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Genetic spectrum of hypertrophic cardiomyopathy revisited. Whole Exome Sequencing reveals extreme genetic heterogeneity and new gene mutations in a multicenter series of 200 patients

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Background and objectives: Hypertrophic cardiomyopathy (HCM) is expected to be caused by a heterozygous mutation in one of the 5 main sarcomere genes (MYBPC3, MYH7, TNNT2, MYL2, TNNI3). However, the routine diagnostic strategy consisting of the sequencing of these 5 genes allows identification of a mutation in only 50% of familial or sporadic cases, limiting accurate genetic counseling in families and predictive diagnosis in at-risk subjects.

Purpose: We aimed at evaluating the value of Whole Exome Sequencing (WES), comparing its diagnostic yield with the routine diagnostic strategy, and clarifying the genetic spectrum of HCM.

Methods: We performed WES in a large series of 200 new unrelated patients with primary HCM using the Agilent SureSelect V6 technology on Illumina HiSeq 2500. Patients were recruited between June 2015 and October 2016 in 5 French centers. In a first step of analysis, a panel of 145 genes involved in various hereditary cardiac diseases was searched for mutations. Bioinformatics analyses were performed in our lab. Only "certainly" (class 5) or "probably" pathogenic (class 4) mutations were considered, according to current guidelines

Results: A total of 565 filtered variants predicted as pathogenic in 111 genes were retained after bioinformatics analysis, literature and databases review. The main results are the following:

- A mutation in 1 of the 5 main sarcomere genes was observed in only 72 (36%) patients, with no mutation on the TNNI3 gene.
- Conversely, 495 other pathogenic mutations were identified in 185 patients, giving a total 92.5% detection rate of at least one pathogenic gene mutation. Among them, the most prevalent mutated genes were FLNC, LDB3, MYPN, ANK2, RYR2 and NEBL. In addition, unexpected diagnosis of treatable affections such as Fabry disease (n=1) and TTR amyloidosis (n=1) were identified by WES analysis
- A single mutation was identified in only 27 patients (13.5% of cases). In 158 patients (79%), multiple variants were identified with 2 to 8 mutations per patient.
- Finally, in only 15 patients (7.5%), no mutation was identified in this panel of 145 genes.

Conclusions: 1. Exome sequencing improves the diagnostic output in HCM with 92.5% of patients carrying at least one pathogenic mutation in a panel of 145 genes involved in various hereditary cardiac diseases

2. Genetic heterogeneity is much larger than expected with multiple variants in sarcomere genes, but also non-sarcomere, and ion channel genes unexpected in HCM.

3. Early unexpected diagnosis of Fabry disease or TTR amyloidosis can be obtained by our strategy of one-step large genetic analysis.

4. Our results suggest that the commonly accepted monogenic model of HCM involving one mutation in one gene is not the major mechanism in HCM. Rather, oligogenism with 1 major and several minor variants is our proposed new pathogenic mechanism in HCM.

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