

## Study of factors influencing susceptibility and age at onset of type 1 diabetes: A review of data from Continental Italy and Sardinia

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### Abstract

**AIM:** To investigate the role of protein tyrosin phosphatase 22 (PTPN22), maternal age at conception and sex on susceptibility and age at onset of type 1 diabetes (T1D) in Continental Italy and Sardinian populations.

**METHODS:** Three hundred seventy six subjects admitted consecutively to the hospital for T1D and 1032 healthy subjects as controls were studied in Continental Italy and 284 subjects admitted consecutively to the hospital for T1D and 5460 healthy newborns were studied in Sardinia. PTPN22 genotype was determined by DNA analysis. Maternal age at conception and age

at onset of disease were obtained from clinical records.  $\chi^2$  test of independence, student *t* test for differences between means and odds ratio analysis were carried out by SPSS programs. Three way contingency table analysis was carried out according to Sokal and Rohlf.

**RESULTS:** The pattern of association between PTPN22 and T1D is similar in Continental Italy and Sardinia: the proportion of \*T allele carriers is 13.6% in T1D vs 6.7% in controls in Continental Italy while in Sardinia is 7.3% in T1D vs 4.4% in controls. The association between T1D and maternal age at conception is much stronger in Sardinia than in Italy: the proportion of newborn from mother aging more than 32 years is 89.3% in T1D vs 32.7% in consecutive newborn in Sardinia ( $P < 10^{-6}$ ) while in Continental Italy is 32.2% in T1D vs 19.1% in consecutive newborns ( $P = 0.005$ ). This points to an important role of ethnicity. A slight prevalence of T1D males on T1D females is observed both in Continental Italy and Sardinia. PTPN22 genotype does not exert significant effect on the age at onset neither in Continental Italy nor and Sardinia. Maternal age does not influence significantly age at onset in Italy (8.2 years in T1D infants from mothers aging 32 years or less vs 7.89 years in T1D infants from mothers aging more than 32 years:  $P = 0.824$ ) while in Sardinia a border line effect is observed (5.75 years in T1D infants from mothers aging 32 years or less vs 7.54 years in T1D infants from mothers aging more than 32 years:  $P = 0.062$ ). No effect of sex on age at onset is observed in Continental Italy while in Sardinia female show a lower age at onset of T1D as compared to males (8.07 years in males vs 6.3 years in females:  $P = 0.002$ ).

**CONCLUSION:** The present data confirm the importance of ethnicity on susceptibility and on the age at onset of T1D.

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**Key words:** Type 1 diabetes; Continental Italy; Sardinia; Protein tyrosin phosphatase 22; Maternal age; Age of onset; Sex

**Core tip:** It is known that the incidence of type 1 diabetes (T1D) is greater in Sardinian than in Italian population. Among the factors considered in this review maternal age only has shown a significant difference between the two populations. Although in both Sardinia and Continental Italy the proportion of mothers aging more than 32 years is higher in children with T1D than in consecutive newborns from the same population, the risk of having a child with T1D in younger women is much greater in Sardinia than in Continental Italy (OR = 17.191 vs 2.018).

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## INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disorder with severe implications for the health of the patients. In western population the prevalence of T1D is increasing suggesting a role of current changes of cultural and environmental factors<sup>[1,2]</sup>.

The incidence of the disease varies among populations, highest in Finland and Sardinia and lowest in Venezuela and China. This points to an important effect of genetic and environmental factors<sup>[3-7]</sup>. Positivity for islet antibodies precedes the onset of disease for years and it has been observed that the rate of positivity varies by ethnicity and age<sup>[1]</sup>.

Among genetic factors HLA is the most important predictor, followed by protein tyrosin phosphatase 22 (PTPN22) and by insulin gene. Other genes are involved in susceptibility to T1D and it is likely that genes at present involved in autoimmunity, have been selected positively in the past being adaptive in particular environments<sup>[1]</sup>.

A role of non genetic factors is suggested by the low concordance rate of T1D among monozygotic twins and by the increasing incidence of the disease in younger children and in those with lower risk HLA genotype, pointing to an important role of environment including dietary, viral and bacterial factors. Epigenetic regulation is emerging as an important factor also<sup>[1,8,9]</sup>.

The role of maternal age at conception is well established<sup>[10-13]</sup>: the incidence of T1D increases with maternal age at conception. It is well known the present tendency in Western populations to conceive in older age as compared

to the past: this is an important non genetic cultural factor.

Compared to Continental Italy the population of Sardinia shows a higher incidence of T1D<sup>[14]</sup>. This prompted us to review our data from Continental Italy and Sardinia concerning the factors that increase the risk of T1D.

In this paper we have studied the role of PTPN22, sex and maternal age on susceptibility to T1D and on age of onset of the disease in the population of Continental Italy and in the population of Sardinia. The survey includes data previous published<sup>[13,15,16]</sup> and unpublished observations from our data base.

