Early-Onset, Coexisting Autoimmunity and Decreased HLA-Mediated Susceptibility Are the Characteristics of Diabetes in Down Syndrome

Rachel J. Aitken, bsc[1]
Kay L. Mehers, phd[1]
Alistair J. Williams, bsc[1]
Jamie Brown, bsc[1]
Polly J. Bingley, md[1]
Reinhard W. Holl, phd[2]
Tilman R. Rohrer, phd[3]
Edith Schober, md[4]
Majedah M. Abdul-Rasoul, md[5]
Julian P.H. Shield, md[1]
Kathleen M. Gillespie, phd[1]

OBJECTIVE—Down syndrome (DS) is associated with an increased risk of diabetes, particularly in young children. HLA-mediated risk is however decreased in children with DS and diabetes (DSD). We hypothesized that early-onset diabetes in children with DS is etiologically different from autoimmune diabetes.

RESEARCH DESIGN AND METHODS—Clinical and immunogenetic markers of autoimmune diabetes were studied in 136 individuals with DSD and compared with 194 age- and sex-matched individuals with type 1 diabetes, 222 with DS, and 671 healthy controls. HLA class II was analyzed by sequence-specific primed PCR. Islet autoantibodies were measured by radioimmunoassay.

RESULTS—Age at onset of diabetes was biphasic, with 22% of DS children diagnosed before 2 years of age, compared with only 4% in this age-group with type 1 diabetes in the general population ($P < 0.0001$). The frequency of the highest-risk type 1 diabetes–associated HLA genotype, DR3-DQ2/DR4-DQ8, was decreased in both early- and later-onset DSD compared with age-matched children with type 1 diabetes ($P < 0.0001$), although HLA DR3-DQ2 genotypes were increased ($P = 0.004$). Antibodies to GAD were observed in all five samples tested from children diagnosed at ≤2 years of age, and persistent islet autoantibodies were detected in 72% of DSD cases. Thyroid and celiac disease were diagnosed in 74 and 14%, respectively, of the DSD cohort.

CONCLUSIONS—Early-onset diabetes in children with DS is unlikely to be etiologically different from autoimmune diabetes occurring in older DS children. Overall, these studies demonstrate more extreme autoimmunity in DSD typified by early-onset diabetes with multiple autoimmunity, persistent islet autoantibodies, and decreased HLA-mediated susceptibility.

Diabetes Care 36:1181–1185, 2013

Children with Down syndrome (DS) are at increased risk of thyroid (1), gut (2), and islet autoimmunity (3,4). In the only population-based study that has addressed the prevalence of DS in type 1 diabetes patients, a more than fourfold increased prevalence was observed (5). It has been suggested that diabetes in children with DS presents particularly early in life; one study from the 1960s showed a peak onset of 8 years of age, compared with 14 years in cases of childhood diabetes (6). In a previous study of DS and diabetes, 22% of participants had developed diabetes by 2 years of age, compared with only 7% of those with type 1 diabetes from the general population (7). A recent study of 159 DS children diagnosed with type 1 diabetes (DSD) demonstrated two peaks in diabetes incidence, one occurring before 2 years of age and the other in early adolescence. The mean age at onset in the 41,983 control subjects with type 1 diabetes was 8.42 years (8). These data suggest that diabetes occurring before 2 years of age in DS children may be etiologically different from type 1 diabetes. In the seminal study of type 1 diabetes pathology by Foulis et al. (9), three cases of DS and diabetes were described. A 14-year-old boy with longstanding diabetes and a 12-year-old boy with recent-onset diabetes both showed evidence of lymphocytic infiltration, with an absence of insulin staining in the 14-year-old boy, typical of type 1 diabetes. The third DS child, however, diagnosed with diabetes at 18 months, whose pancreas was analyzed within 2 weeks of diabetes diagnosis, displayed normal insulin staining with no morphological abnormality.

An age-related association between the HLA class II susceptibility haplotypes DRB1*04-DQB1*0302 (DR4-DQ8) and DRB1*03-DQB1*0201 (DR3-DQ2) and type 1 diabetes in the general population is well established, with an increased frequency in young children with type 1 diabetes (10,11). These haplotypes also appear to contribute to susceptibility to diabetes in DS, but to a lesser degree (12).

