

# Role of molecular genetics in diabetic foot ulcer

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This issue of the journal features an important article by Mrozikiewicz-Rakowska et al<sup>1</sup> on the role of the allelic variant rs2274907 of the *ITLN1* gene in patients with diabetic foot (DF). The paper focuses on the association of the allelic variance of the omentin gene with the occurrence of DF among patients with type 2 diabetes mellitus.

Foot complications in type 2 diabetes are a major physical and socioeconomic burden. Recurrent foot infection is common in patients with type 2 diabetes, and lower joint mobility and high plantar pressure are the major determinants of foot ulcer in susceptible diabetic patients with neuropathy.<sup>2</sup> Among all the complications associated with diabetes, DF is the most expensive—a recent study reported that the cost of diabetes care for a patient with foot ulcers was more than 4 times higher and is a common cause for hospital admission.<sup>3,4</sup> In diabetic patients, foot problems are considered as the major factor contributing to increased morbidity and mortality, and the economic impact of foot disease is substantial.<sup>5</sup> The known risk factors for DF are neuropathy, peripheral arterial disease, and poor glycaemic control. There are certain extrinsic factors like trauma, high plantar pressure, and poor foot care practices that also lead to DF. These are the traditional risk factors implicated in DF.<sup>6,7</sup> However, recent studies have also considered the role of molecular genetics in the development of DF.

Mrozikiewicz-Rakowska et al<sup>1</sup> has assessed the effect of genetic diversity by studying the allelic variance of the *ITLN1* gene and its impact on the development of DF. The study has also reported a higher incidence of ischemic heart disease and comorbidities such as diabetic retinopathy, diabetic neuropathy (DN), dyslipidemia, and obesity. The authors also highlighted that the A allele of *ITLN1*, rs2274907, is sex-specific and is present in men. Thus, men with this single nucleotide variant (SNV) are susceptible to DF.

HSP70 has been proposed to be involved in the wound healing process, which is supported by the finding that its expression is rapidly induced after the skin has been wounded in animal models. Heat-shock proteins (HSPs) are molecular

chaperones synthesized under stressful conditions. They are important in physiological and pathological processes and are highly active within the immune system. In normal physiological conditions, HSPs are expressed at low levels. However, in response to cellular stress, there is an increased expression of HSPs. They protect against tissue injury by maintaining synthesis and proper conformation of proteins by repairing damaged proteins and promoting the healing of injured tissue.

Dhamodharan et al<sup>8</sup> reported a correlation between the SNV of the HSP70-hom gene and the occurrence of foot ulcer in patients with type 2 diabetes. Findings indicate that the HSP70-hom T/T genotype is highly associated with patients with DFU and their functional polymorphism may play an important role in the pathogenesis of DFU in type 2 diabetes in South Indian population.

Wound healing mainly depends on the oxygen concentration at the site of the wound. Relative hypoxia is essential in wound healing because it normally plays a pivotal role in the regulation of all the critical processes involved in tissue repair. Adaptation to low oxygen tension (hypoxia) in cells and tissues leads to the transcriptional induction of a series of genes that participate in angiogenesis, iron metabolism, glucose metabolism, and cell proliferation and survival. The primary factor mediating this response is the hypoxia-inducible factor 1 (HIF-1), an oxygen-sensitive transcriptional activator.

A South Indian study<sup>9</sup> investigated the HIF-1 $\alpha$  gene rs11549465 SNV, a C to T nonsynonymous SNV (g.C45035T) resulting in a substitution of proline to serine (P582S) in exon 12. The study suggests that there was a significant association of T allele containing the genotypes (CT + TT) of the HIF-1 $\alpha$  gene allelic variant in patients with DFU compared with healthy controls. On the other hand, the genomic and allelic frequencies of patients with type 2 diabetes without DFU and healthy controls were not significant. Moreover, the study showed a decreased HIF-1 $\alpha$  gene expression in patients with foot ulcer, suggesting its possible role on the pathogenesis.

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In diabetic foot ulcers (DFUs), the immune cells overexpress proinflammatory cytokines (interleukins [IL] 1 and 6, and tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ]) and chemokines (eg, CCL2, stromal cell-derived factor 1 [SDF-1]) and are not able to clear infections, thereby extending the inflammatory phase. SNVs in the promoter/intronic regions of the cytokine/chemokine genes alter transcript levels and have functional significance. Towards this end, a recent study<sup>10</sup> also investigated the role of IL-6, TNF- $\alpha$ , and SDF-1 SNVs in DFU and correlated it with the serum levels of IL-6, TNF- $\alpha$ , and SDF-1 and other inflammatory/diabetogenic markers. The 3 novel findings were as follows: 1) IL-6-174 CC and GC genotypes provided significant protection against diabetes but not against DFU; 2) TNF- $\alpha$ -308 AA and GA genotypes were associated with significant susceptibility towards diabetes and DFU-DN; and 3) SDF-1 801 AA and GA genotypes provided significant protection against both diabetes and DFU-DN. Overall the IL-6, TNF- $\alpha$ , and SDF-1 SNVs, apart from controlling serum cytokine levels, affected various risk factors of DFU. However, more longitudinal and prospective studies are required to determine whether these SNVs contribute to DF by predisposing to the already known risk factors such as DN or peripheral arterial disease or directly affect the development of DF.

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