypes influence progression from autoimmunity to diabetes development, consistent with the notion that protective genotypes down-regulate responses to environmental insults after initiation of autoimmunity. *Diabetes* 60:685–690, 2011

Genome-wide association studies have identified a number of gene regions associated with type 1 diabetes (1). Candidate genes, along with potential mechanisms of action in disease pathogenesis, have been proposed for many of these susceptibility regions (2). In defining mechanisms, it is necessary to consider that type 1 diabetes has a preclinical

period in which there is autoimmunity against pancreatic β -cell antigens (3). This period is variable and is identified by the presence of persistent islet autoantibodies. Some, but not all, islet autoantibody-positive subjects progress to diabetes (4). For most type 1 diabetes gene associations, it is unknown whether there is an association with the development of autoantibodies or progression to clinical disease after initiation of autoimmunity. Analysis of cohorts in which both the development of islet autoimmunity and progression to diabetes is studied would be informative in determining which stage of diabetes pathogenesis is influenced by the genetic associations.

Here, we have examined the association of single-nucleotide polymorphisms (SNPs) within six type 1 diabetes-associated gene regions with initiation of autoimmunity and development of diabetes in a cohort of prospectively followed first-degree relatives of patients with type 1 diabetes. Unlike HLA class II genes, which strongly associate with the development of islet autoimmunity (5–7), we found that polymorphisms within the *IFIH1* gene were associated with progression to diabetes, but not the development of autoimmunity. The findings are consistent with *IFIH1* gene-associated modification of the response to environmental factors that affect the progression from autoimmunity to diabetes.

RESEARCH DESIGN AND METHODS

Cohort. The BABYDIAB study examined the natural history of islet autoimmunity in children of patients with type 1 diabetes (8). Families were eligible if one or both parents had type 1 diabetes. Recruitment began in 1989 and ended in 2000. Venous blood samples were obtained from children at study visits scheduled at age 9 months and 2, 5, 8, 11, 14, 17, and 20 years. Islet autoantibodies were measured in all collected samples. If children had a positive autoantibody result, visit frequencies and islet autoantibody measurements were subsequently performed at 6- to 12-month intervals. The study was coordinated centrally from Munich and conducted from this site by directly contacting the participating families and their family pediatrician. The BABYDIAB cohort contains 1,650 offspring followed from birth to last sample for a median of 8.8 years (range 0.75–20.1). The cumulative dropout rate was 20.9% by age 8 years. Written informed consent was provided by participating families. BABYDIAB was approved by the Bavarian ethical committee (Bayerische Landesärztekammer number 95357).

Follow-up for diabetes. Families were asked to report the occurrence of symptoms of diabetes. In children with islet autoantibodies, a yearly oral glucose tolerance test was performed. Diabetes onset was defined according to American Diabetes Association criteria, which include unequivocal hyperglycemia with acute metabolic decompensation or the observation (on at least two occasions) of a 2-h plasma glucose >200 mg/dL after an oral glucose challenge, or a random blood glucose >200 mg/dL if accompanied by unequivocal symptoms. Since 1997, fasting blood glucose >126 mg/dL on two occasions was added to the diabetes diagnosis criteria.

Autoantibody measurements. Insulin autoantibodies (IAAs), GAD autoantibodies (GADAs), IA-2A autoantibodies (IA-2As), and ZnT8 autoantibodies (ZnT8As) were measured by radiobinding assays as previously described (8,9). The upper limits of normal were determined using QQ plots and corresponded

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to the 99th percentile of control children. Performances in the Diabetes Autoantibody Standardization Program are shown as laboratory 121 in published reports (10,11). Offspring were considered islet autoantibody positive when two consecutive samples collected after birth were positive.

Thyroid peroxidase antibodies (TPOAs) were measured by radiobinding assay according to the manufacturer's instructions (CentAK anti-TPO; Medipan, Dahlewitz/Berlin, Germany) as previously described (12). Samples were TPOA positive if levels were >50 units/mL, as suggested by the manufacturer and confirmed using QQ plot analysis.

IgA antibodies to tissue transglutaminase autoantibodies (tTGAs) were measured by ELISA according to the manufacturer's instructions (Eurospital, Trieste, Italy) and by radiobinding assay with [³⁵S]methionine-labeled in vitro transcribed/translated recombinant human tissue transglutaminase as previously described (13). Positive thresholds were determined using QQ plots and corresponded to the 95th percentile of control children without diabetes or celiac disease for the ELISA and the 99th percentile of control samples for the radiobinding assay. Samples were positive if they were above thresholds in both assays.

