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Phenotypic Characterization and Prevalence of Latent Autoimmune Diabetes in Adults (LADA) in Indian Population: An Exploratory Study

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Abstract

Background/Objectives: The aim of the present study was to examine the prevalence and characteristics of Latent Autoimmune Diabetes in Adults (LADA) in three Endogamous Ethnic Groups (EEGs) of India, given the paucity of data on LADA in the Indian population. **Methods**: The study participants were recruited from three different EEGs: Chettiyar (CH), Reddy (RE) and Agarwal (AG). Data on pedigrees, phenotypes and environmental covariates were collected using a standardized protocol. To assess the prevalence of LADA among type 2 diabetes (T2D) individuals from the three EEGs, serum samples from 529 individuals were analyzed for GAD65 antibodies. Individuals were defined to have LADA based on the age of diagnosis ≥ 30 years and GAD65 positivity (≥20 U/mL).Group differences were examined using *t*-tests and χ^2 tests, evaluated both before ($p < 0.05$) and after ($p < 0.01$) Bonferroni correction for multiple comparisons. **Results**: The overall prevalence of LADA from three EEGs was found to be 7.6% (Mean age = 52.6 y, Mean age of onset = 46.8 y, Males = 62.5% and Mean BMI = 26.7). Of the examined variables, nominally significant ($p < 0.05$) group differences between T2D and LADA were found regarding hip circumference, HDL-cholesterol, fasting blood glucose, HbA1c and family history of diabetes. However, only group differences related to fasting blood glucose and HbA1c remained significant ($p < 0.01$) after correction for multiple testing. These findings were in line with the previous reports. **Conclusions**: Thus, this exploratory study revealed high occurrence of LADA in the Indian EEGs, in turn suggesting conduct of additional studies in the Indian population to precisely diagnose and characterize LADA for the purpose of its prevention and cure.

Keywords: Latent Autoimmune Diabetes in Adults; type 2 diabetes; epidemiology; Indian population; family study; heritability

1. Introduction

The global burden of diabetes is rising at an alarming rate and has become a major concern for public health. Aside from genetics, environmental factors like growing urbanization and unhealthy lifestyle habits such as physical inactivity and a higher intake of processed, high-calorie foods are driving the rise in diabetes [1]. Given attention to the issue of diabetes heterogeneity, Latent Autoimmune Diabetes in Adults (LADA) is a form of autoimmune disorder in which the development of beta cell failure is slow despite the presence of islet cell auto antibodies [2,3]. LADA itself is considered as a highly heterogeneous form of diabetes, which shares certain genetic, immunological and clinical characteristics with both type 1 diabetes (T1D) and type 2 diabetes (T2D); hence, it is termed type 1.5 diabetes (T1.5D) [4–8]. However, it is debated whether LADA should be considered a distinct form of diabetes; for example, the American Diabetes Association (ADA) considers LADA under the rubric of T1D, while the World Health Organization (WHO) describes it as 'Slowly evolving, immune-mediated diabetes of adults'[5,9,10]. Intriguingly, the available evidence suggests a clear genetic overlap between LADA and T1D [11–13]; while it appears that not only lifestyle factors involved in T2D risk (e.g., obesity, sedentariness and smoking) are related to LADA but also their interactions with specific genetic factors (e.g., HLA, TCF7L2 and FTO genotypes) are shown to be contributing to LADA risk [7,14–16].

Epidemiological investigations revealed that the occurrence of LADA differs based on ethnicity and geography, and it accounts for about 2–12% of all cases of diabetes [3,5,17–19]. Due to the phenotypic similarities between LADA and T2D, around 5–10% of

LADA cases are misdiagnosed as T2D patients, which is mainly due to the lack of awareness and standard diagnostic guidelines [20,21]. Based on the Immunology of Diabetes Society (IDS) guidelines (2005), LADA is broadly defined based on three diagnostic criteria: adult age of onset (>30 years), presence of any diabetes associated autoantibodies, and a period of insulin independency for at least six months from diagnosis [20]. However, the prevalence of LADA is mostly determined by the presence of glutamic acid decarboxylase 65 (GAD65) autoantibodies, along with or without other islet cell autoantibodies, such as protein tyrosine phosphatase insulin-associated 2 (IA-2) autoantibodies and zinc transporter 8 (ZnT8) autoantibodies [22,23]. These broad diagnostic criteria of LADA appear to be suitable for encompassing the heterogeneity observed in this form of diabetes.