PTPN22 codifies for Lyp, a protein tyrosine phosphatase involved in the regulation of T cell receptor signaling. The gene shows a single nucleotide polymorphism C/T at + 1858 resulting in W620 variant that is associated with autoimmune diseases. The variant is a gain of function of the enzyme that more strongly inhibit T-cell receptor-mediated signals, and it has been suggested that the increased susceptibility to autoimmune disorders is due to failure to delete autoreactive T cells during intrathymic selection<sup>[17]</sup>. The association of PTPN22 polymorphism with T1D reported by Bottini *et al*<sup>[15]</sup> in 2004 have been confirmed in many populations<sup>[18-20]</sup>.

T1D shows a slight prevalence of males over females whereas the opposite is observed for other autoimmune disorders<sup>[21]</sup>.

## MATERIALS AND METHODS

We have reviewed data on 376 subjects with T1D and 1032 controls in Continental Italy and on 291 subjects with T1D and 5460 controls in Sardinia. PTPN22, maternal age at conception and age at onset of disease were not determined in all subjects thus the number of subjects is not the same in all tables.

PTPN22 genotype was determined by DNA analysis as previously described<sup>[15]</sup>.  $\chi^2$  square test of independence, Student *t* test for differences between means and Odds ratio analysis were carried out by SPSS programs<sup>[22]</sup>. Three way contingency table analysis was carried out according to Sokal *et al*<sup>[23]</sup>. By this analysis is possible to study the effect of the categories of a third variable on the association between two variables: a statistically significant interaction suggests that the third variable influences the association between the other two.

The number of subjects in the tables are different due to the fact that PTPN22 have not studied in all subjects and the role of maternal age on the incidence of T1D have been evaluated in different samples.

## RESULTS

Table 1 shows the distribution of PTPN22 genotypes in T1D and controls in Continental Italy and in Sardinia. The proportion of \*T allele carriers is slightly higher in Italy than in Sardinia; the positive association between T1D and this genotype is slightly stronger in Continental Italy (OR = 2.19) than in Sardinia (OR = 1.70).

**Table 1** Distribution of protein tyrosin phosphatase 22 genotypes in type 1 diabetes and controls in Continental Italy and in Sardinia

	% Proportion of *T allele carriers	Total n
T1D		
Continental Italy	13.60%	376
Controls	6.70%	1032
T1D		
Sardinia	7.30%	248
Controls	4.40%	205

T1D: Type 1 diabetes.

**Table 2** Maternal age at conception in consecutive newborns and in children with type 1 diabetes in Continental Italy and in Sardinia

	Sardinia		Continental Italy	
	Consecutive newborns	Children with T1D	Consecutive newborns	Children with T1D
% proportion with maternal age > 32 yr	32.70%	89.30%	19.10%	32.20%
Total n	5460	187	792	90
$\chi^2$ test of independence				
$\chi^2$	253.705		7.821	
df	1		1	
P	< 10 <sup>-6</sup>		0.005	
OR analysis				
OR	17.191		2.018	
95%CI	10.569-24.396		1.234-3.331	

Three way contingency table analysis by a log linear model: x = T1D vs controls; y = maternal age ( $\leq 32$  yr vs  $> 32$  yr); z = Continental Italy vs Sardinia. x, y and z interaction: G = 45.703; df = 1; P < 0.0001. T1D: Type 1 diabetes.

**Table 3** Effect of protein tyrosin phosphatase 22 genotype on age at onset of type 1 diabetes

	Continental Italy	Sardinia
	Age at onset (yr)	
	mean $\pm$ SE	mean $\pm$ SE
PTPN22 genotype		
*C/*C	8.56 $\pm$ 0.28	7.44 $\pm$ 0.32
*T carriers	9.85 $\pm$ 1.03	7.43 $\pm$ 1.33
Student t test for differences between means		
	P = 0.100	P = 0.540

PTPN22: Protein tyrosin phosphatase 22.

Table 2 shows the effect of maternal age at birth on susceptibility to T1D. In both Sardinia and Continental Italy the proportion of mothers aging more than 32 years is higher in children with T1D than in consecutive newborns from the same population. The association, however, is much stronger in Sardinia than in Continental Italy (OR = 17.191 vs 2.018). A three way contingency table analysis indicates that the relationship between maternal age and susceptibility to T1D is dependent on the population.

There is a not statistically significant prevalence of males both in Italy and in Sardinia (data not shown).

**Table 4** Maternal age (year) at conception and age at onset of diabetes

		Age at onset of diabetes (yr)			t test for differences between means
		mean	SE	total n	
Sardinia	Maternal age $\leq 32$	5.75	0.89	20	
	Maternal age > 32	7.54	0.31	169	P = 0.062
Continental Italy	Maternal age $\leq 32$	8.02	0.51	61	
	Maternal age > 32	7.89	0.81	28	P = 0.894

Age at onset; Sardinia vs Continental Italy. t test for differences between means. Maternal age > 32, P = 0.720; Maternal age  $\leq 32$ , P = 0.028.