The aim of this study, therefore, was to test the hypothesis that diabetes diagnosed before 2 years of age does not have an autoimmune basis in a well-characterized cohort of individuals with DSD. Distinguishing whether insulin deficiency in these young children is caused by accelerated autoimmunity or an alternative mechanism, such as a β-cell secretary deficit, could have consequences for treatment or provide insights into a more aggressive autoimmune process in children with DS.

From the [1]School of Clinical Science at North Bristol, University of Bristol, Bristol, U.K.; the [2]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany; the [3]Department of Paediatrics and Neonatology, Saarland University Medical Centre, Homburg, Germany; the [4]Department of Paediatrics, Medical University of Vienna, Vienna, Austria; and the [5]Pediatric Endocrine Unit, Mubarak Alkabeer Hospital, Kuwait City, State of Kuwait.
Corresponding author: Kathleen M. Gillespie, k.m.gillespie@bristol.ac.uk.
Received 23 August 2012 and accepted 21 October 2012.
DOI: 10.2337/dc12-1712

RESEARCH DESIGN AND METHODS

Study populations

DS and diabetes. An international collection of clinical details and genetic and serum samples from children with DSD (Diaploidy) was established in 2010. In the U.K., a call for potential participants for a study of diabetes in children with DS was sent out by the Diabetes Research Network and Diabetes UK. Internationally, a call was sent out through the International Society for Pediatric and Adolescent Diabetes. All cases referred were accepted. By June 2012, 136 individuals with DS and a clinical diagnosis of type 1 diabetes had been registered (80 from the U.K., 30 from Austria and Germany, 7 from other European countries and Australia, and 19 from the State of Kuwait). Clinical data on age at diagnosis of diabetes, thyroid and celiac disease, family history of autoimmunity, treatment history, and current height and weight were collected by questionnaire. Three control groups were studied as follows.

1) DS controls. Blood samples were taken from 30 nondiabetic school-aged children with DS (15 male and 15 female, age range 4–21 years) during routine thyroid screening in the area covered by the Gloucestershire Health Authority, U.K. Aliquots of DNA samples from 83 children with DS had been collected as controls for a study of congenital heart disease in DS (13). DNA samples (n = 109) were also available for analysis from a population-based study of children with DS in Manchester, U.K. (14). There was no clinical evidence of diabetes in any of these children.

2) Type 1 diabetes controls. For the HLA analysis, two age-at-onset– and sex-matched children with type 1 diabetes for each child with DS and diabetes were randomly selected from the population-based Bart's Oxford (BOX) study of type 1 diabetes that has been ongoing since 1985 with 95% ascertainment (15). Age-at-onset data from 1,822 probands diagnosed before 21 years of age from this cohort were used to compare with age-at-onset data of the DSD cohort.

3) Healthy control subjects. HLA genotypes from 621 adult white U.K. control subjects with no history of autoimmune disease were provided by Steven Gough (Institute of Biomedical Research, University of Birmingham, Birmingham, U.K.) and have been described previously (16).

Ethical permission

Ethical permission had been granted for all studies described, and written informed consent was obtained from the participant, parent, or guardian, as appropriate, for all samples collected (MREC/02/6/26).

Genetic analysis

DNA samples were genotyped for all HLA class II HLA DRB1 and DQB1 haplotypes by PCR using a DYNAL reli SSO system (Life Technologies, Paisley, U.K.). DRB1*04 alleles were subtyped using a PCR with sequence-specific primers. Haplotypes were derived from established patterns of linkage disequilibrium. The established type 1 diabetes–associated haplotype HLA DRB1*0401-DQB1*0302 was abbreviated to DR4-DQ8, and HLA DRB1*03-DQB1*0201 was abbreviated to DR3-DQ2. Nonrisk haplotypes were described as X.

The analyses of HLA data were restricted to individuals with DSD diagnosed before 21 years of age to avoid the issue that some older individuals with DSD may have type 2 diabetes and to allow age matching with individuals participating in the BOX study of type 1 diabetes (11).