The epidemiological and phenotypic profiles of LADA have been well examined in European ancestry populations, but limited research studies have been conducted on LADA in the Indian population, despite the fact that diabetes burden is high in people of India [24]. In general, the prevalence of LADA in Asian populations has been found torange from 2.6% to 5.7% [25–27]. However, regarding India, around 5% of T2D cases in the state of Gujarat were reported to be positive for the GAD autoantibodies [28], a percentage that was comparatively higher than the prevalence of 1.5% reported by Sachan et al.(2015) in another population of North India [29].This wide degree of heterogeneity can be attributed to differences in the ethnic background and environmental and genetic factors among different populations [24]. Nevertheless, there is a gap in knowledge in understanding the immunological, genetic and environmental factors underlying the phenotypic expression of LADA in the Indian population.

Therefore, the major objectives of this study are to determine the prevalence of LADA and its phenotypic characteristics among T2D individuals recruited from three endogamous ethnic groups (EEGs) representing the Indian population as part of the INDIGENIUS Consortium's family-based studies [30]. A variety of T2D-related phenotypic and environmental covariate data were collected as part of these family studies, in turn giving us a unique opportunity to determine the characteristics of LADA, its prevalence by EEG and the combined sample, and its potential genetic basis based on pedigree-based information. To the best of our knowledge, this exploratory study will be the first of its kind to examine the LADA phenotypic profile using data from three geographically and linguistically diverse EEGs and determine its potential genetic basis.

2. Materials and Methods

2.1. Study Participants

The study participants were recruited from three different endogamous ethnic groups (EEGs) representing the Southern and Northern regions of India, namely Chettiyar (CH) EEG, Reddy (RE) EEG (States of Tamil Nadu and Andhra Pradesh, respectively, Southern region) and Agarwal (AG) EEG (Rajasthan State, Northern region), as part of the Indian Diabetes Genetic Studies in collaboration with US (INDIGENIUS) Consortium studies (Figure 1). The study design and the data and biospecimen collection procedures of the INDIGENIUS Consortium studies were described in detail previously [30]. Briefly, using a family-based study design, 1547 adult participants (aged 18 years or above) from 68 families were recruited (i.e., CH EEG = 517 from 21 families, RE EEG = 500 from 22 families and AG EEG = 530 from 25 families). The pedigree, demographic, phenotypic and environmental/covariate data and blood and urine samples were collected from the study participants using the standardized procedures, as described previously [30]. All study protocols were approved by the site-specific Institutional Ethics Committees or Institutional Review Boards, and all study participants provided their written informed consent to participate in a given study.

Of the 1547 study participants from the three EEGs, 543 (35%) individuals were found to have T2D at the time of the clinic examinations (CH EEG = 169 (33%), RE EEG = 178 (36%) and AG EEG = 196 (37%)). As described previously [30], the T2D diagnosis was based on fasting capillary blood glucose ≥ 126 mg/dl and/or HbA1c ≥ 6.5% [10]. (). Individuals who did not meet these diagnostic criteria, but who reported that they were under treatment with anti-diabetic medications or insulin and who gave a history of diabetes were also considered to have T2D. Only individuals affected with T2D using the above criteria were considered for this study (N = 543), after excluding all non-T2D individuals (N = 1004).

