

## SHORT COMMUNICATION

## THE COMPLEX RELATIONSHIP OF PARAOXONASE GENE POLYMORPHISMS WITH CORONARY ARTERY DISEASE AND LIPID METABOLISM

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Cardiovascular disorder (CVD) is one of the major reasons for mortality in developing and developed countries. According to the World Health Organization (WHO), non-communicable diseases (NCDs) are responsible for 50% of the overall disease burden in Pakistan. And among the NCDs, the most prevalent disease is CVD, as approximately every 1 out of 4 adults suffered from coronary artery disease (CAD). Coronary artery disease mainly causes ischemia or hypoxia of the heart due to coronary vessels stenosis or atherosclerosis.<sup>1</sup> The key risk factors include smoking, dyslipidemia, hypertension, obesity, family history, and type 2 diabetes mellitus. The genetic contribution to CAD is an independent factor that includes genetic polymorphisms such as single nucleotide polymorphisms (SNPs). Genome-wide association studies (GWAS) suggest many genes SNPs involved in the pathogenesis of coronary artery disease.<sup>2</sup> Although many studies identified the genes and single nucleotide polymorphisms but still, the role of these genetic factors is not clearly understood.

Paraoxonase (*PON*) gene cluster is one of the most widely studied genes that consist of three genes *PON1*, *PON2*, and *PON3*, and located on chromosome 7. The *PON2* is the oldest gene among this cluster however, all the 3 genes have a high structural homology. The International Union of Biochemistry and Molecular Biology classified the paraoxonases as arylalkyl phosphatases. The enzymes coded by these gene clusters exhibit the antiatherosclerotic properties that play an essential role in high-density lipoproteins (HDL) or antioxidant properties. The *PON1* activity is highly influenced by both genetic (non-modifiable) and environmental factors (modifiable).<sup>3</sup> It involves a complex interaction between both genetic and modifiable factors. The human *PON1* is a calcium-dependent glycoprotein that is first identified by its ability to hydrolyze various organophosphates. Through lipid peroxides hydrolysis, it reduces the low-density lipoprotein (LDL). Low enzyme levels are associated with cardiac disorders, familial hypercholesterolemia, and diabetes mellitus. To date, approximately 184 SNPs reported, and some coding region SNPs i.e. rs662 and rs854560 are the most widely studied single nucleotide polymorphisms.<sup>4</sup> The most commonly studied Q192R polymorphism is

associated with poor patient outcomes. The risk allele or R allele is associated with abnormal HDL and triglycerides levels and the worst CVD outcome. Furthermore, the levels of paraoxonase levels are also decreased in CVD patients and there is a complex relationship between different variables particularly genetic markers, lipid profile, or environmental factors with *PON* activity.<sup>5</sup> The *PON2* and *PON3* similarly play a crucial role in lipid metabolism and inhibit atherosclerosis due to their protective role against the formation of atherosclerotic plaques in coronary arteries. In *PON2* rs12704796 is significantly associated with coronary heart disease risk.<sup>6</sup> Robertson et al. first reported single nucleotide polymorphism in *PON3* at positions number 107 and 99 but the exact mechanism of these SNPs in the pathophysiology of CAD remains to be understood.<sup>7</sup> The multi-locus model also revealed a gene to gene interaction between *PON2* and *PON3* and gene-environment in the Pakistani cardiac patients.<sup>8</sup>

The single nucleotide polymorphisms in this gene cluster are significantly important in CAD patients. These SNPs may exert their effect by modulating the lipid metabolism and enzyme concentrations in CAD patients, which can be varied according to certain environmental factors and ethnic groups. Thus, in the future, it is suggested to perform a study with more sample size in different populations that can help us in better understanding disease pathophysiology and prevention.

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