Islet autoantibody analysis

Antibodies to GAD65 (GADA), IA-2ic (IA-2A), and ZnT8RA/WA were measured by radioimmunoassay as previously described (15,17). The laboratory-defined assay sensitivities and specificities of GADA were 86 and 99%, and of IA-2A 72 and 93%, respectively, in the Third Diabetes Antibody Standardization Program (18). The interassay coefficient of variation was 9% at 14 WHO units/mL (GADA), 14% at 10 WHO units/mL (IA-2A), and 16% for ZnT8RA and 27% for ZnT8WA, both at 1.8 units/mL. Serum samples were available from 43 individuals with DSD. Due to the nature of the Diaploidy cross-sectional study design, serum samples collected at diagnosis were not available for analysis. Time from diagnosis ranged from 1 to 396 months (median 89 months); samples collected within 10 years of diagnosis were available from 23 individuals, and a further 20 samples were collected between 10 and 39 years from diagnosis. Positivity for islet autoantibodies would be supportive of an autoimmune etiology, whereas a negative postdiagnosis result could not be interpreted.

Data analysis

Differences in age at onset and frequencies of HLA class II genotypes in children with DS and diabetes compared with age-matched children with type 1 diabetes were analyzed using the χ^2 test.

RESULTS

DS and diabetes: subject characteristics

Of 136 individuals with DSD, 69 (51%) were male. Data on clinical diagnosis of other autoimmune diseases were available on 92 subjects. Of these, 68 (74%) had coexisting thyroid disease and 11 (14%) had coexisting celiac disease. Seven of 92 (8%) had coexisting diagnoses of diabetes and thyroid and celiac disease.

Age-at-onset analysis in the DS and diabetes population

Of 118 patients with DSD diagnosed with diabetes before 21 years of age, 22% were diagnosed with diabetes before 2 years of age compared with 5% of 1,822 individuals with type 1 diabetes from the general population notified to the BOX study in the same age-group ($P < 0.0001$). As shown in Fig. 1, there was a biphasic pattern in age at diagnosis, with a peak at 1 year of age and another centered around 10 years of age.

HLA class II analysis

In the healthy control cohort, only 3% had the highest-risk diplotype (DR4-DQ8/DR3-DQ2), 13% had DR4-DQ8/X, 27% had DR3-DQ2/X, and 57% had no risk haplotypes. HLA class II frequencies in the DS control population were very similar to the healthy control population (Fig. 2*A*). As expected, the risk haplotypes were increased in 194 individuals with type 1 diabetes age- and sex-matched with the DSD population: 38% had DR4-DQ8/DR3-DQ2, 40% had DR4-DQ8/X, 17% had DR3-DQ2/X, and 5% had no risk haplotypes. Genetic samples were available from 97 individuals with DSD diagnosed before 21 years of age. HLA frequencies in the DSD cohort were intermediate between the type 1 diabetes and control cohorts. Specifically, 17 (17%) had the highest-risk diplotype (DR4-DQ8/DR3-DQ2); 23 (24%) and 31 (32%) had the moderate-risk DR4-DQ8 and DR3/DQ2 haplotypes, respectively, and 26 (27%) had no risk haplotypes. In contrast, 5% of 194 age- and sex-matched children with type 1 diabetes from the BOX study ($P < 0.0001$) and 64% of 222 DS individuals had no risk haplotypes (Fig. 2*A*). The frequency of the HLA DR3-DQ2/X diplotype (where X is

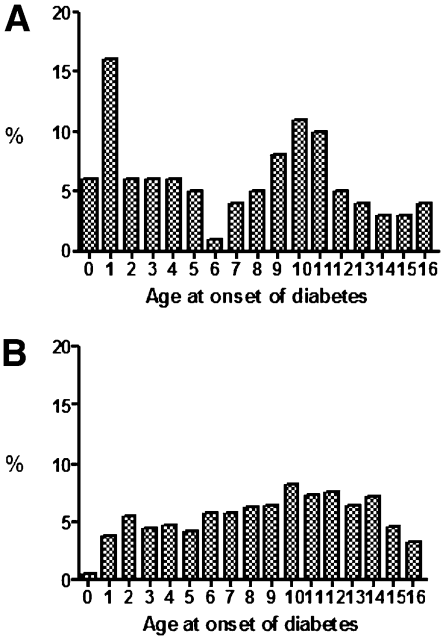

Figure 1—*Age at diagnosis of diabetes in individuals with DS diagnosed with diabetes* (A) *compared with individuals with type 1 diabetes from the BOX study* (B).

not DR4-DQ8 or DR3-DQ2) in DSD (32%), however, was increased relative to age-matched patients from the BOX study (17%, $P = 0.004$).