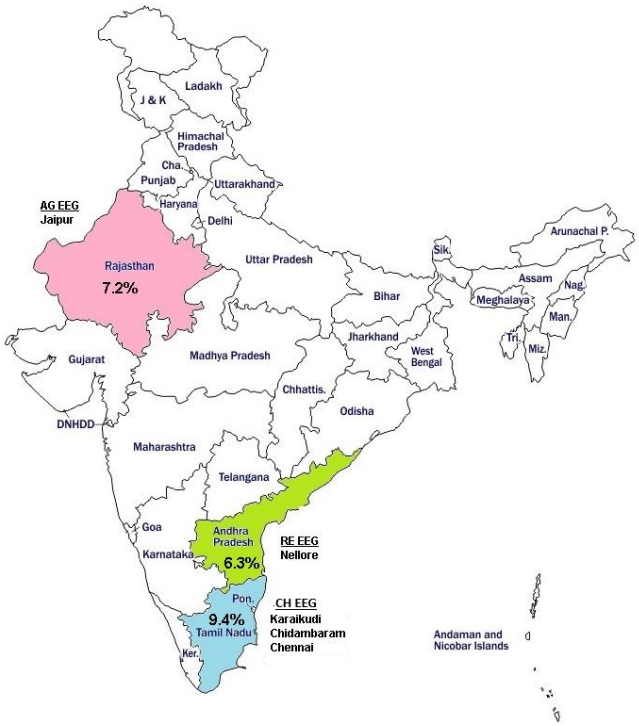

Figure 1. Prevalence of LADA in different ethnic groups in Indian population.

2.2. Measurement of GAD Autoantibody and LADA Diagnosis

Serum samples collected from all the study participants with T2D were analyzed for the presence of glutamic acid decarboxylase antibody-65(GAD65) using the principle of enzyme-linked immunosorbent assay (ELISA). GAD65 levels were determined using an RSR ELISA kit (Cardiff, UK) according to the manufacturer's instructions [31]. Of the 543 T2D individuals, GAD65 data were available for 529 individuals, after excluding 14 samples due to technical issues. Individuals were defined to have LADA based on the age of diagnosis ≥ 30 years and GAD65 positivity (≥20 U/mL). All other T2D individuals with GADA titers below 20 U/mL were considered as those without LADA. The optimal cutoff value for GADA titers was determined based on the 99.5% upper limit of 188 healthy controls evaluated in the Third Diabetes Autoantibody Standardization Program (DASP2003) with a sensitivity and specificity of 82% and 98%, respectively [32].

2.3. Other Phenotypic and Covariate Data

As described previously [30], demographic, anthropometric, biochemical and covariate data were collected from the study participants using the standardized procedures. Data on age, sex, height, weight, waist circumference and blood pressure were collected. Details on the age of onset, type and duration of diabetes, and medication status were recorded. Body mass index (BMI) was calculated by dividing the weight in kilograms by

height in meters-squared. Systolic and diastolic blood pressure and heart rate were measured usingmron HEM -8712 blood pressure monitor,(Kyoto Japan – OMRON Healthcare Co., Ltd., and Accu-Chek instant S glucometer (Roche Diabetes Care India Private Limited, India) was used to determine the fasting and post-prandial capillary blood glucose levels. Fasting total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were measured based on enzymatic photometric method using AU680 Clinical chemistry analyzer (Beckman Coulter Inc., Indianapolis, IN, USA). HbA1c levels were measured based on the principle of high-performance liquid chromatography method using automated D-10 hemoglobin testing system (Bio-Rad Laboratories Inc., Hercules, CA, USA). Fasting serum insulin was quantified based on chemiluminescent immunoassay using DxH 800 analyzer (Beckman Coulter Inc., Indianapolis, IN, USA). From the fasting glucose and insulin levels, insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) [33]. Serum creatinine levels were determined by Jaffe's method using AU5800 Clinical chemistry analyzer (Beckman Coulter Inc., Indianapolis, IN, USA). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation was used to estimate glomerular filtration rate (eGFR) [34]. For the purpose of discussion, it was referred to as CKD-EPI (eGFR). Using the AU5800 Beckman coulter system, hs-CRP levels were measured. Comprehensive self-reported data were collected using a standardized questionnaire, which included information on household details, family history of diabetes, medical history of diabetes and its related disease conditions, medication status, physical activity, dietary intake, smoking status, alcohol consumption, psychological or behavioral attributes, educational status and socioeconomic status [30].

