



Research Article

Association of The SLC2A4 (GLUT4) Rs5435 Polymorphism with Type 2 Diabetes Mellitus: A Hospital-Based Case-Control Study from Tamil Nadu, South India

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Abstract: GLUT4, encoded by SLC2A4, mediates insulin-stimulated glucose disposal into muscle and adipose tissue, and impaired translocation is central to insulin resistance. Evidence linking the synonymous variant rs5435 (Asn130Asn) to type 2 diabetes mellitus is inconsistent across populations, and data from Dravidian populations are sparse. **Methods:** In an age- and sex-matched case-control study at a tertiary hospital in Chengalpattu, Tamil Nadu (March 2021 to February 2022), 50 adults aged 30–50 years with type 2 diabetes mellitus defined by World Health Organization criteria and without a first-degree family history of diabetes were compared with 50 normoglycaemic controls. rs5435 was genotyped by allele-specific amplification refractory mutation system PCR, with gels read blind to group. Odds ratios with 95% confidence intervals were derived from observed counts, and Hardy-Weinberg equilibrium assessed among controls. **Results:** Cases and controls were comparable for age (38.74 ± 5.58 versus 38.66 ± 5.77 years, $p = 0.944$), sex ($p = 0.410$) and body mass index ($p = 0.552$). Control genotypes conformed to Hardy-Weinberg equilibrium ($p = 0.83$). The heterozygous TC genotype was present in 41 of 50 cases (82.0%) and 3 of 50 controls (6.0%), giving an odds ratio of 71.4 (95% CI 18.1–281.5; $p < 0.001$). The minor C allele frequency was 41.0% among cases and 3.0% among controls (odds ratio 22.5, 95% CI 6.7–75.8; $p < 0.001$). No CC homozygote was identified. **Conclusions:** rs5435 was strongly associated with type 2 diabetes mellitus in this population. The effect size is implausibly large for a common variant and requires confirmation of allele assignment by sequencing, followed by replication in adequately powered cohorts.

Keywords: Type 2 Diabetes Mellitus, SLC2A4, GLUT4, Rs5435, Single Nucleotide Polymorphism, South India

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INTRODUCTION

India carries one of the largest absolute burdens of type 2 diabetes mellitus (T2DM) in the world. The ICMR-INDIAB national survey estimated that 101 million Indian adults are living with diabetes and a further 136 million with prediabetes, against a global figure of 537 million affected adults in 2021 [1-2]. What distinguishes the Indian phenotype is not prevalence alone but its timing: disease onset occurs nearly a decade earlier and at an appreciably lower body mass index than in European populations, a pattern that implicates constitutional rather than purely environmental determinants [3]. Consistent with this, heritability estimates for T2DM in family-based cohorts approach 0.69 when onset occurs between 35 and 60 years [4].

Among the constitutional determinants under scrutiny, GLUT4 occupies a central position. Encoded by SLC2A4 on chromosome 17p13, GLUT4 mediates virtually all insulin-stimulated glucose disposal into skeletal muscle and adipose tissue, cycling between intracellular storage vesicles and the plasma membrane under the control of phosphatidylinositol 3-kinase and c-Cbl signalling, with a parallel AMP-activated protein kinase route recruited by muscular contraction [5-7]. Defective GLUT4 translocation is a defining lesion of the insulin-resistant state, and expression of the transporter is reduced in adipose tissue from patients with T2DM [5].

Whether common variation in SLC2A4 contributes measurably to disease risk remains unsettled. The exonic variant rs5435 (Asn130Asn) was associated with diabetes in an urban South Indian cohort [8], yielded only a haplotypic signal among Dravidian subjects from Kerala [9], and behaved as a dominant risk factor in a Bangladeshi case-control series [10]. Synonymous substitutions can no longer be presumed to be neutral, since codon usage influences co-translational folding, splicing fidelity, and transcript stability [11].

We therefore examined the genotype and allele distribution of rs5435 among patients with T2DM and matched normoglycaemic controls at a tertiary hospital in Chengalpattu, Tamil Nadu.

MATERIALS AND METHODS

Study Design and Setting

This hospital-based, age- and sex-matched case–control study was conducted in the Department of Biochemistry, in collaboration with the Department of General Medicine, at the Government Medical College and Hospital, Chengalpattu, Tamil Nadu, between March 2021 and February 2022. Reporting conforms to the STROBE statement and to its STREGA extension for genetic association studies [12-13].