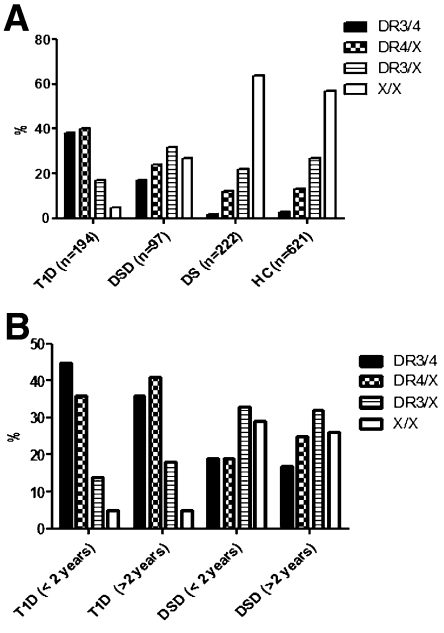

Figure 2—A: *The frequency (%) of type 1 diabetes–associated haplotypes in DSD children relative to age-matched children with type 1 diabetes (T1D), DS alone, and healthy control subjects (HC).* B: *The HLA characteristics of diabetes in children with DS by age at onset compared with type 1 diabetes.*

There was no difference in HLA-mediated risk in DS children who had developed diabetes before and after 2 years of age (Fig. 2*B*), indicating that diabetes in the early-onset cases is unlikely to be etiologically distinct from the diabetes found in older DS children.

Islet autoantibodies

Despite the extended diabetes duration at the time many samples were collected, islet autoantibodies were detected in 72% of the DSD patients for whom serum was available (Table 1). Furthermore, all five samples from DSD children diagnosed before 2 years of age were positive for GADA.

CONCLUSIONS—In this study, we hypothesized that some early-onset cases of diabetes in DS children are not autoimmune. A biphasic distribution in age at onset of diabetes in children with DS previously observed in a European study of 159 children with DS and diabetes compared with 42,000 age-matched individuals with type 1 diabetes (8) was confirmed in our study. We also demonstrated, in the largest analysis to date, that type 1 diabetes–associated HLA genotypes are decreased in children with DSD. To account for this difference in HLA frequencies, we hypothesized that diabetes in some children diagnosed before 2 years of age may be etiologically different from autoimmune type 1 diabetes. Analysis of HLA data by age at onset, however, did not support this hypothesis. This shows that DS children with early-onset diabetes are unlikely to have an etiologically distinct form of diabetes. Two children diagnosed within the first month of life may have an alternative etiological basis for their diabetes; the remaining children were diagnosed at, or after, 6 months of age, consistent with type 1 diabetes (19). Autoimmunity was supported by data obtained from a postdiagnosis analysis of islet autoantibodies; antibodies to GAD were detected in all five serum samples tested from children diagnosed with diabetes before 2 years of age. Although we cannot rule out the possibility that some individuals with DS and early-onset diabetes have an etiologically distinct form of diabetes, we suggest that this is rare and may present in the first 6 months of life.

Our previous study of diabetes in 40 DS children (12) suggested that the frequency of autoimmune diabetes–associated HLA class II genotypes was increased in DSD but to a lesser extent than might be expected. We confirmed, within a substantially enlarged sample, that the frequency of autoimmune-related HLA genotypes was decreased with a concomitant increase in nonautoimmune-related genotypes in children with DSD compared with age-matched children with type 1 diabetes. In young European populations with type 1 diabetes, 5–10% of individuals do not carry DR4-DQ8 and/or DR3-DQ2 (10,11), but this proportion was increased to 27% in our similarly aged cohort of patients with DSD. This difference was not explained by the inclusion of 19 children with DS and diabetes from the State of Kuwait, a population where HLA-mediated susceptibility to diabetes may be different, as the pattern was the same when these individuals were removed from the analysis. This increased penetrance of low-risk HLA class II haplotypes in DSD children mirrors the trend observed in the general population as type 1 diabetes incidence is increasing (20–23). Understanding how autoimmunity occurs in the absence of HLA risk genotypes in children with DS could therefore provide important insights into disease mechanisms in the general population.

