group is the fourth with a total of 46 members. Of the sequences nine were not readily assigned to any other group. The differentiation between the groups was quite clear-cut and robust to alterations in the application of the methodology. Within each group there were maternal lines, which differed only in one or two nucleotide(s) suggesting a high degree of relation.

Our findings suggest that maternal lines of Type 1 diabetic patients are related. An observation which is supported by the analysis of 109 unrelated German Caucasoid individuals where 100 different mtDNA lineages were detected [5].

Acknowledgements. This study was supported by a grant of the Deutsche Diabetesgesellschaft.

I. Klöting, M. Poetsch, B. Müller-Myhsok, I. Rjasanowski, W. Kerner, N. Klöting
Department of Laboratory Animal Science, Medical Faculty, University of Greifswald, Karlsburg

References

1. Field LL (2002) Genetic linkage and association studies of Type 1 diabetes: challenges and rewards. Diabetologia45:21–35
2. Kaprio J (2000) Science, medicine, and the future. Genetic epidemiology. BMJ 320:1257–1259
3. Parson TJ, Muniec DS, Sullvian K et al. (1997) A high observed substitution rate in the human mitochondrial DNA control region. Nat Genet 15:363–367
4. Pfeiffer H, Forster P, Ortmann C, Brinkmann B (2001) The results of a mtDNA study of 1,200 inhabitants of a German village in comparison to other Caucasian databases and its relevance for forensic casework. Int J Legal Med 114:169–172
5. Pfeiffer H, Brinkmann B, Hühne J et al. (1999) Expanding the forensic German mitochondrial DNA control region database: genetic diversity as a function of sample size and microgeography. Int J Legal Med 112:291–298

Corresponding author: I. Klöting, Department of Laboratory Animal Science, Medical Faculty, University of Greifswald, Greifswalder Str. 11, 17495 Karlsburg
E-mail: kloeting@uni-greifswald.de

Gender-associated differences in Type 1 diabetes risk factors?

To the Editor: Several different viruses are associated with Type 1 diabetes, but no studies have observed a gender difference in the impact of infections on diabetes. Childhood Type 1 diabetes is increasing worldwide; this has prompted several study groups to search for risk factors explaining this worldwide increase. All studies investigating risk factors for Type 1 diabetes have been matched for gender, because there is a known difference in incidence between boys and girls [1].

Several viral infections (e.g. rubella, enterovirus) in early life are associated with the risk of Type 1 diabetes [2]. Age is the most important determinant of enterovirus infections but data also supports a male predominance particularly for the more severe disease [3]. Gender differences are found in immunological response to some vaccinations given in early childhood [4].

These observations prompted us to look at gender differences in the effect of neonatal infections in a population based case-control study based on the Danish National Diabetes Register.

In 1996 a Danish national prospective register of childhood diabetes was opened. The ascertainment in the register during the first 4 years was more than 99%. All children below the age of 15 years with Type 1 diabetes diagnosed from 1996 to 1999 were invited to participate in a case-control study. Two control subjects per case were randomly selected from the National Population Register matched by date of birth and gender. Information on hospitalisation and perinatal diagnosis such as preterm delivery (<37 weeks), small or large for date (>2 standard deviation from the expected mean), and neonatal jaundice and infections were obtained from the hospital discharge register. Data on maternal and paternal age and ethnicity were obtained from the Danish population register. Additionally all cases and controls received a questionnaire including questions on smoking during pregnancy, early life nutrition, growth, siblings and family history of diabetes. Immigrants and offspring of immigrants were excluded from the study. For the study 602 diabetic children were eligible and 1459 control subjects were matched by gender and date of birth. Hospital information was available for 598 cases and 1445 control subjects. Questionnaire data were available for 490 (81%) cases and 696 (48%) of control subjects. We estimated the effect of neonatal infections among boys and girls with multiple logistic regression using all cases and control with hospital information. The model included age, gender and interaction between gender and infections. Of the children 49 had an infectious diagnosis in the neonatal period and 28 of those had either meningitis or sepsis, the remaining diagnoses were upper respiratory tract infections. There was no information on treatment with antibiotics.

Interestingly we found an increased risk of diabetes in boys with any neonatal infections [OR=2.42 (CI 1.14–5.15) p=0.02] and a decreased risk in girls with neonatal infections: [OR=0.40 (CI 0.12–1.38) p=0.15]. The estimated odds ratio for boys was six times the estimated odds ratio for the girls [CI 1.41–25.5) p=0.015] which corresponds to the significant interaction between gender and neonatal infections). There was no association between diabetes and neonatal infections [OR=1.23 (CI 0.67–2.28) p=0.51] when the interaction term was omitted.

The difference between boys and girls remained after adjustment for confounders such as introduction of cow's milk (<2 month), maternal age at delivery, family history of diabetes, smoking during pregnancy and birth order with an odds ratio in boys of 4.36 (CI 1.29–14.8), and in girls of 0.49 (CI 0.10–2.36).

DOI 10.1007/s00125-003-1049-0
Received: 30 September 2002 / Revised: 4 November 2002
Published online: 27 February 2003

The number of hospitalised infections in first year of life were also analysed for interaction with gender. This showed no difference between boys and girls (p=0.94).

