IMPORTANCE OF CYP2C19 GENOTYPING IN MAVACAMTEN THERAPY: PHARMACOGENOMIC IMPLICATIONS IN HYPERTROPHIC CARDIOPATHY.

Hypertrophic cardiomyopathy (HCM) is a relatively common and often inherited cardiac disease, with a complex phenotypic and genetic expression. The prevalence of HCM in Spain is estimated at approximately 1/500 people, being a disease that often goes unnoticed but is an important cause of sudden death, especially in young people. It is typically defined by the presence of left ventricular hypertrophy with a maximum left ventricular wall thickness ≥ 15 mm in adults (Fig. 1) or a left ventricular wall thickness Z-score > 3 in children. The diagnosis of HCM is established with non-invasive imaging studies, including echocardiography and/or cardiac magnetic resonance imaging.

The clinical manifestations of MCH are highly variable. The most common symptoms are dyspnea, chest pain, palpitations and dizziness or syncope. Complications of the disease can be ventricular arrhythmias with a risk of sudden death, especially in young people and athletes, heart failure and atrial fibrillation. The expression and penetrance of the disease can vary even within the same family. MCH is mostly inherited in an autosomal dominant manner, but it can also present autosomal recessive inheritance in some cases.

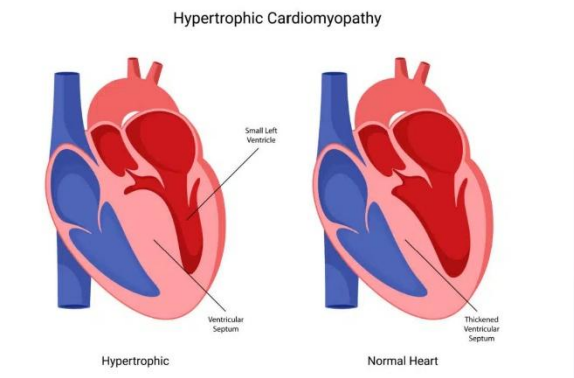


Figure 1. Comparison between normal patient and patient with MCH

The main cause of non-syndromic MCH is the presence of pathogenic variants in one of the genes that encode the components of the sarcomere. The genes *MYBPC3* (which encodes myosin binding protein C) and *MYH7* (which encodes β myosin) are the most frequently altered genes, accounting for 50% and 33% of cases, respectively.

Cardiac myosin is a motor protein located in the sarcomere (functional unit of muscle). Its most important portion is the myosin head, which contains ATPase activity. This enzyme is responsible for the hydrolysis of ATP to obtain energy that allows myosin to stretch actin and generate contraction (Fig. 2). In MCH, cardiac myosin is overactive, causing hypercontractility that contributes to myocardial thickening and outflow tract obstruction.

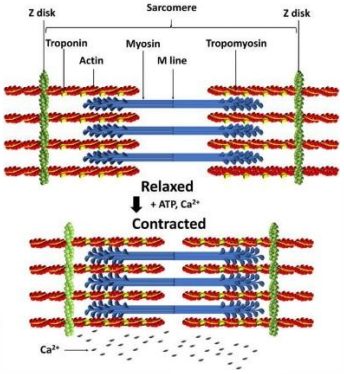


Figure 2. Mechanism of sarcomere contraction

Mavacamten is a recent drug for the treatment of MCH. It acts in a very different way to beta-blockers or calcium antagonists. It is the first drug to act on sarcomere mechanics. It is a cardiac myosin ATPase inhibitor that reduces excessive myocardial contractility, improving symptoms and cardiovascular function.

The hepatic metabolism of mavacamten occurs mainly through the cytochrome P450 enzyme system, highlighting the CYP2C19 isoenzyme as a critical metabolic pathway. This enzyme presents multiple allelic variants that affect its activity, directly impacting the pharmacokinetics of the drug. Therefore, *CYP2C19 genotyping* can guide personalized therapeutic decisions.

