Prevalence and Regional Distribution of Autoantibodies Against GAD65Ab in a European Population Without Diabetes: The EPIC-InterAct Study

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Geographical differences in type 1 diabetes (T1D) prevalence in Europe have been well documented, but little is known about the geographical distribution of autoantibodies specific to GAD65 (GAD65Ab) in the general population without diabetes, which is reported to range between 0.4 and 3%. However, these studies used different methods to define GAD65Ab positivity with cutoff values based on the 97–99th centile or at +3 SD above the mean among healthy individuals without T1D or type 2 diabetes (T2D). In doing so, the prevalence of GAD65Ab among the study cohorts was, by definition, 1–3%. The application of different cutoff levels greatly impairs the direct comparison of prevalence data between studies. Our aims were to *1*) explore the prevalence of GAD65Ab positivity using a cutoff defined by specific competition of antibody binding to radiolabeled GAD65 with added autoantigen across eight European countries and *2*) compare characteristics of age, sex, and BMI in relation to GAD65Ab positivity. A center-stratified random subcohort of 16,835 (4.9%) individuals was selected from the original European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study (1). After exclusion of individuals with known diabetes, GAD65Ab were analyzed in 15,802 (men/women 5,927/9,875, mean age 52.4 ± 9.2 years) samples. The cutoff for GAD65Ab positivity was determined through a competition assay at ≥65 WHO units/mL, and all samples were analyzed at a single laboratory using a radioligand binding assay (2).

In all, 316/15,802 (2.0%) samples were GAD65Ab positive. Sweden, Denmark, U.K., and Spain had the highest and France had the lowest prevalence of GAD65Ab positivity (Table 1); however, these differences were not statistically significant ($P = 0.80$). We did not detect any association between GAD65Ab positivity and age, sex, or BMI.

This lack of geographical differences in GAD65Ab prevalence in healthy adults is in contrast to the established differences in incidence of T1D in children in Europe, with the Scandinavian countries having the highest incidence, while lower incidence rates are found in southern Europe with the exception of Sardinia (3). These differences have been attributed mainly to genetic, but also environmental, differences between the countries. A detailed analysis of the underlying HLA types of the participants in our subcohort will be necessary to determine whether GAD65Ab positivity in healthy individuals is associated with distinct HLA haplotypes, as has been previously established in T1D patients (4). Moreover, in contrast to previous studies (5), we found no association between GAD65Ab positivity and age, sex, or BMI. We conclude that GAD65Ab positivity in healthy adults is not associated with geographical location, BMI, age, or sex. While the practice of defining autoantibody positivity on the basis of a distribution is useful when

Table 1—Prevalence of GAD65Ab positivity in the subcohort by country

	n	%	95% CI
Sweden	2,730	2.2	1.6–2.7
Denmark	2,092	2.2	1.5–2.8
Germany	2,045	1.5	1.0–2.0
The Netherlands	1,476	1.9	1.2–2.6
U.K.	1,301	2.2	1.4–2.9
France	580	1.2	0.3–2.1
Spain	3,570	2.2	1.8–2.7
Italy	2,008	1.9	1.3–2.5
Overall	15,802	2.0	1.8–2.2

Data are presented as total number (*n*), prevalence (%) of GAD65Ab positivity, and 95% CI.

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comparing antibody frequencies between control subjects and patients, it is less informative when analyzing antibody levels in a population cohort or when comparing the prevalence of positivity between populations.

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