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AGE OF ONSET OF TYPE 2 DIABETES CORRELATES WITH GENETIC VARIABILITY IN THE GENOMIC AREA OF IGF2

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Abstract

Four polymorphic sites in insulin gene genomic area were analyzed by DNA analysis in 91 subjects with T2D. Two sites included in IGF2 area show a statistically significant association with age of onset of T2D. Such association is highly significant in females (p=0.002) and in obese subjects (p=0.004).

Introduction

The possible role of genetic factors on the age of onset of Type 2 Diabetes (T2D) has been scarcely considered in the literature [1,2]. In the present note we report a study suggesting that genetic variability within the genomic area of Insulin like Growth Factor 2 (chromosome 11p15.5) influences the age of onset of T2D.

Materials and methods

A sample of 91 patients with T2D from Penne-a rural town in the eastern side of Italy- considered in a previous study [3] has been reexamined. Verbal informed consent was obtained by these patients to participate to the study that was approved by the I.R.B.

In the insulin gene region we have examined one variable number of tandem repeated polymorphism (VNRT) and three RFLPs: the position of the 4 sites, probes, restriction enzymes and size of fragments are shown in Appendix 1 and 2 [3]. In a previous study the possible relationship between genetic variability within this area and glycemic levels was investigated with negative results. We have now considered the relationship with age of onset of T2D.

DNA analysis was performed as previously reported [3].

Statistical analysis was performed using commercial software (SPSS). Haplotype frequencies are maximum likelihood estimates (program Mendel, Department of Biostatistics, University of Michigan, Ann Arbor, MI).

Results

Table 1 shows the age of onset of T2D in relation to BamH1A and BamH1B genotypes. For both loci the age of onset is lower in the genotype *1/*1 than in carriers of the *2 allele. The difference, however, does not reach the level of statistical significance. The joint BamH1A*1/*1/BamH1B*1/*1 genotype, however, shows a statistically significant lower age of onset compared to other joint genotypes (47.33 yrs vs 55.58 yrs; p=0.022).

Appendix 3 shows the proportion of the joint genotype BamH1A*1/*1/BamH1B*1/*1 in relation to age of onset grouped into three classes corresponding to the first quartile, to the second plus the third quartiles, and to the fourth quartile. A statistically significant correlation is observed with a very high frequency of this joint genotype in subjects with an age of onset ≤ 47 yrs and a very low frequency in those with an age of onset >67 yrs (O.R. for age of onset ≤ 47 yrs =3.933, 95% C. I. 1.110-14.501).

Appendix 4 shows the proportion of BamH1A*1/BamH1B*1 haplotype in relation to age of onset of diabetes. There is a significant correlation with a high frequency of this haplotype in subjects with an age of onset ≤ 47 years (O.R. =2.42 ,95% C.I. 1.106-5.337).
Table 2 shows the age of onset of T2D in relation to the joint genotype BamH1A*1/*1/BamH1B*1/*1 separately for males and females a for obese and non obese. The relationship reported in table 1 is present and is very marked in females only (p=0.002) and in non obese subjects (p=0.004). A variance analysis has shown a statistically significant interaction of this joint genotype with sex (p=0.023) and with obesity (p=0.015).
We have also carried the analysis shown in Appendix 3 separately for males and females and for obese and non obese subjects. The correlation between the joint BamH1A*1/*1/BamH1B*1/*1 genotype and age of onset is highly significant in females (p=0.01) but not in males (p=0.695) and it is significant in non obese (p=0.026) but not in obese patients (p=0.213).
No statistically significant association has been observed between the age of onset and the other two loci of insulin area considered.

Discussion and Conclusion

The present analysis suggests that in the area of IGF2 between BamH1A and BamH1B loci is included a site (or an area) involved in the age of onset of diabetes. The gene (or area) associated to an early age of onset seems to be carried by the haplotype BamH1A*1/BamH1B*1.

The association is present and highly significant in females and in non obese subjects only. Hormonal influences could explain the difference between sexes while obesity may overshadow the effect of genetic variability in the IGF2 area.

The relatively low number of subjects examined represents a limitation of the study. If confirmed, this observation may have practical importance for the identification of subjects predisposed to an early onset of T2D who need preventive measures against the manifestation of overt disease in a relatively young age.
Conflict of interest: None declared

References

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Figure legends

Appendix 2: Human INS/IGF2 gene region showing the position of the VNTR and the approximate location of the 3 RFLPs (from ref. 3)

Appendix 3: Proportion of joint BamH1*1/*1/BamH2*1/*1 genotype in relation to age of onset of the disease. Linear correlation:p=0.027.

Appendix 4: Proportion of BamH1*1/BamH2*1 haplotype in relation to age of onset of the disease. Linear correlation:p=0.020

Table 1. Age of onset in relation to BamH1A and BamH1B genotypes

	Mean age of onset (yrs)	S.E.	N°
BamH1A			
genotype *1/*1	52.66	1.55	50
carriers of *2 allele	57.22	1.85	41
t- test for difference between means	p=0.060		
BamH1B			
genotype *1/*1	50.07	3.44	15
carriers of *2 allele	55.64	1.28	74
t- test for difference between means	p=0.089		
JOJNT GENOTYPE BamH1A/BamH1B			
joint genotype BamH1A*1/*1/BamH1B*1/1	47.33	3.54	12
other joint genotypes	55.58	1.31	74
t- test for difference between means	p=0.022		

Table 2. Age of onset of T2D in relation to the joint genotype BamH1A/BamH1B. Effect of sex and obesity .