Genotyping. HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles were typed using PCR-amplified DNA and nonradioactive sequence-specific oligonucleotide probes as described previously (5). Classification into high-risk HLA genotypes was based on The Environmental Determinants of Diabetes in the Young (TEDDY) study inclusion genotypes for first-degree relatives (14): DR4-DQA1*030X-DQB1*0302^o/DR3-DQA1*0501-DQB1*0201; DR4-DQA1*030X-DQB1*0302^o/DR4-DQA1*030X-DQB1*0302^o; DR4-DQA1*030X-DQB1*0302^o/DR8-DQA1*0401-DQB1*0402; DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201; DR4-DQA1*030X-DQB1*0302^o/DR4-DQA1*030X-DQB1*020X; DR4-DQA1*030X-DQB1*0302^o/DR1-DQA1*0101-DQB1*0501; DR4-DQA1*030X-DQB1*0302^o/DR13-DQA1*0102-DQB1*0604; DR4-DQA1*030X-DQB1*0302/DR4-DQA1*030X-DQB1*0304; DR4-DQA1*030X-DQB1*0302^o/DR9-DQA1*030X-DQB1*0303; DR3-DQA1*0501-DQB1*0201/DR9-DQA1*030X-DQB1*0303, where ^o includes DQB1*0302 and *0304.

Additional genes were selected from associations reported in 2007 (1). Tested were the originally described *PTNP2* rs1893217 and *CD25* rs11594656 SNPs (1) and, to facilitate typing in the multiplex method, the proxy SNPs *PTNP2* rs6679677, *ERBB3* rs705704, *KIAA0350* rs12935413, and *IFIH1* rs2111485. SNP genotyping was performed with the MassARRAY system using iPLEX chemistry (Sequenom, San Diego, CA) as previously described (15). Reproducibility was assessed by duplicate genotyping in 16.3% of samples (discordance rate <0.5%). SNPs were tested for deviation from Hardy-Weinberg equilibrium by χ^2 or Fisher exact test. DNA samples for genotyping were available from 1,350 children.

Statistical analysis. The study design was a priori established to examine overall genotype association with diabetes and subsequently examine

relationships to islet autoantibodies and progression to diabetes only in diabetes-associated genes. The probability of diabetes and autoantibodies was estimated by Kaplan-Meier analysis. Hazards ratios (HRs) were determined using Cox proportional hazards model (with and without adjustment for HLA risk genotype). Within islet autoantibody-positive children, Kaplan-Meier analysis was used to calculate the probability of progression to diabetes where follow-up time was calculated from the age when autoantibodies were first detected to the age of type 1 diabetes diagnosis, or last contact. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 18.0; SPSS, Chicago, IL).

RESULTS

IFIH1 SNP rs2111485 was associated with diabetes development in the BABYDIAB cohort (HR 2.08; 95% CI 1.16–3.74; $P = 0.014$; Table 1). The probability of type 1 diabetes was 5% (95% CI 3.2–6.8) by age 15 years for children with GG genotypes and 2% (95% CI 0.8–3.2) for children with GA or AA genotypes ($P = 0.004$; Fig. 1A). The association remained when adjusted for HLA genotypes (HR 1.98; 95% CI 1.01–3.56; $P = 0.023$; Table 1), and *IFIH1* genotypes were able to stratify diabetes risk in children with high-risk HLA genotypes (Fig. 1B). No significant association with diabetes development could be observed for SNPs in the other five gene regions (Table 1).