2.4. Statistical Analyses

For descriptive statistics, we used frequencies and percentages for nominal (or categorical) and ordinal variables; and mean and standard deviation for quantitative variables. To address non-normality and the influence of extreme values, continuous variables were subjected to a rank-based inverse normal transformation using the Van der Waerden method [35]prior to statistical analyses. Group differences were examined using *t*-tests for continuous variables and χ^2tests for dichotomous or categorical variables. Given the exploratory nature of this study, two-sided *p*-values below 0.05 were considered nominally significant. To account for multiple comparisons across the five broad variable domains—obesity measures, glycemic traits, lipid traits, renal function measures and self-reported non-clinical variables (e.g., demographic, social and personal history factors such as income status and family history of diabetes)—a Bonferroni-adjusted significance threshold of $p < 0.01$ (0.05/5) was used to determine statistical significance. Unadjusted *p*-values were retained to facilitate the interpretation of observed variable differences, with findings between 0.01 and 0.05 interpreted as exploratory. All analyses were conducted using IBM® SPSS23 and Stata MP 19 (StataCorp, College Station, TX, USA).

3. Results

Of the 529 T2D individuals, 40 of them were defined to be LADA cases. The overall prevalence of LADA was found to be 7.6%. Specifically, the frequency of LADA cases among the three EEGs were found to be 15 of 159 T2D (9.4%), 11 of 176 T2D (6.3%) and 14 of 194 (7.2%) in CH EEG, RE EEG and AG EEG, respectively (Figure 1). Thus, the prevalence of LADA was observed to be highest in CH EEG and lowest in RE EEG.

The demographic and phenotypic information by LADA status (LADA vs. T2D) are described in Table 1. Of the 40 individuals with LADA, 25 were males (62.5%) and 15 were females (37.5%). The mean age and age of diabetes onset of LADA group was found to be 52.6 years and 46.8 years, while they were 56.0 years and 48.7 years in T2D group respectively. Thus, the mean age and age of diabetes onset of LADA individuals tend to be lower

compared to the T2D individuals. As expected from case definition, mean GAD antibody levels differed between individuals with LADA (86.55 U/mL) and those with T2D (2.82 U/mL). Of the clinical and non-clinical variables examined (Table 1), nominally significant ($p < 0.05$) group differences between T2D and LADA were found regarding hip circumference (100.49 cm vs. 96.12 cm), HDL-Cholesterol (42.66 mg/dL vs. 48.42 mg/dL), fasting blood glucose (154.72 mg/dL vs. 180.0 mg/dL), HbA1c (7.98% vs. 8.85%) and family history of diabetes (yes = 75.1% vs. 57.5%), respectively. However, only group differences related to fasting blood glucose and HbA1c remained significant ($p < 0.01$) after correction for multiple testing.

Table 1. Baselinedemographic and clinical characteristics of the study population by diabetes status (T2D vs. LADA) and for the combined sample.

Variable	N	T2D	N	LADA	N	Total	*p*-Value
Female/male	210/279		15/25		225/304		0.50*
Age (years)	489	55.97 (13.5)	40	52.64 (10.5)	529	55.72 (13.3)	-
Age of onset	489	48.69 (11.5)	40	46.85 (11.3)	529	48.53 (11.5)	0.38
BMI	489	27.60 (4.9)	40	26.69 (4.5)	529	27.53 (4.8)	0.25
Hip circumference (cm)	489	100.49(11.9)	40	96.12 (9.5)	529	100.16 (11.8)	*0.02*
Waist circumference (cm)	489	98.97 (12.7)	40	96.55 (9.5)	529	98.78 (12.5)	0.24
Systolic blood pressure (SBP) (mmHg)	489	135.5 (19.5)	40	131.3 (18.3)	529	135.18 (19.4)	0.19
Diastolic blood pressure (DBP) (mmHg)	489	84.13 (11.4)	40	82.4 (9.3)	529	84.0 (11.3)	0.35
HDL-C (mg/dL)	489	42.66 (14.8)	40	48.42 (16.3)	529	43.10 (15.0)	*0.02*
LDL-C (mg/dL)	489	98.76 (37.6)	40	106.5 (46.4)	529	99.3 (38.3)	0.22
Triglycerides (mg/dL)	489	150.6 (95.6)	40	171.7 (139.0)	529	152.37 (99.5)	0.20
Total cholesterol (mg/dL)	489	160.82 (49.1)	40	174.8 (53.1)	529	161.88 (49.5)	0.09
Fasting blood glucose (FBG) (mg/dl)	488	154.72 (52.4)	40	180.0 (67.3)	528	156.63 (54.0)	**<0.001**
Fasting Insulin (FI) (uU/mL)	489	13.55 (26.8)	40	20.5 (38.5)	529	14.07 (27.8)	0.14
HbA1C (%)	489	7.98 (1.9)	40	8.85 (2.5)	529	8.04 (2.0)	**0.01**
HOMA-IR	488	5.17 (11.9)	40	8.44 (15.9)	528	5.42 (12.3)	0.12
Serum creatinine (mg/dl)	489	0.76 (0.7)	40	0.77 (0.5)	529	0.76 (0.57)	0.92
CKD-EPI (eGFR)	489	101.80 (28.7)	40	106.24(38.6)	529	102.14 (29.5)	0.36
hs-CRP (mg/L)	489	0.53 (0.9)	40	0.35 (0.3)	529	0.51 (0.8)	0.20
GAD65 titer (U/mL)	489	2.82 (3.8)	40	86.55(115.6)	529	9.15 (38.6)	**-**
Study Site							
Chennai	144 (29)		15 (38)		159 (30)		0.532*
Jaipur	180 (37)		14 (35)		194 (37)		
Nellore	165 (34)		11 (28)		176 (33)		
Total	489 (100)		40 (100)		529 (100)		
Income Level							
Low	12 (2)		1 (3)		13 (2)		0.821*
Middle	411 (84)		35 (88)		446 (84)		
Upper	66 (14)		4 (10)		70 (13)		
Total	489 (100)		40 (100)		529 (100)		
Educational status							
Uneducated	40		4 (10)		44		0.981*