There are limitations to this work. Although it is the largest existing cohort of DSD individuals from whom serum and DNA are available, the Diaploidy study is relatively small. This is, however, a difficult group to recruit as co-occurrence of both conditions is rare. The cohort is not population based, and definitive studies of incidence are therefore not possible. The analysis of islet autoantibodies years after diagnosis is not ideal, as antibody levels tend to fall post-diagnosis, although antibodies to GAD are known to be the most persistent (24). Indeed, in this study, at least one islet autoantibody was detectable in 75% of post-diagnosis samples, with multiple islet autoantibody positivity detectable in serum from eight individuals >10 years after diagnosis.

There is a wide variation in reported prevalence rates of thyroid disorders in the DS population. The prevalence of autoimmune thyroid disease has been reported to be at least fourfold higher in children with DS than in the general population (25–27), but a recent longitudinal study suggests that that this may be an overestimation (28). Celiac disease may be 10 times more common in DS populations (2,29). Our study suggests that individuals with DS are at risk for extreme autoimmunity;

Table 1—*Residual islet autoantibody positivity in 43 individuals with DSD from whom serum was available*

Time from diagnosis	Three islet antibodies	Two islet antibodies	GADA alone	IA-2A alone	ZNT8R/W alone	Negative
<10 years (%)	2 (11)	4 (21)	7 (37)	0	0	6 (31)
>10 years (%)	2 (8)	6 (25)	9 (38)	1 (4)	0	6 (25)

co-occurrence of clinically diagnosed thyroid disease and diabetes was observed in 74% and clinically diagnosed celiac disease and diabetes was observed in 14% of individuals with DSD. This was based on data collected by questionnaire. The precise etiology of thyroid disease is therefore unclear, and data on antithyroid antibodies at diagnosis are unavailable.

Overall, a clinical picture of DSD is emerging with earlier-onset diabetes, coexistence of other organ-specific autoimmune diseases with persistent islet autoantibodies, and decreased HLA-mediated susceptibility. Why might this be? Overexpression of type 1 diabetes–associated genes on chromosome 21 combined with generalized immunological dysfunction in DS appears probable. A genome-wide association study identified (30) and replicated (31) a chromosome 21q22.3 type 1 diabetes–associated locus. The candidate gene is the ubiquitin-associated and SH3 domain–containing A (*UBASH3A*), which is expressed in spleen and peripheral blood lymphocytes (32) and regulates T-cell signaling (33,34). Overexpression of *UBASH3A* may therefore provide one candidate for the increased frequency of autoimmune disease in DS. Immune cell dysfunction in DS is well established. A smaller thymus in DS children has been reported several times, (35,36) and total lymphocyte numbers, including CD4 and CD8 T-cell subsets are decreased, particularly in the first 2 years of life. Recent analysis of protein and gene expression in surgically removed thymuses from 14 DS patients compared with 42 age-matched control subjects showed reduced expression of AIRE, a chromosome 21 gene product that regulates ectopic expression of tissue-specific antigens in thymic medullary epithelial cells, a crucial mechanism for thymic T-cell selection (37). This mechanism could contribute to the increased risk of multiple autoimmunity and the earlier onset of diabetes that we have observed.

In conclusion, diabetes in DS children is associated with a lower frequency of high-risk HLA class II susceptibility genes than children matched for age at onset of diabetes with type 1 diabetes from the general population, but this is not caused by a subset of children with an etiologically different early-onset form of diabetes. HLA DR3-DQ2/X combinations are increased in DSD children, but this does not fully explain their increased frequency of endocrine autoimmunity. Our data show high rates of coexisting organ-specific autoimmunity with a high prevalence of residual islet autoimmunity and lower frequencies of class II HLA diabetes susceptibility haplotypes in DSD. Understanding how this occurs may provide insights into the mechanisms underlying type 1 diabetes in the general population.