Participants

Cases were adults aged 30–50 years attending the diabetic clinic with type 2 diabetes mellitus defined by World Health Organization criteria, namely fasting plasma glucose ≥ 126 mg/dL together with a 2-hour post-prandial value >200 mg/dL [14]. Individuals with a first-degree family history of diabetes were excluded to limit confounding by shared familial background, as were those with hypertension, anaemia, malnutrition, pancreatitis or malignancy, each of which may independently disturb glycaemia. Controls were normoglycaemic adults attending the same general medicine outpatient department, matched to cases for age and sex, with fasting plasma glucose <100 mg/dL, 2-hour post-load glucose <140 mg/dL, HbA1c $<6.0\%$, no personal or first-degree family history of diabetes or autoimmune disease, and no hypertension. Fifty participants were recruited consecutively into each group. Sample size was governed by the specimens and genotyping reagents available within the study period rather than by an a priori calculation. In a post hoc estimate, 50 participants per group and an observed control minor allele frequency of 3% gave 80% power at a two-sided α of 0.05 to detect an allelic odds ratio of approximately 5.3; the study was therefore capable of identifying only substantial effects.

Ethical Approval

The protocol was approved by the Institutional Ethics Committee of Government Medical College, Chengalpattu, and the study was conducted in accordance with the Declaration of Helsinki [15]. Written informed consent was obtained from each participant in the local language after the purpose of the study, the procedures involved, and the implications of genetic testing were explained. Specimens were coded at collection, and all subsequent laboratory work was performed under those codes.

Specimen Collection and DNA Extraction

Five millilitres of peripheral venous blood were drawn into ethylenediaminetetraacetic acid under aseptic precautions. The buffy coat was separated by centrifugation at 2,500 rpm for 20 min, and genomic DNA was extracted using a silica-membrane spin-column kit (HELINI Biomolecules, Chennai, India) employing proteinase K digestion in a chaotropic lysis buffer. DNA concentration and purity were assessed spectrophotometrically; extracts yielded approximately 20 ng/ μ L with A260/280 ratios exceeding 1.7 and were stored at -20°C until amplification.

Genotyping of rs5435

rs5435 was genotyped by allele-specific amplification refractory mutation system (ARMS) PCR [16], using a commercial human SNP genotyping kit supplying separate wild-type and mutant primer mixes. Each 25 μ L reaction contained 10 μ L master mix, 5 μ L primer mix and 10 μ L template DNA (5–20 ng). Cycling comprised enzyme activation at 95°C for 5 min, followed by 35 cycles of 95°C for 30 s, 58°C for 30 s and 72°C for 30 s, with a final extension at 72°C for 5 min. Amplicons were resolved on 2% agarose stained with ethidium bromide at 100 V for 45 min against a 100 bp ladder and visualised under ultraviolet transillumination. The wild-type T allele generated a 196 bp product and the variant C allele a 350 bp product; heterozygotes displayed both bands. A no-template control was included in every run, and gels were read independently by two observers blinded to case–control status, with discordant calls resolved by repeat amplification.

Biochemical Measurements

Fasting and 2-hour post-prandial plasma glucose levels were measured by the glucose oxidase–peroxidase end-point method, with absorbance read at 505 nm [17]. HbA1c was determined by cation-exchange high-performance liquid chromatography using NGSP-certified, DCCT-aligned calibration. Internal quality-control material was analysed alongside each batch of samples.

Statistical Analysis

Analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables, all of which satisfied tests of normality, are presented as mean $\pm$ SD and compared by unpaired Student's *t* test; categorical variables are presented as *n* (%) and compared by Pearson's χ^2 test. Departure from Hardy–Weinberg equilibrium was assessed

among controls alone, since cases are not expected to conform under a true association [18]. Odds ratios with 95% confidence intervals were derived directly from the observed genotype and allele counts, taking the TT genotype and the T allele as reference. A two-sided p-value below 0.05 was regarded as significant.

RESULTS

Participant Characteristics

One hundred participants were enrolled, comprising 50 patients with type 2 diabetes mellitus and 50 normoglycaemic controls. The two groups were closely comparable in age, sex distribution and body mass index, none of which differed significantly, confirming that matching was achieved (Table 1). Both groups were obese by Asian-Indian criteria, so adiposity is unlikely to account for any difference observed between them.