To determine whether the association with diabetes observed in the cohort was at the stage of autoimmunity development or the progression to clinical diabetes, we examined *IFIH1* associations with islet autoantibody development. No *IFIH1*-associated difference in the development of autoantibodies was observed ($P = 0.80$; Fig. 2A). Autoantibody appearance curves were similar between susceptible and protective *IFIH1* genotypes for IAAs ($P = 0.44$), GADAs ($P = 0.24$), and ZnT8As ($P = 0.20$) and slightly, but not significantly, higher for susceptible genotypes for the later marker IA-2A ($P = 0.06$). Moreover, no significant difference between *IFIH1* genotypes was found for the probability of developing autoantibodies to thyroid

TABLE 1
Gene associations with development of type 1 diabetes in the BABYDIAB cohort

Gene, SNP	<i>n</i> †	Genotype	Frequency (%)			HR* (<i>P</i>)
			Total cohort	Type 1 diabetes	No diabetes	
<i>ERBB3</i> rs705704	1,350	AA	11.0	14.9	10.8	1.46 (0.65–3.3)
		AG	48.8	51.1	48.7	0.20 (0.16)
		GG	40.2	34.0	40.4	
<i>PTNP2</i> rs1893217	1,347	CC	2.9	2.1	2.9	0.76 (0.10–5.5)
		CT	26.8	27.7	26.8	0.96 (0.96)
		TT	70.3	70.2	70.3	
<i>IFIH1</i> rs2111485	1,337	GG	40.6	59.6	39.9	2.08 (1.16–3.74)
		GA	47.1	29.8	47.7	0.014 (0.023)
		AA	12.3	10.6	12.4	
<i>PTNP2</i> rs6679677	1,345	AA	2.0	2.1	2.0	1.16 (0.16–8.4)
		CA	25.4	34.0	25.1	0.54 (0.64)
		CC	72.6	63.8	72.6	
<i>CD25</i> rs11594656	1,333	TT	54.9	63.0	54.6	1.34 (0.74–2.5)
		TA	38.9	32.6	39.1	0.47 (0.49)
		AA	6.2	4.3	6.3	
<i>KIAA0350</i> rs12935413	1,350	GG	43.9	46.8	43.7	1.07 (0.60–1.9)
		GA	45.7	42.6	45.8	0.96 (0.99)
		AA	10.4	10.6	10.4	

*HRs (95% CI) are shown for the homozygous expected susceptible genotype vs. other genotypes; *P* value is for diabetes development using Cox proportional hazards model across all genotypes; *P* values shown in parentheses are adjusted for HLA DRB1-DQB1 "risk" or "other" genotype on the basis of TEDDY risk genotypes (14). Genotypes are shown with the expected type 1 diabetes susceptible genotype first.
†Number with successful genotype.