	(8)		(8)	
School	255 (52)	20 (50)	275 (52)	
Graduate	158 (33)	13 (33)	171 (33)	
Postgraduate	36 (7)	3 (7)	39 (7)	
Total	489 (100)	40 (100)	529 (100)	
Treatment Regimen				
Insulin	12 (2.5)	1 (2.5)	13 (2.5)	0.587*
OHA and insulin	28 (5.7)	4 (10.0)	32 (6.0)	
Only OHA	265 (54.2)	18 (45.0)	283 (53.5)	
No medication	184 (37.6)	17 (42.5)	201 (38)	
Total	489 (100)	40 (100)	529 (100)	
Family History of Diabetes				
Yes	367 (75.1)	23 (57.5)	390 (73.7)	*0.015**
No	122 (24.9)	17 (42.5)	139 (26.3)	
Total	489 (100)	40 (100)	529 (100)	

The *t*-test was performed for continuous variables with rank transformed data using Van der Waerden method. * χ^2test was used for dichotomous or categorical traits (e.g., T2D = Type 2 diabetes and LADA = Latent autoimmune diabetes in adults);N = Sample size; BMI = Body Mass Index; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HbA1c = Hemoglobin A1c; hs-CRP = high-sensitivity C-reactive protein; CKD-EPI (eGFR) = Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR); OHA = Oral hypoglycemic agents; Continuous variables are expressed as mean (standard deviation) and Discrete variables are shown as counts (percentages) (N %); Nominally significant findings ($p < 0.05$) are shown in italics; findings that remain significant after multiple-testing correction ($p < 0.01$) are shown in bold. NOTE: All *p*-values reported here are not corrected for non-independence.

As shown in Table 1, with respect to the treatment regimen at the time of patient recruitment, the percentage of patients receiving insulin treatment (2.5%) was similar in LADA and T2D individuals. However, a higher percentage of LADA individuals (10.0%) were taking combined therapy of insulin and oral hypoglycemic agents (OHA) than the individuals with T2D (5.7%). In contrast, the individuals receiving only OHA as a treatment regimen were found to be relatively higher in T2D group (54.2%) than in LADA group (45.0%).

We used the variance components approach to determine heritability of LADA using a liability model , and GAD65 titer was analyzed as a quantitative trait [36,37]. The GAD65 titer values were inverse normalized for analysis. The models included age and sex terms and study site (two dummy variables) as covariates irrespective of their significance. The heritability (h^2) of LADA was found to be 0.24 but it failed to reach statistical significance ($h^2 = 0.24$ [SE = 0.38], $p = 0.257$). For theGAD65 titer, h^2 was found to be 0.40 (SE = 0.095), and it was statistically significant ($p = 6 \times 10^{-7}$).