Genotype Distribution of rs5435

Only two genotypes were encountered: the homozygous wild-type TT and the heterozygous TC; the homozygous variant CC was not observed in either group (Table 2, Figure 1A). Genotyping succeeded in all 100 specimens, with no failed or ambiguous reactions and concordant no-template controls throughout. The homozygous and heterozygous banding patterns were readily distinguished on electrophoresis (Figure 2).

Among controls the genotype distribution conformed to Hardy–Weinberg equilibrium ($\chi^2 = 0.05$, $p = 0.83$). Cases departed markedly from equilibrium ($\chi^2 = 24.15$, $p < 0.001$), which is the expected consequence when a variant is genuinely enriched in an affected group rather than an indication of genotyping error. Heterozygosity was present in 41 of 50 cases (82.0%) but in only 3 of 50 controls (6.0%), giving an odds ratio of 71.4 (95% CI 18.1–281.5; $p < 0.001$). Because no CC homozygotes were identified, the heterozygote and dominant models are numerically identical, and recessive and additive models could not be fitted.

Table 1: Demographic and Anthropometric Characteristics of Cases and Controls

Variable	Cases (n = 50)	Controls (n = 50)	Test statistic	p value
Age (years)	38.74±5.58	38.66±5.77	t = 0.07	0.944
Male sex, n (%)	17 (34.0)	21 (42.0)	$\chi^2 = 0.68$	0.410
Female sex, n (%)	33 (66.0)	29 (58.0)	—	—
Body mass index (kg/m ²)	31.57±5.56	30.92±5.34	t = 0.60	0.552

Values are mean±SD unless stated otherwise. Continuous variables compared by unpaired Student's t test, categorical variables by Pearson's χ^2 test

Table 2: Genotype Distribution of SLC2A4 rs5435 in Cases and Controls

Genotype	Cases, n (%)	Controls, n (%)	Odds ratio (95% CI)	p value
TT	9 (18.0)	47 (94.0)	1.00 (reference)	—
TC	41 (82.0)	3 (6.0)	71.4 (18.1–281.5)	<0.001
CC	0 (0.0)	0 (0.0)	Not estimable	—

Table 3: Allele Distribution of SLC2A4 rs5435 in Cases and Controls

Allele	Cases, n (%)	Controls, n (%)	Odds ratio (95% CI)	p value
T	59 (59.0)	97 (97.0)	1.00 (reference)	—
C	41 (41.0)	3 (3.0)	22.5 (6.7–75.8)	<0.001

Allele counts are out of 100 alleles per group (50 participants). Pearson's $\chi^2 = 42.07$, 1 df

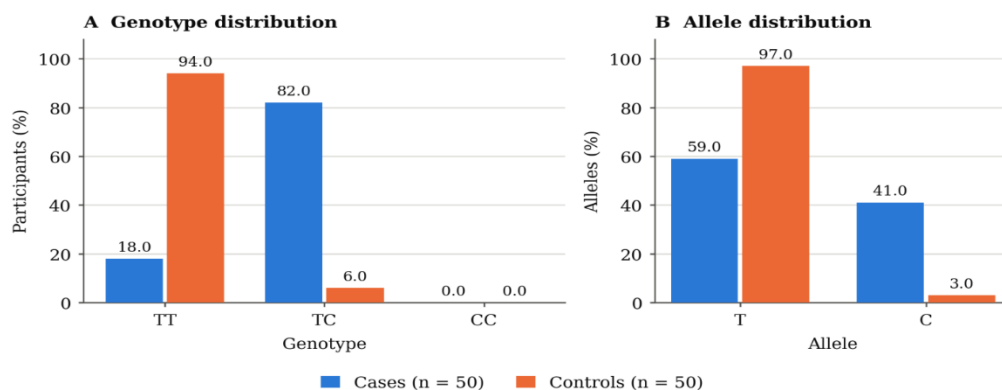


Figure 1: Distribution of SLC2A4 rs5435 Genotypes and Alleles in Cases and Controls

