IN VITRO METHOD FOR EARLY DIAGNOSIS OF AORTIC-VALVE DISEASE

Summary:

There is an unmet medical need of finding reliable methods for the diagnosis of calcific aortic valve disease (CAVD) at early stages. Approximately 2–4 % of people aged over 65 will develop CAVD, and 25 % of individuals in this age group with disease symptoms, have a 50 % increased risk of cardiovascular related events. Moreover, there is an associated risk of 80 % of progression over 5 years, to heart failure, aortic valve replacement or death. The early diagnosis of CAVD by detecting aortic valve calcification could allow us to improve patient´s clinical management.

CNIC researchers have identified four differentially expressed genes whose circulating expression levels can determine if a subject is suffering from aortic valve calcification, either in a clinical or subclinical stage. These genes can also be used for the differential diagnosis between CAVD and subclinical aortic-valve calcification. Diagnosis/biotech companies are sought for a license agreement.

Innovative aspects:

Calcific aortic valve disease (CAVD) is a chronic disorder typified by ectopic mineralization and fibrosis of the aortic valve (AV), which may progress to the stage of aortic stenosis (AS). Untreated severe AS leads to heart failure, with valve replacement remaining the only available treatment. Severe AS is preceded by aortic sclerosis, a subclinical form of CAVD that develops over many years without hemodynamic consequence.

Studies performed in the last decade have underlined that lipids and inflammation are important mediators of AV calcification and fibrosis. CAVD is an active process that shares mechanistic features with atherosclerosis.

Transcriptional profiling of CAVD has helped to identify hundreds of genes differentially expressed between calcified and normal valves. Multi-omics have provided a high-resolution expression atlas and established potential drivers of disease progression. Despite this progress, there is no medical therapy that has been proven to be effective in preventing the progression to severe disease.

Current methods for diagnosis aortic valve disease are mainly performed when symptoms appear. In addition, detecting calcification in the aortic valve may not be accurate enough by echocardiography. Moreover, computed tomography, the reference imaging modality to detect calcium, implies higher radiation exposure, the requirement for a high degree of technical expertise and may not be available in medical centers with very limited resources. Therefore, there is a need to find new biological markers that could complement imaging modalities to detect early changes, especially early calcification.

A search for genes shared between gene datasets from CAVD patients and datasets generated from asymptomatic subjects from the Progression of Early Subclinical Atherosclerosis (PESA) cohort with subclinical aortic valve disease (with calcification and without functional stenosis) identified several marker genes for calcification in peripheral blood of asymptomatic individuals. When combined in multiplex quantitative RT-PCR assays, these marker genes showed high sensitivity and specificity for predicting CAVD.

Specifically, by comparing the CAVD transcriptomes and whole blood from datasets of the subclinical PESA study population, CNIC researchers have identified six differentially expressed genes, four of which were specific for aortic valve calcification and found to predict

subclinical disease in addition to calcific aortic valve disease. This analysis therefore identified a gene expression signature in blood that is highly predictive of valve disease and aortic valve calcification in otherwise healthy individuals.

These blood-based biomarkers with predictive potential are an important step in clinical management of CAVD. They could improve the diagnosis of exclusion of CAVD in the emergency department or health centers (before seeing the cardiologist) and avoid late diagnoses with severe ventricular dysfunction, so that they will arrive in better conditions for surgery.

Therefore, these biomarkers will help predict disease as well as improve prognosis, subclinical disease management, and risk stratification and thus reduce disease-associated morbidity and mortality.

Competitive advantages:

- An in vitro method for the diagnosis of CAVD or subclinical aortic-valve calcification was designed by measuring the circulating expression levels of 6 genes with prognostic implications.
- The combination of at least 4 genes is a new tool for the diagnosis and differential diagnosis between CAVD and subclinical aortic-valve calcification.
- The expression levels of these genes could be measured using a kit, which has a clear utility at clinical level to rapidly rule out important aortic diseases before the patient is examined by the cardiologist using imaging techniques.
- The presence of calcification could be discarded in primary care services or the patient referred to the cardiologist at an earlier disease stage to avoid a late surgery indication with increased risk for complications.

Key words: CAVD, inflammation, biomarker, peripheral blood, gene signature.

Technology type: prevention, diagnostics, biomarkers.

Patent information: EP applied, suitable for international extension

Stage of development: Performed with 52 case-control blood samples from the PESA study and 12 CAVD patients. Validated in 25 of 52 PESA cases and 35 of 52 PESA controls and in independent cohort of 16 CAVD patients

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