NEWS
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Statin Safety Linked to Vascular Genes by Novel PhysioGenomics™ Technology at Genomas

(Hartford, CT) - Research conducted by Genomas®, Inc. and collaborators at Hartford Hospital, University of California - San Francisco and Yale University School of Medicine has demonstrated a strong association between serum markers of muscle injury during statin treatment and variability in genes related to vascular function. The research, published in the December issue of the London-based journal *Pharmacogenomics*,* suggests that vascular smooth muscle function may contribute to the muscle side effects of statins.

Statins are highly effective at reducing coronary disease risk and are currently the most prescribed drugs in the USA. The main side effects are various muscular ailments ranging from mild pain to disabling weakness. Until now, most of the muscular effects of statins had been ascribed to skeletal muscle, as suggested by clinical manifestations of muscular ailments and by muscle biopsies. However, these study results relate serum creatine kinase (CK) activity during statin therapy to two genes affecting vascular tone and raise the possibility that statins may affect smooth muscle. The genes are angiotensin II receptor-1 (AGTR1) and nitric oxide synthase-3 (NOS3).

Paul D. Thompson, M.D., Director of Preventive Cardiology, Hartford Hospital, commented: "These results are intriguing and suggest that statins may affect skeletal muscle by a totally unexplored pathway. We will be undertaking the required clinical validation in other cohorts as the next step in this research."

Gualberto Ruaño, M.D., Ph.D., President, Genomas, stated: "Establishing the link between statins and vascular smooth muscle is a powerful demonstration of our PhysioGenomics technology. The proprietary vascular gene markers add to our expanding intellectual property portfolio to be deployed into PHYSIOTYPE™ Diagnostic Systems for statin safety and personalized cardiovascular medicine."

Last October, Genomas launched its HILO*met* PHYSIOTYPE System for individualized drug safety and announced an agreement with Clinical Laboratory Partners (CLP), Newington, CT for its distribution. The HILO*met* system and tests have significant applications in the management of depression, hyperactivity disorder and thromboembolism, conditions where medications require individualized adjustment and patients require careful monitoring to avoid side effects. The company had introduced these tests as analogous to 'DNA seatbelts' for drugs and patient safety.

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SCIENTIFIC BACKGROUND

*The full citation for the publication is *"Physiogenomic analysis links serum creatine kinase activities during statin therapy to vascular smooth muscle homeostasis", by* Ruaño G, Thompson PD, Holford TR, Wu AHB, et.al, ***Pharmacogenomics,*** Vol. 6, No. 8 (December), 2005. The paper can be accessed at *www.genomas.net* in the Publications section.

PhysioGenomics – a medical application of sensitivity analysis – utilizes as input the variability of genes, measured by single nucleotide polymorphisms (SNPs) and determines how the SNP frequency among individuals relates to the variability in physiological characteristics, the phenotype. Using this approach, genetic associations to a phenotype are used to suggest physiological mechanisms underlying it.

To search for physiologic factors possibly influencing statin muscle injury, the team examined the relationship between genes affecting vascular function and serum CK activity in 102 patients on statin therapy from Hartford Hospital. Muscle breakdown leads to elevated CK activity in the blood. Hence, serum CK levels can be used as a clinical indicator of the extent of muscle injury. PhysioGenomics analysis and a cross section of serum CK levels in these patients suggested that genetic variants in two vascular genes are highly significantly associated with CK activity in patients on statin therapy.

The endothelium regulates vascular tone through the release of vasoactive substances, such as angiotensin II and nitric oxide. Angiotensin II stimulates a variety of pro-atherogenic responses, such as expression of adhesion molecules, platelet aggregation, thrombosis and cell migration. The scientists included its receptor, AGTR1 in the survey, and found it to demonstrate the most significant genetic association to serum CK activity. Nitric oxide, the most important vasodilator, is generated by endothelial nitric oxide synthase (NOS3). NOS3 was the second ranking gene in the survey, and also very significantly associated with serum CK activity.

ABOUT GENOMAS

Genomas Inc. is a biomedical company advancing personalized health with revolutionary diagnostic PHYSIOTYPE™ systems to treat metabolic conditions induced by drugs and by obesity in cardiovascular and psychiatric medicine. PHYSIOTYPE systems provide physicians with the unprecedented capability to prescribe personalized drug treatments avoiding side effects and to recommend highly effective preventive exercise and diet programs for each patient. Genomas is located in Hartford, CT on the campus of Hartford Hospital with which it has established a research and development partnership in personalized medicine. For more information please access www.genomas.net

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