Acknowledgments—This work was funded by grants from the European Foundation for the Study of Diabetes/Novo Nordisk/Juvenile Diabetes Research Foundation (to K.M.G.), the Halley Stewart Charitable Trust (to K.M.G.), and the German Ministry of Education and Research (BMBF) Competence Network Diabetes Mellitus (FKZ 01GI0859 to R.W.H.).

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

R.J.A., K.L.M., J.B., and J.P.H.S. researched data and wrote the manuscript. A.J.W. and P.J.B. coordinated sample collection and analysis and contributed to discussion. R.W.H., T.R.R., E.S., and M.M.A.-R. coordinated sample collection and analysis. K.M.G. researched data, conducted analyses, and wrote the manuscript. All authors reviewed, edited, and discussed the draft manuscript. K.M.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors are extremely grateful to all DSD individuals who participated in this study. The authors acknowledge the help of the Down's Syndrome Association (U.K.) and the Diabetes Research Network for help in identifying DSD individuals from the general U.K. population. The authors are also grateful to the clinicians who contributed samples and data to this study. The authors acknowledge the excellent technical assistance of Kyla Chandler (University of Bristol) and Saba Rokni (University of Bristol) and the administrative support of Dr. Claire Matthews (University of Bristol).

References

1. Vanhaelst L, Hayez F, Bonnyns M, Basteinie PA. Thyroid auto-immune disease and thyroid function in families of subjects with Down's syndrome. J Clin Endocrinol Metab 1970;30:792–797
2. Gale L, Wimalaratna H, Brotodiharjo A, Duggan JM. Down's syndrome is strongly associated with coeliac disease. Gut 1997;40:492–496
3. Anwar AJ, Walker JD, Frier BM. Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. Diabet Med 1998;15:160–163
4. Van Goor JC, Massa GG, Hirasing R. Increased incidence and prevalence of diabetes mellitus in Down's syndrome. Arch Dis Child 1997;77:186
5. Bergholdt R, Eising S, Nerup J, Pociot F. Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: a nationwide population-based study. Diabetologia 2006;49:1179–1182
6. Burch PR, Milunsky A. Early-onset diabetes mellitus in the general and Down's syndrome populations. Genetics, aetiology, and pathogenesis. Lancet 1969;1:554–558
7. Shield JP, Wadsworth EJ, Hassold TJ, Judis LA, Jacobs PA. Is disomic homozygosity at the APECED locus the cause of increased autoimmunity in Down's syndrome? Arch Dis Child 1999;81:147–150
8. Rohrer TR, Hennes P, Thon A, et al. Down's syndrome in diabetic patients aged <20 years: an analysis of metabolic status, glycaemic control and autoimmunity in comparison with type 1 diabetes. Diabetologia 2010;53:1070–1075
9. Foulis AK, Liddle CN, Farquharson MA, Richmond JA, Weir RS. The histopathology of the pancreas in type 1 (insulin-dependent) diabetes mellitus: a 25-year review of deaths in patients under 20 years of age in the United Kingdom. Diabetologia 1986;29:267–274.
10. Caillat-Zucman S, Garchon HJ, Timsit J, et al. Age-dependent HLA genetic heterogeneity of type 1 insulin-dependent diabetes mellitus. J Clin Invest 1992;90:2242–2250
11. Gillespie KM, Gale EA, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood diabetes. Diabetes 2002;51:210–214
12. Gillespie KM, Dix RJ, Williams AJ, et al. Islet autoimmunity in children with Down's syndrome. Diabetes 2006;55:3185–3158
13. Baptista MJ, Fairbrother UL, Howard CM, Farrer MJ, Davies GE, Trikka D, et al. Heterotrisomy, a significant contributing factor to ventricular septal defect associated