4. Discussion

The present study aimed to assess the prevalence of LADA and to characterize the LADA individuals among people with type 2 diabetes recruited as part of the INDIGENIUS consortium studies. LADA prevalence varied descriptively across the three EEGs, with the highest prevalence observed in the Chettiyar group (9.4%), followed by the Agarwal (7.2%) and Reddy (6.3%) groups. However, these differences were not statistically significant ($p = 0.532$). Our study demonstrated that the overall prevalence of LADA in the EEG's was 7.6%, which was higher than the prevalence rates reported by the previous studies [28,29] conducted in Indian population. This finding mirrors the potential influence of ethnic, geographic and genetic backgrounds as they relate to the occurrence of LADA in Indian populations. However, the variation in the prevalence rates could also be due to differences in the study design, lack of appropriate control groups, sex, the type and number of autoantibodies tested, and the sensitivity and specificity of the assay. Further, studies in different populations have shown that around 4–12% of T2D patients are GAD antibody positive [38], and the findings of the present study are in line with the reported data. To the best of our knowledge, this is the first study to examine the prevalence of LADA across different ethnic communities within an Indian population using a uniform, cross-sectional ascertainment scheme. Although prevalence rates varied descriptively, these differences were not statistically significant.

To examine the data further, we opted for the use of combined data from the three EEGs, because of the small sample sizes per EEG. The overall sex-based prevalence of LADA was found to be higher in males (62.5%) compared to females (37.5%); likewise, more males (57.1) were affected with T2D than females (42.9%). These descriptive profiles appear to be similar to those reported by previous studies that showed higher occurrence of T2D and LADA in males than females [28,29,39,40], suggesting that males are more likely to be affected with LADA than females. According to Nordstorm et al. (2016)[41], the increased prevalence of T2D in males compared to females was possibly linked to the larger amount of visceral fat accumulation observed in men compared to women. However, it would be interesting to examine whether such relationships between visceral fat deposition and LADA exist in future studies.

The mean age of individuals with LADA was found to be lower than the individuals with T2D. This finding is consistent with the previous reports [28,29,39,42,43]. Individuals with LADA are usually characterized by early age of diabetes onset (>30 years) along with the presence of auto antibodies. In the present study, the mean age of LADA onset was relatively lower compared to age of onset of T2D. Aside from the issue of significance, the findings of lower mean age and mean age of LADA onset compared to the T2D counterparts are in accordance with the previous studies focused on LADA [28,29,39].

As reported in Table 1, differences in clinical and non-clinical variables between T2D and LADA were examined using appropriate statistical tests. Given the exploratory nature of this study, only variables with $p< 0.05$ are discussed, with an emphasis on those meeting the Bonferroni-adjusted threshold ($p< 0.01$).In regard to the association between LADA and obesity, LADA individuals are known to be leaner compared to individuals with T2D [28,29,39,40,43–45]. In this study, of the three examined obesity-related traits (i.e., BMI, waist circumference and hip circumference), only hip circumference exhibited nominally significant differences. Although it reached only nominal significance, the association between LADA and higher HDL cholesterol compared to T2D in the present study aligns with previous reports [25,26,46,47].].

The main contrasting variables between T2D and LADA were those related to glycemic measures, and the findings of the present study support previous research [28,29,39,40,43–45,47]. The results revealed that glycemic traits—such as fasting glucose and HbA1c levels—were significantly higher ($p< 0.01$) in LADA compared to T2D. Specifically, participants with LADA showed an effect size (Cohen's d) of 0.42 for elevated

glucose concentrations, and 0.39 for elevated HbA1c levels. Thus, individuals with LADA appear to have poorer glycemic control, which may reflect progressive autoimmune β-cell loss and/or delayed intensification of therapy (e.g., insulin initiation). Regarding the link between a family history of diabetes and LADA, the nominally significant finding of this study aligns with previous reports indicating a stronger association with T2D than with LADA [48,49].