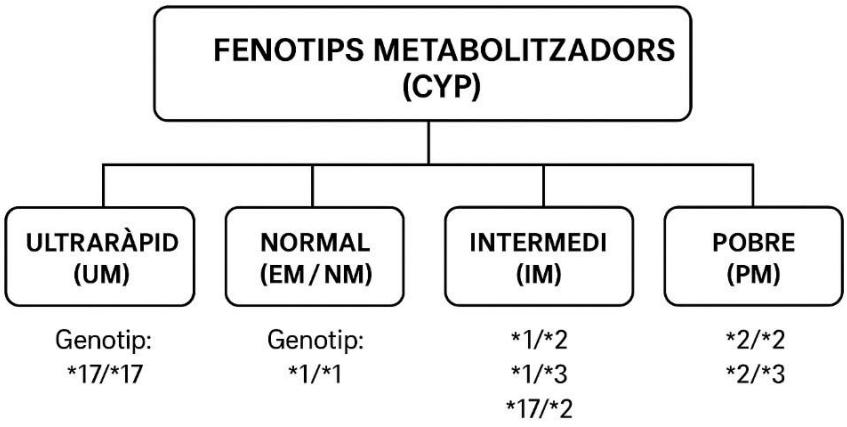
The *CYP2C19 gene* encodes an enzyme responsible for the metabolism of several drugs, including mavacamten. Among the most studied variants are:

CYP2C19*1: Functional allele (normal activity)

CYP2C19*2 and *3: Non-functional alleles (reduced or no activity)

CYP2C19*17: Gain-of-function allele (increased activity)

The combination of these alleles determines the metabolic phenotype:



Mavacamten exhibits nonlinear pharmacokinetics, meaning that with increasing doses, the response to the drug does not increase proportionally. This is mainly due to the saturation of metabolic processes (e.g. CYP2C19 metabolism). As a result, small increases in dose produce larger increases in plasma concentration. Reduced CYP2C19 activity, such as that found in poor metabolizers, is associated with higher plasma concentrations of the drug, increasing the risk of adverse effects such as systolic dysfunction or heart failure.

Clinical studies have shown that patients with poor metabolizer genotypes require close monitoring, dose reduction, or extension of the administration interval to avoid toxicity.

Pharmacogenomics guides, such as those of the *Clinical Pharmacogenetics Implementation Consortium* (CPIC), recommend considering genotyping before initiating treatment with drugs that have a narrow therapeutic range and are metabolized by polymorphic enzymes.

In poor metabolizers:

The initial dose should be adjusted to 2.5 mg per day. The maximum dose for these patients may be up to 5 mg per day. Clinical response should be assessed by frequent monitoring of left ventricular systolic function and assessment of signs of heart failure.

In intermediate, normal and ultra-rapid metabolizers:

The recommended initial dose is 5 mg per day. The maximum dose for these patients can reach 15 mg per day. Monitoring should also be carried out to assess the clinical response to the drug.

CYP2C19 genotype

In our laboratory we have expanded the portfolio of pharmacogenetic tests, incorporating *CYP2C19 genotyping.*

The technique chosen to determine the *CYP2C19 genotype* is a real-time PCR technique with **TaqMan ® probes** . **TaqMan ® probes** are real-time PCR tools designed to detect single nucleotide variants (SNPs).

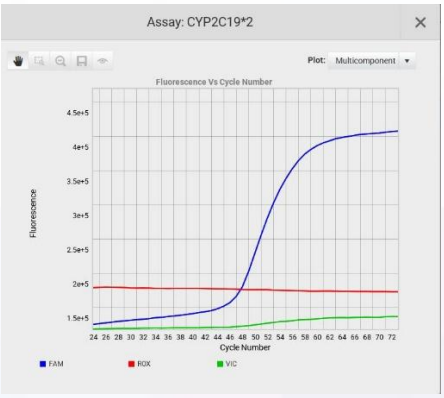


Fig 2. Patient with genotype no. 2.

We study alleles 2 (c.681G>A rs4244285) and 3 (c.636G>A rs4986893), considered non-functional, which determine the poor metabolic phenotype. This phenotype is the only one that currently involves a change in the therapeutic regimen, which implies a reduction in the drug dose.

The technique used is very robust and efficient, and allows us to have a very short response time, which is essential to be able to treat patients with the drug at the appropriate dose, quickly and efficiently.

The integration of *CYP2C19 genotyping* into clinical practice represents an advance towards personalized medicine in the treatment of MCH. Its application allows optimizing the efficacy of mavacamten, minimizing risks and improving therapeutic outcomes.

Bibliography.

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