Madhukar Saxena, J Diabetes Metab 2014, 5:10
http://dx.doi.org/10.4172/2155-6156.S1.028

OMICS Group Conferences
Accelerating Scientific Discovery

5th World Congress on
Diabetes & Metabolism
November 03-05, 2014 Embassy Suites Las Vegas, USA

IL-1β, IL-1Ra and *IL-18* gene variants in type 2 diabetes

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Type 2 diabetes mellitus (T2DM) is a complex disease characterised by elevated fasting or post-prandial systemic glucose concentrations. Multiple loci pre-disposing to T2DM have been discovered, many of which have emerged from genome-wide association studies. The interleukin (IL-1) gene cluster within chromosome 2q13-14 contains genes coding for both anti- and pro-inflammatory cytokines, including *IL-1*β and *IL-1Ra.* These cytokines are produced by a variety of cell types, for example, monocytes, magrophages and keratinocytes. The IL-1 family consists of two pro-inflammatory cytokines viz. IL-1α, IL-1β and a naturally occurring anti-inflammatory agent, the IL-1 receptor antagonist (*IL-1Ra* or *IL-1RN*). It has been recently suggested that prolonged exposure of human islets to high glucose trigger IL-1β production by the β-cells themselves leading to nuclear factor activation and upregulation of Fas signaling thus triggering "autocrine apoptosis". Therefore, genes encoding these cytokines are important candidates which may be implicated in pathogenesis of T2DM and associated complications. DNA was isolated from venous blood samples, quantified and subjected to Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) using suitable primers and restriction endonucleases. The genotypic, allelic and carriage rate frequencies distribution in patients and controls were analyzed by PSAW software (ver. 17.0). Odd ratios (OR) with 95% confidence interval (CI) was determined to describe the strength of association by logistic regression model. All three genetic variants *IL-1β* (-511 C/T), *IL-18* (-607 A/C) and *IL-1*Ra VNTR (intron 2) showed significant association (P<0.000). However, significant associations were also observed with biochemical parameters. Moreover in haplotypic analysis, none of the combinations of alleles showed significant association with the disease. However, it was observed that I and II alleles of *IL-1*Ra may be involved in the T2DM predisposition. This is the first report from India showing the association of IL-1 superfamily gene variants with T2DM. The study will probably increase our insight into the proposed impact of IL-1 in the development and/or progression of T2DM and plays a prominent role with respect to its susceptibility in North-Indian population.

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