Implementing an appropriate treatment strategy for LADA is vital to mitigating disease progression by preserving or ideally restoring residual beta-cell function. Evidence indicates that certain non-insulin therapies, particularly metformin and thiazolidinediones, can play a supportive role in protecting these pancreatic beta cells [50,51]. Although causal relationships cannot be established in this observational study, it is worth noting that the number of individuals receiving combination therapy (oral hypoglycemic agents [OHAs] and insulin) was higher in LADA cases compared to those with T2D. However, a significant proportion of LADA patients (45.0%) were receiving only OHAs, potentially because insulin initiation is driven by clinical management choices, the natural history of the disease and symptomatic presentation at diagnosis [17,52]. Future prospective studies are needed to evaluate the effectiveness of different treatment strategies and their subsequent impact on β-cell function and clinical outcomes in individuals with LADA.

In addition to the above findings, this study uniquely determined the extent to which LADA (as a discrete trait) and GAD65 titer levels (as a quantitative trait) are heritable. The heritability of LADA was found to be 24% but it failed to reach statistical significance. However, the heritability of the GAD65 titer values was determined to be 40% with statistical significance. Regarding the difference in heritability estimates observed above, it is important to note that dichotomization of a continuous or quantitative trait is shown to result in loss of much information and that precision of an estimate and the power to detect a genetic signal is diminished [37].

The findings of this exploratory study must be interpreted in light of several limitations. A major limitation of this study is the use of combined data from three EEGs for statistical reasons. However, the overall findings are in agreement with the previous findings. Another limitation is that the study relied solely on GAD65 positivity to define LADA: the incorporation of ZnT8 and IA-2 antibodies and C-peptide values (predictor of insulin dependency) would have provided a more comprehensive metabolic and immunological profile. However, ZnT8, IA-2 and C-peptide data were not available for this study. Given that GAD65 has well-established diagnostic utility in adults with suspected LADA, it is used as the principal marker of islet autoimmunity. We acknowledge that use of a panel of multiple autoantibodies significantly reduces the risk of misclassifying LADA, and that there is a need for future studies incorporating a broader panel of islet autoantibodies, together with C-peptide measurements, for more comprehensive characterization of LADA. It should be noted that this study was not adequately powered to distinguish group differences in LADA prevalence, and that larger studies specifically designed to compare LADA prevalence across Indian ethnic populations are needed to determine whether true ethnic differences exist. It should be noted that the unadjusted *p*-values were retained to facilitate the interpretation of variable differences, with results between 0.01 and 0.05 considered exploratory. Lastly, to explore the influence of additive genetic factors on LADA or GAD65 titer values, the data were pooled; hence, data should be interpreted with caution.

5. Conclusions

This study revealed a high prevalence of LADA in Indian EEGs. Despite the use of data from limited number of LADA individuals, several of the findings, significant or nominally significant, are in agreement with published studies. The familial occurrence of

LADA observed predominantly in families affected by T2D, with no corresponding occurrence of T1D in this study sample, is an interesting finding that warrants further investigation with population-based studies with systematic analysis of LADA, T1D and T2D to determine their relative prevalence using comparable diagnostic criteria and treatment management in order to characterize the individuals appropriately [53,54]. Overall, individuals categorized as LADA in this study are inferred to have worse glycemic control and differential rate of beta cell destruction. The findings from this study warrant additional studies in the Indian population to precisely diagnose and characterize LADA individuals among individuals with T2D, given the increasing epidemiological burden of T2D in India. It is important to identify specific life or environmental risk factors associated with LADA for developing potential intervention strategies [7,15]. Importantly, longitudinal follow-up is needed to precisely understand the pathophysiology and clinical implications of the disease to identify the optimal therapeutic options for LADA individuals. Lastly, the overall genetic basis of LADA found in this study, together with the information from ongoing genetic studies of LADA elsewhere, mirrors the immediate need not only to identify the specific genetic determinants of LADA but also to determine their interactions with specific environmental or lifestyle factors.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Sri Ramachandra Institute of Higher education and research.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Given attention to the Institutional Ethics Committees policies and the INDIGENIUS Consortium data access policy, restrictions will apply to the availability of data used for this study publicly. However, data will be made available from the authors upon reasonable request, and data access requests should be submitted to the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

LADA	Latent Autoimmune Diabetes in Adults
EEGs	Endogamous Ethnic Groups
T2D	Type 2 diabetes
GAD65	Glutamic acid decarboxylase 65

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