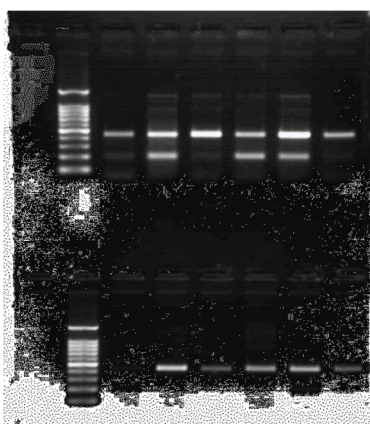


Figure 2: Representative Agarose Gel Electrophoresis of ARMS-PCR Products for SLC2A4 rs5435

(A) Genotype frequencies, expressed as a percentage of participants in each group. (B) Allele frequencies are expressed as a percentage of the 100 alleles carried by each group. No CC homozygote was observed in either group. Genotype comparison, TC versus TT: odds ratio 71.4 (95% CI 18.1–281.5), $p < 0.001$. Allele comparison, C versus T: odds ratio 22.5 (95% CI 6.7–75.8), $p < 0.001$.

Two representative electrophoretic runs are shown. Genomic DNA was amplified with allele-specific primer mixes and the products resolved on 2% agarose stained with ethidium bromide at 100 V for 45 min, with a 100 bp ladder in the left-hand lane of each run and a no-template negative control included in every reaction set. The wild-type T allele yields a 196 bp product and the variant C allele a 350 bp product; homozygous TT specimens therefore give a single band and heterozygous TC specimens give two. Reproduced without alteration from the original gel documentation.

DISCUSSION

Summary of Study Findings

In this age-, sex- and body mass index-matched case–control study of 100 adults from Chengalpattu, heterozygosity at SLC2A4 rs5435 was markedly over-represented among patients with type 2 diabetes mellitus. The TC genotype was carried by 82.0% of cases against 6.0% of controls, and the minor C allele accounted for 41.0% of alleles among cases against 3.0% among controls. No CC homozygote was encountered in either group. Control genotypes conformed closely to Hardy–Weinberg expectations while those of cases did not, a pattern consistent with genuine enrichment of the variant in the affected group rather than with technical error. The direction of the association is therefore unambiguous, although the width of the confidence intervals means its magnitude is not.

Comparison with Existing Literature

Published findings on rs5435 are inconsistent, and the present result sits at the extreme end of the reported range. Bodhini and colleagues, genotyping 1,006 patients and 1,017 normoglycaemic subjects from the Chennai Urban Rural Epidemiology Study by polymerase chain reaction–restriction fragment length polymorphism, reported a modest but significant association, with an odds ratio of 1.26 (95% CI 1.00–1.57) for variant carriers relative to the common homozygote [8]. Nair and colleagues, examining 1,002 patients and 1,000 controls of Dravidian ancestry in Kerala, found no single-marker association, although a four-SNP haplotype incorporating rs5435 was marginally associated ($p = 0.01$) and the authors noted an appreciable difference in minor allele frequency between groups [9]. In a smaller Bangladeshi series of 127 patients and 112 controls, in which the exons of SLC2A4 were sequenced and rs5435 typed by a TaqMan assay, the allelic comparison was null (odds ratio 1.31, $p = 0.13$) yet a dominant model reached significance ($p = 0.042$); in silico modelling indicated that the variant introduces an energetically unfavourable loop into the mRNA secondary structure [10].

The allelic odds ratio of 22.5 observed here exceeds anything previously reported for this variant by more than an order of magnitude, and lies well outside the range plausible for a common polymorphism in a polygenic disorder. Two explanations warrant serious consideration. The first is generic: initial reports of genetic associations characteristically overstate effect size, and small studies are the most vulnerable to this inflation, a phenomenon documented across hundreds of candidate-gene investigations [20–21]. The second is specific to these data. Allele designations are not concordant across studies in the Chennai cohort, the CC genotype served as the common reference, and T was the minor allele, whereas here TT was carried by 94% of controls, and C was the minor allele. Because rs5435 is annotated on both

strands in different sources, this reversal most probably reflects the orientation of the commercial ARMS primer set rather than a true inversion of allele frequencies between two Tamil Nadu populations separated by some sixty kilometres. Sanger sequencing of a subset of specimens would resolve the question and should precede any further interpretation of the effect size.

