LQT5 Masquerading as LQT2. A Dominant Negative Effect of a Rare Polymorphism on KCNH2 Current

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Introduction: KCNE1 encodes an auxiliary subunit of cardiac potassium channels. Loss of function variations in this gene have been associated with the LQT5 form of the LQTS, secondary to reduction of IKs current. We present a case in which a D85N rare polymorphism in KCNE1 is associated with a LQT2 phenotype.

Methods: An 11 year old competitive athlete presented with mild bradycardia and a QTc interval of 470ms. An LQT2 phenotype, consisting of low-voltage bifid T waves, was evident in the right precordial ECG leads. During the tachycardia phase following adenosine, QTc increased to 620 ms. Genetic analysis included segregation analysis and direct sequencing of LQT 1-6 genes. Electrophysiology studies were done by using whole-cell patch-clamp techniques in transfected TSA201 cells.

Results: Genetic analysis revealed a rare heterozygous polymorphism in KCNE1 predicting substitution of asparagine for aspartic acid at position 85 of minK (D85N). Patch clamp experiments showed that KCNE1-D85N, when co-expressed with KCNH2 in human embryonic kidney cells, significantly reduces the rapidly activating delayed rectifier channel current (IKr). Homozygous co-expression of D85N reduced tail current by 85%, whereas heterozygous co-expression reduced the current by 52%, demonstrating for the first time a potent dominant negative effect of D85N to reduce IKr.

Conclusions: Our results suggest that a rare polymorphism KCNE1-D85N, underlies the development of a LQT2 phenotype in this young athlete by interacting with KCNH2 to cause a dominant negative effect to reduce IKr. Our data provide further evidence in support of the promiscuity of the potassium channel f subunits in modulating the function of multiple potassium ion channels leading to a diversity of clinical phenotypes.