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Cost-effectiveness analysis of genetic cascade screening in arrhythmogenic cardiomyopathy

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Background: Arrhythmogenic cardiomyopathy (AC) is an autosomal dominant inherited disease with incomplete penetrance and variable expression, and an important cause of sudden cardiac death in young adults. In the absence of genetic diagnosis, long-term follow-up of all first degree relatives is mandatory. Although the reported yield of the genetic test in AC probands is 50–60%, there is scarce data on the economic impact of the genetic cascade screening strategy.

Objectives: To study the cost-effectiveness of the genetic cascade strategy in AC families.

Methods: 151 patients from 41 families were consecutively enrolled in a Spanish referral Inherited Heart Disease centre. The cost of the genetic testing in each family was calculated adding the price of the proband study (NGS panel, €1380 in 2015) and cascade genetic screening (€200 each patient). The estimated price of the clinical work-up and follow-up of relatives without causal mutations who were discharged after genetic testing computed as cost-savings (diagnostic work-up costs €819, follow-up visit costs €236/each). Incremental cost was the difference between the cost of genetic testing and the cost-savings generated by the genetic results. We also calculated the number of patients in each family who obtained benefit from the information provided by the genetic test.

Results: We found 19 pathogenic mutations in 20 probands (detection rate = 49%), and 13 variants of unknown significance among the five main desmosomic genes (PKP2, DSP, DSG2, DSC2 and JUP). Among relatives, 12 had AC, 10 borderline diagnosis and 25 were carriers of mutation. 22 non-carriers could be discharged. The total incremental cost of the genetic cascade strategy was €12,514 (41 probands and 68 relatives genotyped) and 69 individuals benefited specifically from genetic results information. The incremental cost per causal mutation was €626 and the cost-per-patient benefit is €181 (Figure 1, red dot). Simulation studies showed that this strategy would be cost-saving if the price of the proband's genetic test was below €1,074. The number of major diagnostic criteria in the proband (excluding genetics), and the number of children at risk (<14 years old) were independent predictors of the cost-effectiveness ratio in each family (p<0.011 for both).

Methods and results: We clinically evaluated a family with AC with an early onset in children. The index case, a 14-year old girl died suddenly and autopsy revealed AC. Three other siblings at the ages of 12, 22 and 24 years were also affected by the disease and had defibrillators implanted. Whole exome analyses identified a novel variant in a new disease gene involved in cell-extracellular matrix connection: Integrin linked Kinase (ILK). We also found a second variant in another child with AC which appeared to be de novo. Localization experiments of mutant and wild-type ILK in transfected H9c2 and C2C12 cells demonstrated an aberrant cytoplasmic localization in cells transfected with mutant ILK. Next, we developed several transgenic zebrafish lines expressing human wild-type and three mutants of ILK under the control of the cardiac-specific myl7 promoter, and found that two of the mutant alleles are lethal before about 2–3 weeks of age (i.e. larval stages). We developed two hypotheses: (1) mutant fish die due to progressing heart failure or (2) due to electrical problems leading to arrhythmias and sudden death. Fractional shortening was measured as an indicator of heart failure, and was decreased at 3dpf in both mutants. Next, we established a technique to patch the atrium and ventricle directly at 3dpf to determine action potentials. However, we found no significant difference between wildtype and mutant embryos. We continue further experiments to determine the cause of death in mutant fish.

Conclusion: We identified novel missense variants in the ILK gene in two unrelated families. ILK is an important linker protein involved in the cell-extracellular matrix connection: Integrin linked Kinase (ILK). We also found a second variant in another child with AC which appeared to be de novo. Localization experiments of mutant and wild-type ILK in transfected H9c2 and C2C12 cells demonstrated an aberrant cytoplasmic localization in cells transfected with mutant ILK. Next, we developed several transgenic zebrafish lines expressing human wild-type and three mutants of ILK under the control of the cardiac-specific myl7 promoter, and found that two of the mutant alleles are lethal before about 2–3 weeks of age (i.e. larval stages). We developed two hypotheses: (1) mutant fish die due to progressing heart failure or (2) due to electrical problems leading to arrhythmias and sudden death. Fractional shortening was measured as an indicator of heart failure, and was decreased at 3dpf in both mutants. Next, we established a technique to patch the atrium and ventricle directly at 3dpf to determine action potentials. However, we found no significant difference between wildtype and mutant embryos. We continue further experiments to determine the cause of death in mutant fish.

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