SUMO4 163G>A variation is associated with nephropathy in type 2 diabetes in Indian population
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Background and Objectives

- Diabetic nephropathy- leading cause of end stage renal disease
- 25% to 40% of patients with diabetes develop diabetic nephropathy
- In India diabetic nephropathy is the commonest (44%) cause of ESRD.
- The pathogenesis of DN appears to be multifactorial
- Genetic susceptibility plays an important role in the pathogenesis DN
- Single nucleotide polymorphisms (SNPs) are considered to be useful markers to identify genetic variants that may confer susceptibility to etiologically complex diseases
- SUMO4 (small ubiquitin-related modifier 4) mRNA was recently found to be mainly expressed in the kidney
- Substitution of methionine with valine at codon 55 (M55V) of SUMO4 may induce higher nuclear factor-κB activity which is known to mediate the development of diabetic nephropathy
- This study was designed to investigate the association of SUMO4 163G>A variation with nephropathy in type 2 diabetes mellitus (T2DM).

Subjects and Methods

Study design
This case–control study carried out at PGIMER Chandigarh. Study was approved by the institute Ethics Committee and written informed consent was taken.

Patient selection
- A total of 417 type 2 diabetic subjects: 216 without nephropathy (DM) and 201 with nephropathy (DN)
- Diabetic nephropathy (DN) group: (a) eGFR<60ml/min (b) proteinuria 500mg/day
- Type 2 diabetes (DM): a) duration of onset > 5 years
b) negative for dipstick urinary protein
- Urinary albumin >150 mg/day

Polymorphisms selected for the study

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism Position</th>
<th>Effect</th>
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<tbody>
<tr>
<td>SUMO4</td>
<td>163G&gt;A (M55V) 5q25. at 163 nucleotide region in coding region</td>
<td>Enhances protein stability and modulates subcellular localization</td>
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</tbody>
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Genetic analysis
- Genomic DNA isolated from peripheral blood leukocytes using standard phenol-chloroform method
- Polymorphism analyzed using specific primer pairs by PCR-RFLP

Primer pairs & Restriction Enzymes used for genotyping

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Primers</th>
<th>Restriction enzyme</th>
<th>Restriction digestion product (base pair)</th>
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Statistical analysis
Data are expressed as the means±SD. Continuous and nominal variables were compared with t-test and χ2 test in DM and DN groups. Parameter with skewed distribution were analysed with Mann–Whitney U test. Hardy Weinberg equilibrium (HWE) was tested for each SNP using the data obtained by genotyping healthy controls. Allelic and genotypic associations of SNPs were evaluated by Pearson’s χ2 test and odds ratio (OR) and 95% confidence intervals (CI). One-Way ANOVA was used for more than two variables.

Conclusions
- The duration of diabetes was higher in DN compared to DM (p=0.001) and prevalence of retinopathy, neuropathy and hypertension was higher in DN.
- GA & AA genotype was higher in DM compared to DN. GG genotype was significantly more frequent in DN as compared to DM (p=0.018, OR=1.72 (1.1-2.7)).
- G allele was more frequent in DN compared to DM (p=0.017, OR=1.4, (1.1-1.8)). GG+GA genotype was associated with duration of diabetes (p=0.01).

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