The divergence between the Chennai and Kerala studies is itself instructive, since both were large, both were conducted in Dravidian populations, and both used comparable case definitions. Where a variant is not itself causal but is merely correlated with an unobserved functional site, the strength of that correlation varies between populations, so a marker that performs well in one Dravidian subgroup may fail in another; differences in ascertainment, in the glycaemic threshold applied to controls, and in the proportion of undiagnosed disease among those controls compound the effect. This is the ordinary reason why candidate-gene findings replicate poorly, and it argues for caution rather than for discarding either result. It also underlines why population-specific work retains value in India, where type 2 diabetes presents a decade earlier and at lower adiposity than in European populations and where the genetic architecture cannot be assumed to be transferable [3,4].

Biological plausibility, by contrast, is not in doubt. rs5435 is a synonymous substitution at Asn130, and synonymous variants can no longer be dismissed as functionally inert. The canonical demonstration came from ABCB1, in which a silent change altering codon usage yielded a P-glycoprotein of identical amino acid sequence but altered conformation and substrate specificity, apparently through effects on the timing of co-translational folding [19]. Analogous mechanisms, disruption of exonic splicing enhancers, activation of cryptic splice sites, and destabilisation of mRNA secondary structure, offer credible routes by which a silent change in SLC2A4 might impair GLUT4 expression or trafficking [11]. Given the position of GLUT4 as the terminal effector of insulin-stimulated glucose disposal [5,7], even a modest reduction in functional transporter density would be expected to manifest clinically as insulin resistance.

Clinical Implications

The clinical implications are modest at this stage and should not be overstated. An association demonstrated in 100 individuals, however strong the point estimate, does not constitute a screening test, and nothing in these data justifies genotyping patients in routine practice. The more defensible near-term implication is for research design: rs5435 merits inclusion in candidate variant panels assembled for Indian populations, and the strength of the signal observed here argues for its incorporation into adequately powered replication cohorts rather than for its clinical deployment. Should replication confirm even a fraction of this effect, family-based risk stratification in first-degree relatives of affected individuals, a group already at elevated risk and already the target of lifestyle intervention, is the setting in which genotyping would most plausibly earn its place. That prospect remains hypothetical until replication is achieved.

Strengths and Limitations

The study has several genuine strengths. Cases and controls were matched for age and sex and did not differ in body mass index, making adiposity the single most powerful confounder in this setting and an unlikely explanation for the observed difference. Cases with a first-degree family history of diabetes were excluded, so the association cannot be attributed to gross familial aggregation. Control genotypes satisfied the Hardy–Weinberg equilibrium, consistent with sound genotyping and the absence of gross stratification in the control sample. Genotyping was complete, with no failed or ambiguous reactions, and both biochemical assays were standardised. The limitations are equally clear and, in several respects, substantial. Fifty participants per group confers 80% power only for allelic odds ratios of approximately 5.3 or greater, so the study was constitutionally incapable of detecting the modest effects that characterise most common variants in type 2 diabetes; the correspondingly wide confidence intervals mean the point estimates convey direction and approximate magnitude but not precision. A single variant was examined without adjustment for other susceptibility loci, dietary pattern, physical activity or ancestry, and no ancestry-informative markers were genotyped, so residual population stratification within Dravidian subgroups cannot be excluded [21]. Recruitment was hospital-based, and controls were drawn from the same outpatient department, which limits generalisability to the source population. The complete absence of CC homozygotes precluded recessive and additive modelling and may itself signal a limitation of the allele-specific assay rather than a true feature of the population. Genotyping was not confirmed by sequencing. Finally, the cross-sectional design permits no inference about causal sequence, and analyses relating genotype to the glycaemic indices measured at enrolment are not reported here.

CONCLUSION

In this hospital-based case–control study from Tamil Nadu, the SLC2A4 rs5435 polymorphism was strongly associated with type 2 diabetes mellitus, the heterozygous TC genotype and the minor C allele both being substantially more frequent among cases than among matched normoglycaemic controls. The finding is directionally consistent with an earlier report from urban South India, though the effect size observed here is implausibly large for a common variant

and is best interpreted as evidence of association rather than as a usable estimate of risk. Confirmation of the assay's allele assignment by sequencing, followed by replication in an adequately powered, ancestry-matched cohort, is required before rs5435 can be considered an established susceptibility marker in this population.

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