**Table 5** Effect of sex on the age at onset of type 1 diabetes

	Continental Italy	Sardinia
	Age at onset (yr)	
	mean $\pm$ SE	mean $\pm$ SE
Sex		
Males	8.50 $\pm$ 0.39	8.07 $\pm$ 0.40
Females	8.93 $\pm$ 0.39	6.30 $\pm$ 0.40
Student t test for differences between means		
	P = 0.433	P = 0.002

Table 3 shows the effect of PTPN22 on the age of onset of the disease. No effect is observed in Sardinia. In Continental Italy the mean age at onset is greater in \*T carriers than in \*C/\*C genotype but the difference is not statistically significant.

The effect of maternal age on the age at onset of disease is shown in Table 4. No significant effect is observed in Continental Italy while in Sardinia a border line significant effect is observed with a lower age at onset in the mother aging 32 years or less.

The effect of sex on the age at onset of T1D is reported in Table 5. No effect is observed in Continental Italy while in Sardinia females show a lower age at onset of disease.

## DISCUSSION

The most important result emerging from our analysis regards the role of maternal age at conception on susceptibility to T1D and on the age of onset of the disease. The effect of maternal age at conception on susceptibility and on age of onset of disease is more marked in Sardinian than in Italian population.

The effect of maternal age at conception on the susceptibility to T1D has been observed in many populations<sup>[10-12]</sup> including Sardinia<sup>[13]</sup>. In Sardinia this effect is stronger compared to other populations and this may be connected with the high risk of T1D observed in Sardinian population<sup>[14,24,25]</sup>. Moreover in Sardinia a clear correlation between maternal age at delivery and age at onset of diabetes has been also observed<sup>[13]</sup>. Changes of hormonal pattern due to maternal aging may be involved in modifi-

cations of maternal-fetal immunological relationship<sup>[26-28]</sup>. Maternal age could influence the maturation of fetal immune system through modifications of intrauterine environment. T1D (a Th1 mediated disease) is more frequent in children conceived by older women, whereas atopic disorders (Th2 mediated diseases) are more frequent in children conceived by younger women<sup>[13,29-31]</sup>.

The incidence of T1D varies among population and at present the causes of this phenomenon is not yet clarified. The most important predictor is HLA followed by PTPN22 and insulin gene. Other minor genetic factors and epigenetic regulation are probably involved. Maternal and environmental factors could also have an important role<sup>[1-13]</sup>.

Sardinian population differs from the population of the Continental Italy for many genetic factors including HLA, PTPN22 and glucose 6 phosphate dehydrogenase (G6PD). Our review does not show important effect on the susceptibility to T1D due to difference in genotype frequency of PTPN22 between the two populations but points to an important role of maternal age at conception.

In Sardinia there is high incidence of G6PD deficiency. Some studies<sup>[32]</sup> suggest that G6PD heterozygous women enjoy a more favorable pregnancy outcome compared to normal women suggesting that adaptation to endemic malaria could have involved genetic factors important in human reproduction and in the maternal fetal relationship resulting in a more marked role of maternal age in the susceptibility to T1D. A prevalence of Th1 orientation during pregnancy could have had an adaptive role in the malaria environment: this could explain the stronger effect of maternal age on susceptibility and on age at onset of T1D observed in Sardinian as compared to Continental Italian population.

From a practical point of view from the present analysis emerges the advice to females of Sardinia origin to conceive at young age to reduce the risk of T1D in the offspring.

## COMMENTS

### Background

The incidence of Type 1 diabetes (T1D) varies among populations, highest in Finland and Sardinia and lowest in Venezuela and China. This points to an important effect of genetic and environmental factors.

### Research frontiers

In this paper authors have studied the role of protein tyrosin phosphatase 22 (PTPN22), sex and maternal age on susceptibility to T1D and on age of onset of the disease in the population of Continental Italy and in the population of Sardinia.

### Innovations and breakthroughs

The most important result emerging from authors' analysis regards the role of maternal age at conception on susceptibility to T1D and on the age of onset of the disease. The effect of maternal age at conception on susceptibility and on age of onset of disease is more marked in Sardinian than in Italian population.

### Applications

From a practical point of view the present analysis suggests to advice females of Sardinia origin to conceive at young age to reduce the risk of T1D in the offspring.

### Terminology

PTPN22 codifies for a protein-tyrosin-phosphatase involved in the regulation of

T cell receptor signaling. The PTPN22 polymorphism (chromosome 1) has two alleles, \*C1858 (encoding the R620 variant, here simply called \*C) and \*T1858 (encoding the W620 variant, here simply called \*T), and has three genotypes, \*C/\*C, \*C/\*T and \*T/\*T. The \*T/\*T genotype is very rare. The W620 variant is associated to autoimmune disorders.

### Peer review

This manuscript describes the role of genetic and non-genetic factors in the development of Type 1 diabetes. It is well written.

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