	Age of Onset (yrs)		Age of Onset (yrs)	
	Mean	S.E.	Mean	S.E.
SEX	MALES		FEMALES	
joint genotype BamH1A*1/*1/BamH1B*1/1	53.52	8.64	44.38	3.14
other joint genotypes	52.97	1.91	57.92	1.72
t- test for difference between means	p=0.965		p=0.002	
OBESITY	BMI≤30		BMI>30	
joint genotype BamH1A*1/*1/BamH1B*1/1	40.25	5.25	50.71	4.94
other joint genotypes	56.46	1.52	54.14	2.39
t- test for difference between means	p=0.004		p=0.528	

Appendix 1: Polymorphic sites studied in the INS gene (from ref 3).

GENE REGION	VNTR	RFLP	PROBE	RESTRICTION ENZYME	SIZE (kb)
INS (11p-15.5)					
INS	PVII		pHINS310	PVII	0.6/1.5/2.4
IGF2		BamH1A	pHINS311	BamH1	2.2/1.2
		BamH1B	pHINS311	BamH1	18.0/17.0
		APAI	pHIGF2-11	APAI	3.6/2.3-1.3

Appendix 2

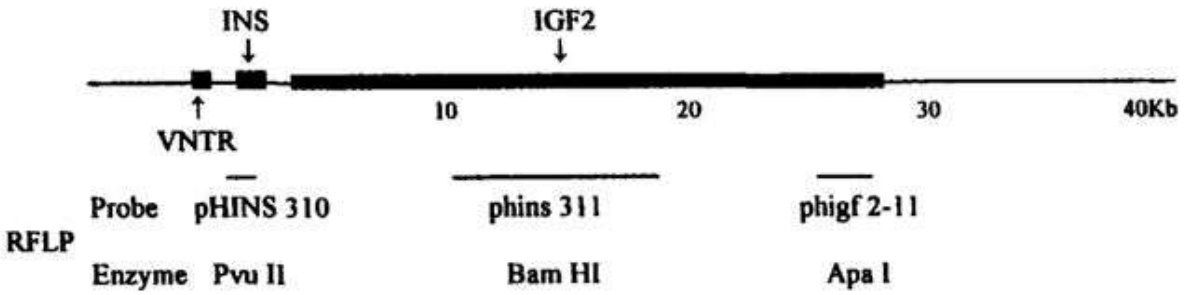

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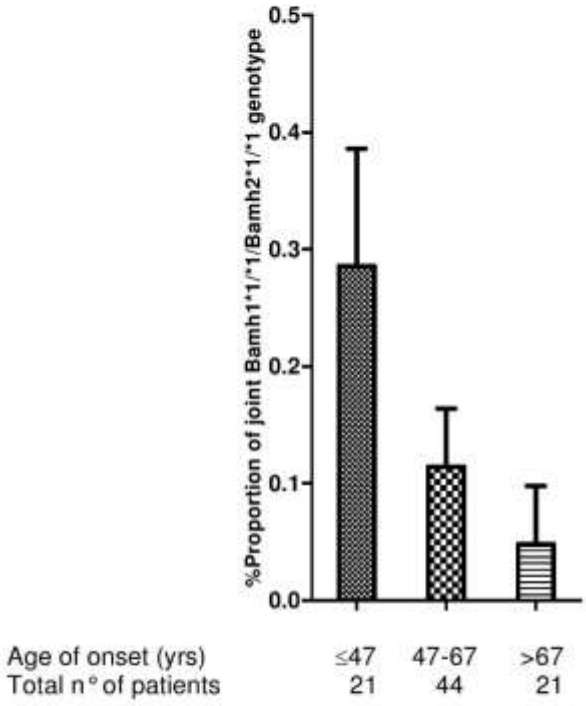
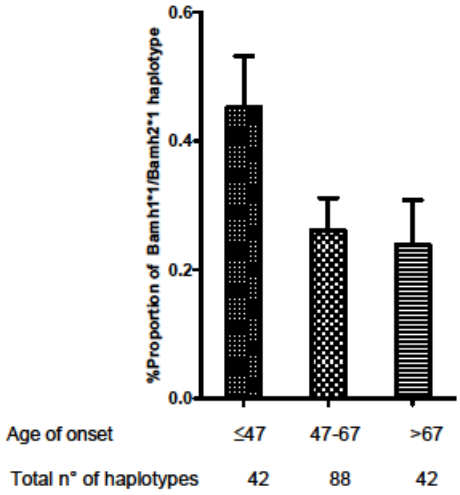
Fig 2: BAM disease (1).pzf:Data 1 - Sun Apr 27 15:24:35 2014



Appendix 3

Fig 3. BAM disease (2).pzf:Data 1 - Sun Apr 27 15:26:02 2014



Appendix 4