with Down syndrome? Human Genet 2000;107:476–482
14. Gibson PA, Newton RW, Selby K, Price DA, Leyland K, Addison GM. Longitudinal study of thyroid function in Down's syndrome in the first two decades. Arch Dis Child 2005;90:574–578
15. Bingley PJ, Bonifacio E, Williams AJ, Genovese S, Bottazzo GF, Gale EA. Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. Diabetes 1997; 46:1701–1710
16. Simmonds MJ, Howson JM, Heward JM, et al. Regression mapping of association between the human leukocyte antigen region and Graves disease. Am J Hum Genet 2005;76:157–163
17. Long AE, Gooneratne AT, Rokni S, Williams AJ, Bingley PJ. The role of autoantibodies to zinc transporter 8 in prediction of type 1 diabetes in relatives: lessons from the European Nicotinamide Diabetes Intervention Trial (ENDIT) cohort. J Clin Endocrinol Metab 2012;97:632–637
18. Torn C, Mueller PW, Schlosser M, Bonifacio E, Bingley PJ; Participating Laboratories. Diabetes Antibody Standardization Program: evaluation of assays for autoantibodies to glutamic acid decarboxylase and islet antigen-2. Diabetologia 2008;51: 846–852
19. Edghill EL, Dix RJ, Flanagan SE, et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes 2006;55:1895–1898
20. Hermann R, Knip M, Veijola R, et al. Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes–indication of an increased environmental pressure? Diabetologia 2003;46:420–425
21. Fourlanos S, Varney MD, Tait BD, et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. Diabetes Care 2008;31:1546–1549
22. Steck AK, Armstrong TK, Babu SR, Eisenbarth GS. Stepwise or linear decrease in penetrance of type 1 diabetes with lower-risk HLA genotypes over the past 40 years. Diabetes 2011;60:1045–1049
23. Gillespie KM, Bain SC, Barnett AH, et al. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. Lancet 2004; 364:1699–1700
24. Decochez K, Tits J, Coolens JL, et al. High frequency of persisting or increasing islet-specific autoantibody levels after diagnosis of type 1 diabetes presenting before 40 years of age. The Belgian Diabetes Registry. Diabetes Care 2000;23:838–844
25. Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Anneren G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. Arch Dis Child 1998;79:242–245
26. Ivarsson SA, Ericsson UB, Gustafsson J, Forslund M, Vegfors P, Anneren G. The impact of thyroid autoimmunity in children and adolescents with Down syndrome. Acta Paediatr 1997;86:1065–1067
27. Prasher VP. Down syndrome and thyroid disorders: a review. Downs Syndr Res Pract 1999;6:25–42
28. Prasher V, Ninan S, Haque S. Fifteen-year follow-up of thyroid status in adults with Down syndrome. J Intellect Disabil Res 2011;55:392–396
29. Book L, Hart A, Black J, Feolo M, Zone JJ, Neuhausen SL. Prevalence and clinical characteristics of celiac disease in Downs syndrome in a US study. Am J Med Genet 2001;98:70–74
30. Todd JA, Walker NM, Cooper JD, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 2007;39:857–864
31. Grant SF, Qu HQ, Bradfield JP, et al. Follow-up analysis of genome-wide association data identifies novel loci for type 1 diabetes. Diabetes 2009;58:290–295
32. Wattenhofer M, Shibuya K, Kudoh J, et al. Isolation and characterization of the UBASH3A gene on 21q22.3 encoding a potential nuclear protein with a novel combination of domains. Hum Genet 2001;108:140–147
33. San Luis B, Sondgeroth B, Nassar N, Carpino N. Sts-2 is a phosphatase that negatively regulates zeta-associated protein (ZAP)-70 and T cell receptor signaling pathways. J Biol Chem 2011;286:15943–15954
34. Chen X, Ren L, Kim S, et al. Determination of the substrate specificity of protein-tyrosine phosphatase TULA-2 and identification of Syk as a TULA-2 substrate. J Biol Chem 2010;285:31268–31276
35. Levin S, Schlesinger M, Handzel Z, et al. Thymic deficiency in Down's syndrome. Pediatrics 1979;63:80–87
36. Larocca LM, Lauriola L, Ranelletti FO, et al. Morphological and immunohistochemical study of Down syndrome thymus. Am J Med Genet Suppl 1990;7:225–230
37. Lima FA, Moreira-Filho CA, Ramos PL, et al. Decreased AIRE expression and global thymic hypofunction in Down syndrome. J Immunol 2011;187:3422–3430