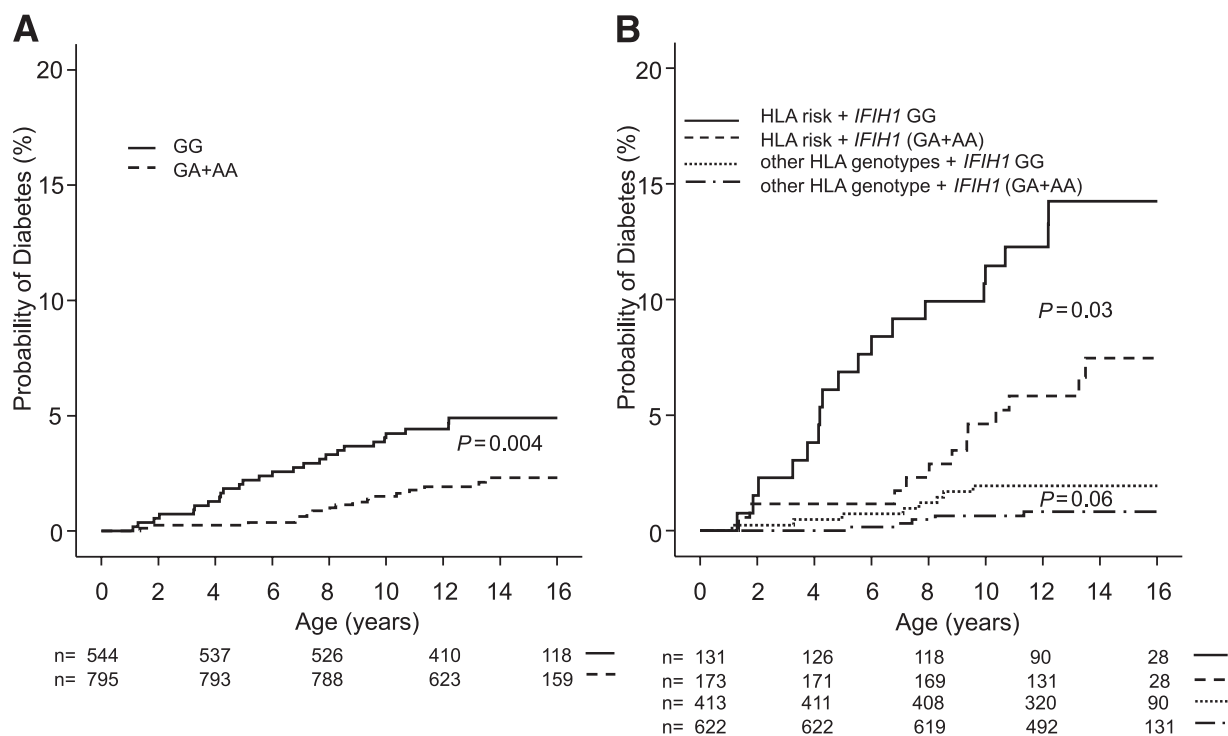


FIG. 1. Cumulative risk for the development of type 1 diabetes by *IFIH1* genotypes. **A:** Children are grouped with respect to *IFIH1* SNP *rs2111485* genotype into those carrying GG genotype (—) and the GA or AA genotype (- - -). **B:** Children are grouped by *IFIH1* genotypes after stratification of HLA genotypes (solid and dashed lines are children with TEDDY HLA risk genotypes, and the dotted and dot-dashed lines represent children with low-risk HLA genotypes). *P* values are provided for comparison of *IFIH1* GG vs. GA and AA genotypes in the total cohort (A) and for high-risk ($P = 0.03$) and low-risk ($P = 0.06$) genotypes. Follow-up (x-axis) is from birth. Numbers below the x-axis indicate the number of diabetes-free children remaining on follow-up.

autoantigens and transglutaminase antigen ($P = 0.55$ and 0.66 ; Fig. 2*F* and *G*).

Among 137 islet autoantibody-positive children, 47 developed diabetes (median, 4.66 years after their first islet autoantibody-positive sample). In contrast to the lack of association with islet autoantibody development, a significant association of the *IFIH1* GG genotype with progression from islet autoantibody positivity to diabetes was observed (31 vs. 11% within 5 years; $P = 0.006$; Fig. 3). This remained significant (HR 1.9; $P = 0.05$) after adjustment for islet autoantibody status of the child as single or multiple and HLA genotype.

DISCUSSION

Understanding the mode of action of genes influencing the development of type 1 diabetes requires knowledge as to whether genes influence the development of islet autoimmunity and/or progression from autoimmunity to diabetes. Here we have examined association in a cohort of genetically at-risk children who were followed from birth for both development of islet autoantibodies and diabetes. An association of the *IFIH1* gene with diabetes development in this cohort allowed us to determine at what stage the gene is likely to influence diabetes development. Unlike HLA class II genes, which strongly influence the risk for developing islet autoantibodies (5–7), association of the *IFIH1* gene was restricted to the progression to diabetes after development of islet autoimmunity. In view of the involvement of the *IFIH1* gene in responses to virus infection (16,17), the findings are consistent with a role of infection in determining the progression to diabetes after islet autoimmunity has been initiated.

The findings are from a unique cohort characterized by a family history of type 1 diabetes, perspective follow-up from birth with relatively frequent testing for islet autoantibody development, monitoring for diabetes development, and testing and monitoring for the development of thyroid- and celiac disease-associated autoimmunity up to age 20 years. To minimize the number of comparisons, we chose association with diabetes as the outcome and selected genes that showed association both alone and together with HLA genotypes in a multiple Cox proportional hazards model. The disadvantage of this approach is that modest numbers developed diabetes, allowing us to identify only moderate to strong genetic associations. Thus, the findings from our study are not informative for SNPs in the five gene regions, where we found no association with type 1 diabetes. A potential caveat is that not all islet autoantibodies may be specific for type 1 diabetes (18). The findings were, however, significant for the *IFIH1* SNP after adjustment for multiple islet autoantibodies, which is a specific characteristic of type 1 diabetes. Finally, because our study is in subjects with a type 1 diabetes family history, we cannot make conclusions for case subjects without a family history. Analyses in the Finnish Diabetes Prediction and Prevention (DIPP) study (6) and the multicenter TEDDY study (14) are informative in this respect.

