Thème : cardiomyopathie

Results of a systematic large gene screening in hypertrophic cardiomyopathy (HCM) : the French GEnetic REgister of in hypertrophic cardioMYopathy (GEREMY).

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Introduction. Systematic genetic screening in HCM is recommended by the EU and US guidelines, but, besides its interest for familial screening, its performance and influence on the management of index cases is controversial.

Objectives. REMY (REgister of hypertrophic cardioMYopathy), a prospective national observational register, multicenter and hospital-based, promoted by the French Society of Cardiology, included more than 1700 patients, with age ≥15years, left ventricular hypertrophy ≥15mm in sporadic cases (≥13mm if familial) unexplained by abnormal cardiac loading condition. GEREMY aimed to include, after informed consent, the genotyped REMY index patients from 2 large university centers (HEGP-Paris, Henri Mondor-Créteil) using a custom-made NGS panel of 12 genes (Truseq Custom Amplicon Low Input, Illumina). Funding for this Investigator Sponsored Study was provided by Sanofi Genzyme.

Methods. The NGS panel included 10 sarcomere genes (MYH7, MYBPC3, TPM1, TNNT2, TNNI3, CSRP3, MYL2, MYL3, ACTC1, LMNA) and the GLA and TTR genes. Analysis and interpretation of variants were performed using Seqnext (JSI), Polydiag (Imagine Institute), Alamut® (Interactive Biosoftwares) and then confirmed by Sanger. In case of a negative study and depending on patient profile, screening was performed on a larger NGS panel of 45-80 genes. Genetic variants of unknown significance were not considered.

Results. Among 436 patients, morbid sarcomere gene mutations were identified in 172 cases (39.4%), a minority (n=19, 11%) only with the larger NGS panel. Multiple mutations were identified in 11(6.4%) patients, including one with 3 morbid genes involved, all with a severe form of the disease. The performance of the technique was maximal between 20-40 years and in presence of a family history of HCM. Most frequent mutations were localized on the MYBPC3 (60%), MYH7 (17%), TNNI3 (5%), CRSP3 (4.4%), and TNNT2 (3.8%) genes, while other genes were involved in ~1%. Non-sarcomeric genetic etiologies were diagnosed in 24(5.5%) patients including hereditary TTR amyloidosis (n=15), Fabry disease (n=2), Mitochondrial diseases, Leopard or Noonan syndromes (n=7). Among patients with a negative genetic study (n=240), 60 (25%, 13.8% of the total cohort) had amyloidosis (AL=19, senile=51).

Conclusions. Systematic genotyping with a 12 gene panel showed a good performance (35%) as compared to larger panels, also allowing diagnosis of patients with multiple mutations (2.5%). Screening for GLA and TTR gene mutations leads to substantial new diagnoses of Fabry disease (~0.5%) and hereditary amyloidosis (~1%). AL and senile amyloidosis represent 25% of etiologies in case of negative genetic screening. An extension of this study is ongoing and additional results will be available.