

## **Autoantibodies to IA2ic and to Phogrin increase the prediction for insulin requirement in patients with Type 2 Diabetes**

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**Background and aims:** ICA and GADA are detected in a subset of Type 2 diabetic (T2D) patients (pts) and their presence is correlated with the need for insulin requirement (IR) within 6 years from diagnosis. Little is known about the prevalence of autoantibodies (AA) against IA2 autoantigens and their role in the prediction of the IR in T2D pts. Thus, we carried out a retrospective study in these pts aimed to investigate the frequency of two different IA2 AA, the ones recognising the intracellular fraction of the IA2 (IA2icA) and the ones related to IA2 $\beta$  (IA2 $\beta$ A) or phogrin. Age at onset, clinical and metabolic characteristics, and HLA genotyping have been correlated with the presence of the two IA2 AA investigated.

**Materials and Methods:** IA2icA and IA2 $\beta$ A were measured in 3,600 white Caucasian newly diagnosed T2D pts, aged between 25 and 65 years, recruited to the UKPDS. The need for IR within 6 years from diagnosis has been evaluated in 2,263 pts, who were not assigned to insulin. Both IA2icA and IA2 $\beta$ A were measured by radioimmunoassay with human recombinant autoantigens. DR3/DR4 genotyping was available in 1,342 pts.

**Results:** IA2icA and IA2 $\beta$ A were detected in 93 (2.6%) and 58 (1.6%) pts, respectively. IA2icA alone were present in 42 (1.2%) pts, IA2 $\beta$ A alone in 7 (0.2%), whereas a combination of the two IA2 AA was detected in 51 (1.4%) pts. Due to the small number of pts positive for IA2 $\beta$ A alone, the analysis has been carried out only by considering the 93 IA2icA positive pts. IA2icA positive pts showed higher levels of FPG, HbA1c and insulin sensitivity, and lower values of age at diagnosis, BMI and  $\beta$ cell function, compared to the pts without IA2icA ( $p < .00001$  for all variables). The proportion of pts with IA2icA decreased significantly with the age at diagnosis (16.2% in the age group 25-35 years and 1.2% in the age group 55-65 years;  $p < .00001$ ). The frequency of DR4 allele was significantly higher in IA2icA positive pts than in the negative ones (66% vs 36%, respectively;  $p < .0001$ ). The sensitivity of IA2icA for IR was 17.5%, while the positive predictive value was 73% compared to 8.9% registered within IA2icA negative pts (OR 15.2; 95% CI 5.56-41.5).

**Conclusions:** In T2D pts, the presence of IA2icA is highly predictive of the need for the future IR, despite being of low sensitivity. As in Type 1 diabetes, IA2icA are frequently associated with the DR4 haplotype and are more likely to be found in younger pts. The measurement of IA2 $\beta$ A does not provide any additional information.