LQT2 or HERG defect (1)

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Name: LQT2

Gene: HERG HUMAN ETHER-A-GO-GO

Chromosome: 7 mapped for the first time in 1994 by Jiang et al (2)

Other works identify the HERG mutation in chromosome 7, mutation 7p35-36. The gene kvLQT1 is the protein IsK(mink) associated to the defect in the fast rectifier outward potassium current Ikr (3) (4)

Mutation: 7P35-36

Channel affected in TAP: Ikr "delayed rectifier current"

Phase of TAP affected: 3

Trigger: noises. It is advisable to remove from the bedroom alarm clocks or phones. In this variant a significant number of cases present the events in the presence of emotional stress or in rest, while only a 13% occur during exercise.

Phenotype: NDN

Relative incidence: 35% of the total

Particular characteristics of ECG:
1) T wave with low amplitude and a notched appearance;
2) Moderate dependence of heart rate on QT interval;
3) KCNH2 in the L413P and L559H mutations are associated with bifid T wave in ECG

Drugs that improve repolarization:
K+ channel openers such as nicorandil, improve repolarization in this variety by shortening the QT interval and reducing transmural dispersion of repolarization.

Drugs that worsen repolarization:
Drugs that simulate LQT2 variant: Sotalol is a drug that possesses class III antiarrhythmic properties by the isomer: **d**. and beta blocker properties (class II) by the isomer: **l**. This is then, a drug made up by the racemic mixture of two isomers: **d** and **l**. The **l** isomer is a noncardioselective beta blocker (class II) with no ISA activity or membrane stabilizer, and the second one, a drug with class III properties. The increase of QT is due to its class III antiarrhythmic action of the **d** isomer by prolonging phase 3 of the TAP, by blocking the Ikr channels that could cause the appearance of proarrhythmic effects such as TdP or pleomorphic ventricular tachycardia (6).
The **d** isomer (d-sotalol) could be similar to the LQT2 variant, because it blocks the Ikr channels prolonging to a larger extent the TAP duration of the M cells than in the subendocardial and subepicardial cells, thus causing repolarization dispersion that is translated into ECG with flattened, low-amplitude T wave and QT prolongation.

Hypocalemia magnifies this effect, besides causing notched T wave. Treatment: LQT1 and LQT2 benefit the most from ß-blocker therapy. LQT3 and SCN5A defect.

Summary:

1) In the LQT2 variant, the channel affected is the rapid component of the delayed rectifier repolarizing current;

2) The HERG mutation (human ether-a-go-go-related gene) is found in chromosome 7p35-36;

3) The kvLQT1 gene and the IsK(mink) protein are associated to the defect in the fast rectifier outward potassium current Ikr (3) (4)

4) The congenital QT syndrome that affects the K+ current (HERG defect of the K+ current) is called LQT2;

5) In variants 1 and 2, events are observed since birth until adolescence;

6) This is a dominant Mendelian nuisance that codifies the rapid component of the delayed rectifier repolarizing K+ currents and causes the LQT2 variant;

7) The LQT2 variant is the second most frequent form: 35%;

8) The Ikr channel or rapid component of the delayed rectifier repolarizing current is the one affected by the congenital long QT syndrome type 2 (LQT2 or HERG) (3);

9) This is a voltage-dependent channel that could possibly be associated to peptide 1 related to Mink(MiRP1). This is an auxiliary beta subunit that could be associated to LQTS;

10) The alpha subunit of this channel is affected by the alteration in the 561 amino acid, with an A substitution and a V one having been described;

11) The HERG mutation could be located within the channel pore or outside of it (1);

12) Patients with mutations located in the pore, present a much higher tendency to risk of arrhythmias than those with a mutation located outside of the pore (1);

13) Recently, three missense mutations were identified (V612L, T613M, and L615V) located in the pore helix subunit of the HERG channel. The V612L and T613M mutations, when expressed in isolation, do not induce ion currents, and the L615V induces a mild current;

14) The coexpression of mutations and the wide type of HERG subunit causes a dominant negative effect that varies for each mutation (7);

15) A new missense V65M mutation has been identified in the KCNE2 gene, known as the HERG/MiRP1(V65M) mutation, which causes an inactivation time accelerated with a lower density of Ikr currents, worsening the repolarization capacity of my cites (8);

16) Some mutations cause the loss of function, and others dominant negative suppression of the HERG function. These mutations are predictors of a spectrum that causes a decrease of the Ikr current and delayed repolarization consistent with the long QT interval observed in patients carriers of LQTS (9);

17) By using a method called DHPLC (Denaturing High Performance Liquid Chromatography), genetic mutations are detected fast and with high sensitivity. Thus, Jongbloed et al employing this new method, detected 9 mutations in the LQT2: 4 missense, 2 nonsense, 1 insertion and 2 deletion ones (10);

18) German authors identified a family with variant 2 of genes (HERG). The genetic analysis revealed in all the members of the family the mutation (888 delG insAA), not described before, which causes amino acid chain truncation (360X) of the I(Kr) current that proved to present a high degree of malignancy and requires aggressive therapeutics in surviving relatives (11);

19) The clinical expression of LQTS is equally variable in carriers from families, whether with equal or different mutations. These facts show a complexity in the clinical phenotype in this dominant Mendelian entity, and suggest that one or more genetic modifications contribute for its clinical expression (12).

Referentes

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