The *IFIH1* gene encodes helicase C domain 1, which mediates induction of the interferon response to viral RNA (16,17). The association of *IFIH1* polymorphisms including rare variants with type 1 diabetes (19,20) has been noteworthy because of their link to the inflammatory response caused by infectious agents, including enteroviruses. Viral infection is hypothesized to cause islet

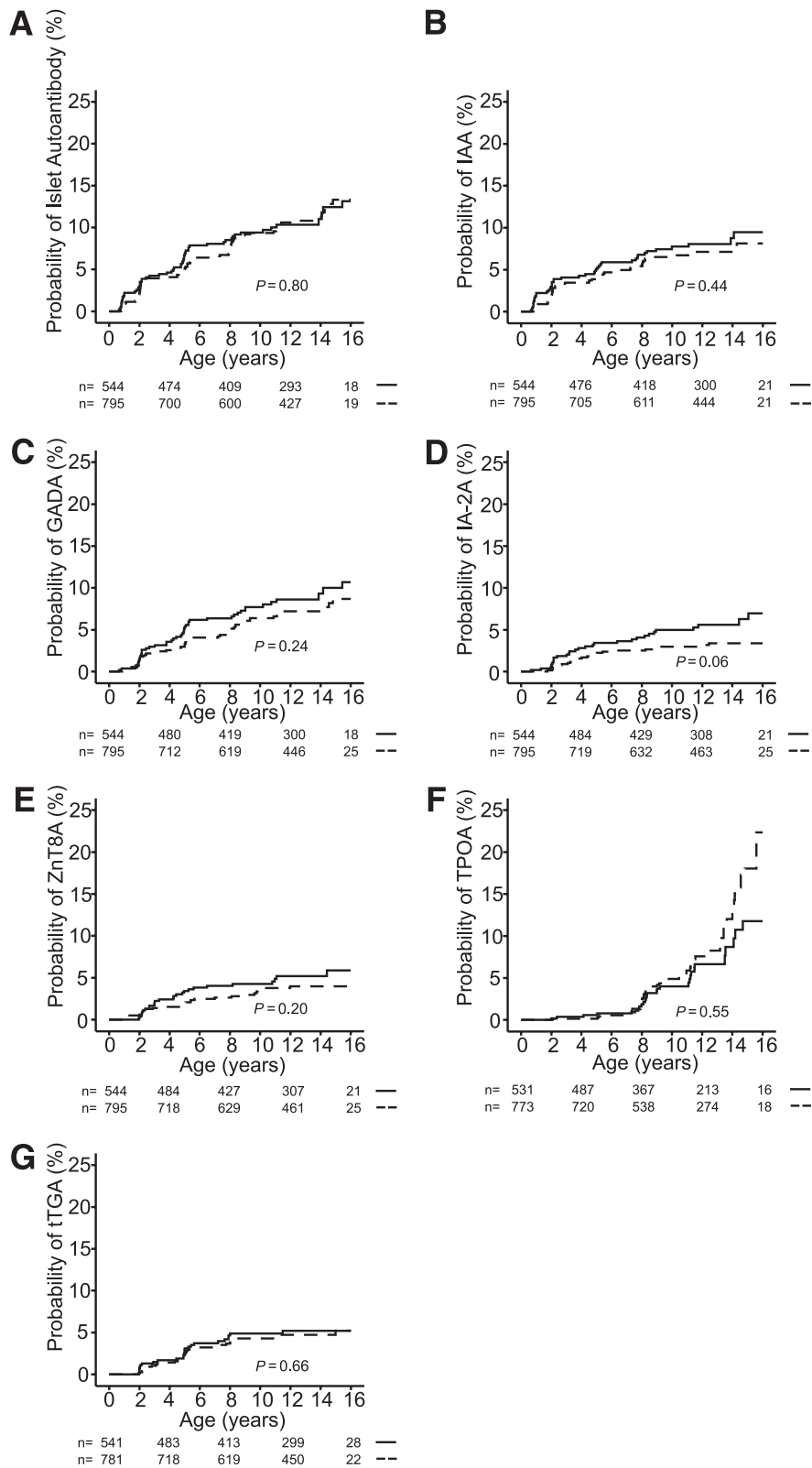


FIG. 2. Cumulative risk for the development of autoantibodies. Cumulative risk is shown for at least one islet autoantibody (A), IAAs (B), GADAs (C), IA-2As (D), ZnT8As (E), TPOAs (F), and tTGAs (G) by *IFIH1* genotypes. Children are grouped with respect to *IFIH1* SNP *rs2111485* genotype into those carrying the GG genotype (—) and the GA or AA genotype (- - -). Follow-up (x-axis) is from birth. Numbers below the x-axis indicate the number of autoantibody-negative children remaining on follow-up with respect to age.

