Nº328

Type 1 Diabetes Genetics Consortium (T1DGC)

DOES INTRAUTERINE EXPOSURE TO MATERNAL DIABETES ACCELERATE THE ONSET OF TYPE 1 DIABETES (T1D) IN OFFSPRING? RESULTS FROM THE TYPE 1 DIABETES GENETICS CONSORTIUM (T1DGC).

Ana M Wägner[1,2], Angelo Santana[3], Julia C Wiebe[1], Marta Hernández[4], Javier Nóvoa[1,2], Dídac Mauricio[4,5,] T1DGC.

1. Endocrinology Dept. Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Spain. 2. Dept of Medical and Surgical Science. Universidad de Las Palmas de Gran Canaria.3. Dept of Mathematics and Statistics. Universidad de Las Palmas de Gran Canaria. 4. Endocrinology Dept. Hospital Universitari Arnau de Vilanova, Lleida, Spain. 5. Institut de Recerca Biomédica, Lleida,Spain.

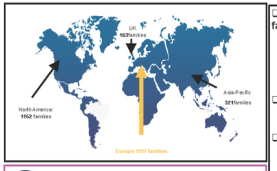
Background and Aim

The Type 1 Diabetes Genetics Consortium (T1DGC) is an international effort aimed at the study of the genetics and pathogenesis of T1D.

The T1DGC included families with at least 2 siblings with T1D. We previously showed that male gender, high-risk HLA and negative antibodies at the time of recruitment were associated with early onset of the disease.

The aim of this study was to assess the role of maternal factors on the age of T1D onset in their offspring in the T1DGC dataset

Methods



Type 1 Diabetes Genetics Consortium (T1DGC)

2663 families with unequivocal HLA haplotypes

3228 mothers

- ❑ **Inclusion criteria for families:**
  - at least 2 siblings with T1D
  - diagnosed before the age of 35
  - Insulin within 6 months
  - interruption < 6 months
- ❑ **Definitions**
  - Early onset: <6 years
  - Childhood onset < 15 years
- ❑ **Classification of mothers**
  - Type of diabetes
  - Diagnosis before or after the birth of their first affected child
- ❑ **Data analysis, using "R"**
  - Multivariate analysis (GAM)
  - Wilcoxon-Mann-Whitney's test
  - Decision tree analysis

❑**Predictors of early and childhood onset of T1D in affected siblings:**

Independent variables

- Gender
- Time since diagnosis
- Antibody positivity at the time of recruitment
- Presence of other autoimmune diseases
- Number of risk and protective HLA haplotypes
- Maternal age
- Birth order

❑**Classification of mothers** according to presence and type of diabetes ant time of onset (before or after delivery of affected child)

❑**Comparison of age of onset** of the first child with diabetes in the different groups

❑**Adjustment** for potential confounders (maternal age/maternal onset of diabetes) was performed separately in mothers with T1D and T2D

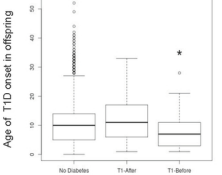
❑Effect of **paternal age of onset** (of T1D or T2D) on offspring age of onset was also analysed

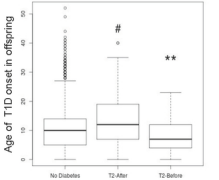
Results

- Median (range) age of onset of the disease in affected siblings was 9 (0-49) years
- In multivariate analysis, **maternal age** ($p<1.25*10^{-13}$) was positively associated with both early and childhood onset of the disease, whereas**birth order**($p<0.013$) was negatively associated. The previously described markers were also confirmed (data not shown).
- The distribution of the mothers into the different groups, maternal age of onset, maternal age at the time of birth of the first affected child and his/her age of onset are shown in the table

	No diabetes	T1D		T2D	
		Before delivery	After delivery	Before delivery	After delivery
n	2995	53	31	21	128
Maternal age at delivery	26.3(4.7)	26.4(4.1)	23.1(3.5)	29.9(6.1)	26.1(4.7)
Maternal age of onset	--	13.81 (8.4)	33.84 (8.9)	27.5 (5.6)	46.4 (10.9)
Age of onset of T1D	11.0(7.7)	7.8(5.8)*	12.4(8.8)	8.4(5.7)**	13.9(9.6)#

*p<0.02 compared with no diabetes and T1D-after, **p<0.02 compared with T2D-after, #p<0.002 compared with no diabetes





- **Multivariate analysis** also showed that, for **mothers withT1D,** the age of onset in the first affected offspring was significantly associated with maternal age of onset, rather than with maternal age at delivery or the presence of maternal T1D before or after delivery. Decision tree analysis also showed similar results (data not shown).
- **For mothers with T2D**, age of onset of T1D in the first affected offspring was significantly associated with maternal age of onset of T2D (positively) and with advanced maternal age (negatively), but not with the presence/absence of T2D at the time of delivery Furthermore, the effect of paternal age of onset was similar to that of maternal age of onset.

Conclusions

Both increasing maternal age and advanced birth order are associated with an earlier onset of T1D.

Delivery after the diagnosis of maternal diabetes is associated with an earlier onset of the disease in offspring.

However, adjustments for maternal age of onset and maternal age of delivery show that maternal (and paternal) age of onset is a main predictive factor of the age of onset in the offspring.

These results suggest that genetic factors, rather than intrauterine hyperglycaemia, may have a predominant effect on the age of onset of the offspring who develop T1D.

Acknowledgements

This research uses resources provided by the Type 1 Diabetes Genetics Consortium (**T1DGC**), a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (**NIDDK-DK062418**), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD). Juvenile Diabetes Research Foundation International (**JDRF**)

European Foundation for the Study of Diabetes (**EFSD**/JDRF/Novo Nordisk Programme for Type 1 Diabetes 2008)

Instituto de Salud Carlos III (PI08/1113, P10/02310, P11/02441), Ministerio de Ciencia e Innovación, Spain