To our knowledge this is the first study indicating a gender difference in the impact of neonatal infections on the risk of Type 1 diabetes in children. The results are not likely to be caused by recall bias since all information is based on register data collected prior to diabetes onset and less than 1% of the patients have missing information. The analysis is based only on hospital records and since boys are more often hospitalised in the first year of life there could be a selection bias towards higher registration rate of infections in boys. However, if we assume that this higher registration rate is the same in diabetic and non-diabetic cases, this should not influence the results.

The results might be explained by a gender difference in susceptibility to T cell-mediated autoimmune diabetes and gender difference in response to infections [5]. The observation of an interaction between gender and risk factors affecting the development of the immune regulatory system is of crucial relevance. Accordingly the effects of those risk factors should be taken into account in analyses where boys and girls are analysed together because of opposite effects in boys and girls. This result suggests that all studies on risk factors of autoimmune diabetes which possibly occur through an effect on the immune regulatory system have to be analysed separately for each gender or with interaction. This has implications for the evaluation of risk factors such as infections, vitamin D supplement and breastfeeding, especially when considering the impact of these risk factors in early childhood.

J. Svensson, B. Carstensen, H. B. Mortensen, K. Borch-Johnsen, the Danish Study Group of Diabetes in Childhood (DSBD)
Steno Diabetes Centre, Gentofte, Denmark

References

1. Karvonen M, Pitkaniemi M, Pitkaniemi J, Kohtamaki K, Tajima N, Tuomilehto J (1997) Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data. World Health Organization DIAMOND Project Group. Diabetes Metab Rev 13:275–291
2. Szopa TM, Titchener PA, Portwood ND, Taylor KW (1994) Diabetes mellitus due to viruses – some recent developments see comments. COMMENT: Comment in: Diabetologia 37:222. Diabetologia 36:687–695
3. Morens DM, Pallansch MA (1995) Epidemiology. In: Rotbart H (ed.) Human enterovirus infections, pp 3–23
4. Aaby P, Samb B, Simondon F et al. (1994) Sex-specific differences in mortality after high-titre measles immunization in rural Senegal. Bull World Health Organ 72:761–770
5. Lisse IM, Aaby P, Whittle H, Jensen H, Engelmann M, Christensen LB (1997) T-lymphocyte subsets in West African children: impact of age, sex, and season. J Pediatr 130:77–85

Corresponding author: J. Svensson MD, Steno Diabetes Centre, Niels Steensons Vej 2, 2820 Gentofte, Denmark
E-mail: JaSv@novonordisk.com

Does the −11377 promoter variant of *APM1* gene contribute to the genetic risk for Type 2 diabetes mellitus in Japanese families?

To the Editor: Although the physiopathological bases of Type 2 diabetes mellitus are well established, with an important role of generalized insulin resistance hitting key organs for glucose homeostasis – like muscle, liver and beta-cell – little is known about its molecular determinants and about the genetic factors involved in the transition between obesity and Type 2 diabetes. A considerable amount of evidence has suggested that a polymorphism in fat-expressed PPAR-γ, the major thiazolidinedione target, could contribute, even modestly, to the genetic risk for Type 2 diabetes [1]. In contrast, genome wide scans presented evidence of linkage between a region of chromosome 3q27, the metabolic syndrome and Type 2 diabetes in American and French Caucasian subjects [2], and also with coronary heart disease in Indo-Mauritians [3]. We recently replicated the linkage with diabetes in Japanese Type 2 diabetic families [4]. A strong positional candidate gene located on 3q27 is *APM1*, which encodes for the adipocyte complement related protein (Acrp30, also named adiponectin) which is specifically expressed in differentiated adipocytes. It was recently shown that its proteolytically-cleaved product (gAcrp30) lowers glucose concentrations through fatty acid oxidation without variations of insulin and glucagon concentrations, and prevents the development of high-fat diet induced obesity [5]. Furthermore, decreased expression of adiponectin correlates with insulin resistance in mouse models of obesity or lipoatrophy, and physiological doses of adiponectin decrease insulin resistance in these mice by lowering triglyceride content in muscle and liver [5]. In human, hypoadiponectinaemia was reported in obese and Type 2 diabetic subjects, and adiponectin concentrations are closely associated with insulin sensitivity in different ethnic groups [6]. We have recently shown that sequence variations in *APM1* gene are associated with circulating adiponectin concentrations and modulate the risk for insulin resistance and diabetes in French Caucasians [7]. A previous study has also suggested a large heritability for plasma adiponectin concentrations in humans [8].

In the Japanese population, we have done a case control study and reported an association between two single nucleotide polymorphisms (SNP) in the *APM1* gene and Type 2 diabetes [9]. To confirm such relevant associations in another Japanese population, we studied 359 diabetic Japanese subjects from the 164 sib-ships where indication of linkage at 3q27 was found [4]. One affected subject without obesity was randomly chosen from each family (average BMI: 22.7±2.8 and 23.2±3.6 kg/m2 for men and women, respectively), and 183 non-diabetic Japanese subjects was the control group (average BMI: 22.3±3.1 and 22.5±3.4 kg/m2 for men and women, respectively). The 11 most frequent polymorphisms of the *APM1*

DOI 10.1007/s00125-003-1050-7
Published online: 1 March 2003