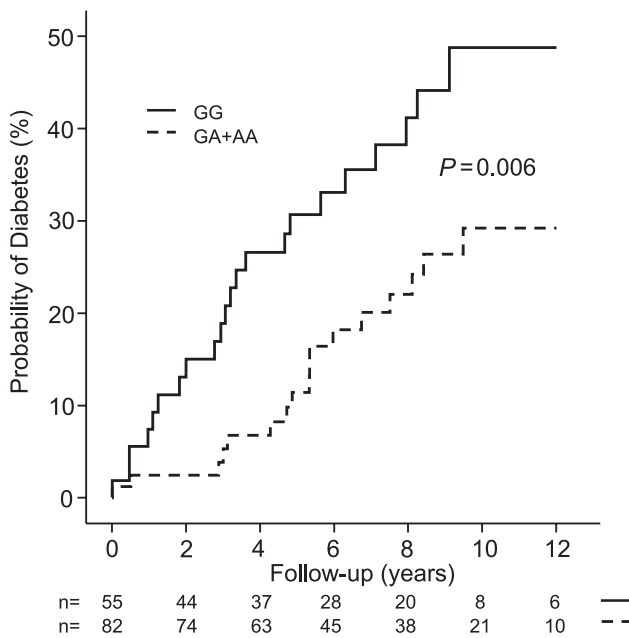


FIG. 3. Cumulative risk for the progression from islet autoimmunity to type 1 diabetes by *IFIH1* genotypes. Islet autoantibody-positive children are grouped with respect to *IFIH1* SNP *rs2111485* genotype into those carrying the GG genotype (—) and the GA or AA genotype (- - -). Follow-up (x-axis) is from the age of the first islet autoantibody-positive sample. Numbers below the x-axis indicate the number of diabetes-free children remaining on follow-up.

autoimmunity and/or influence progression to diabetes (21–23). Data in humans are inconclusive, whereas data from the murine models lean toward effects at the progression stage (24). Our study provides unique insight into this debate. First, a common polymorphism of the *IFIH1* gene had an odds ratio for diabetes development of around 2 in our cohort, potentially implying relatively strong effects in children with a type 1 diabetes family history. Second, we found no association with the initiation of autoimmunity, as defined by the development of islet autoantibodies, and the development of thyroid- or celiac disease-associated autoantibodies. Examining individual islet autoantibodies found no association with the development of IAAs or GADAs, which appear early in the disease process, and borderline association with IA-2As, which in our cohort appear later than IAAs or GADAs. Of interest, the development of all these autoantibodies is strongly influenced by the HLA class II genotype (5–7,10,11), whereas progression to diabetes after the appearance of islet autoantibodies is only minimally associated with HLA class II (6,25). In contrast, we observed a strong effect of the *IFIH1* genotype on the rate of progression to disease from first islet autoantibody detection.

With respect to pathogenesis, our findings would be consistent, with infection playing a more prominent role in diabetes development after the onset of islet autoimmunity than during initiation of autoimmunity. The findings also have potential implications for type 1 diabetes prevention. They suggest that intervention in autoantibody-positive children to delay or prevent the onset of type 1 diabetes is possible and furthermore suggest that interference with host response to infection may be a means to achieve successful intervention.

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No potential conflicts of interests relevant to this article were reported.

C.W. acquired and reviewed data, undertook statistical analysis and interpretation of the results, and drafted the manuscript. C.L. and K.A. prepared and kept the biobank samples used for genotyping (including the preparation of protocols for DNA preparation and storage), assisted in obtaining data, performed analysis, and critically reviewed the manuscript. H.G. performed the genotyping. T.I. established the genotyping and critically reviewed the manuscript for intellectual content. A.-G.Z. was the principal investigator, designed the BABYDIAB study and concept, was involved in the interpretation of the results and the writing of the manuscript, and critically reviewed the manuscript for intellectual content. E.B. designed the study analysis and the concept, performed the statistical analysis with C.W., was involved in the interpretation of the results, wrote the manuscript, and critically reviewed the manuscript for intellectual content.

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