Editorial Editörden

Why genotype patients with inherited heart disease?

Neden kalıtsal kalp hastalığı olan hastalarda genotipleme gerekir?

Isn't it enough to diagnose and treat genetic heart disease? The syndromes of hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), Brugada, long QT syndromes and familial dilated cardiomyopathy are complicated enough, and the treatment options and choices are vexing. Why add another layer of diagnostic complexity? Why genotype?

First, genotype analysis may simplify the process of screening first degree family members for inheritance of disease-causing mutations. Our HCM patients have a variety of reactions to the notion of family screening. Some are concerned that they have passed mischief on to their offspring and want to know as soon as possible. Others lapse into a sort of denial that might be paraphrased "if it's not causing trouble, why look for it?" Some parents experience debilitating guilt.

When, after counseling, probands decide to screen offspring and encourage siblings, there are now two strategies available. The first, the old paradigm, is to perform echocardiography and electrocardiography (ECG) every year or so on children between 10 and 21 years and then, if no abnormalities are noted till then, to screen every 5 years afterwards. This last recommendation is because some HCM mutations do not manifest hypertrophy until mid-life. Imagine then doing this in a family with 4 children: The parent must bring the children back and forth for testing a cumulative of 30 times or more before age 21. Not likely.

The newer paradigm streamlines the process and may be more definitive. Here the proband is genotyped, which in HCM involves screening the most common genes. This panel varies from 8 to 18 genes screened depending on the commercial vender. Currently about 50% of patients will be found to have a disease-causing mutation and thus are genotype-positive (1, 2). Armed with this information the first- degree relatives can now be tested for just this one identified gene. This targeted analysis costs less than the full panel. Those relatives found to be positive can be screened with echocardiography and ECG more intensively and sequentially, while those who test negative are followed less intensively, if at all. Given the cumulative cost of non-invasive testing for all children and siblings, this may turn out to ultimately be cost-effective compared with repeated non-invasive testing of all relatives.

The costs of genotype analysis are coming down in the United States. There are now 4 commercial labs that genotype patients for cardiac inherited diseases. It appears that competition is driving costs down and making testing more accessible to the average patient. Also, selected insurers are beginning to reimburse for the expense.

Another clinical scenario where genotype analysis has become useful is to assist when the diagnosis of inherited heart disease is ambiguous. This occurs in HCM when left ventricular thickening is present, but the patient has other conditions that may explain the left ventricular hypertrophy that is present, i.e. hypertension or athletic training. Another scenario occurs in patients with mild hypertrophy, but startling systolic anterior motion of the mitral valve and left ventricular outflow obstruction. In these situations, finding a positive disease-causing mutation can allow a definitive diagnosis of HCM. But, if the testing is negative (50% of the time in known HCM), no diagnostic information is gained. Genotype also differentiates HCM caused by mutations coding for sarcomeric proteins from "phenocopies": hypertrophy caused by mutations that result in glycogen storage diseases or galactosidase deficiency- Fabry disease (3). Enzyme replacement therapy may improve cardiac function in Fabry disease (4). Genotype can also resolve ambiguous diagnoses in Brugada and long QT syndromes.

Prognosis

In computer parlance, the "killer app" or killer application was a software innovation that made a computer indispensable. For businesses, early in the personal computer era, it was the spreadsheet. For the personal home computer, it was word processing. For genotype analysis in inherited cardiac disease, the killer app will be prognosis - risk stratification for sudden death. In long QT syndrome this is already in practice. Genes for long QT 2 and 3 have been found to portend a worse prognosis than long QT 1 (5). In hypertrophic cardiomyopathy, the hope of gene-specific risk stratification has temporarily been thwarted by of the number of genotypes that cause HCM. Even though there are 13 main genes there are >900 mutations that can cause the disease. Many families have "private mutations" of one of these genes, not found in any other family. The consequent lack of large numbers of patients with any one gene has inhibited prognostic study. Early hopes that certain genes might be more lethal have not been confirmed to date (6). However, in HCM probands the detection of any disease-causing mutation is associated with a combined end-point of premature mortality and progression to NYHA III or IV symptoms, compared with a better prognosis in gene-negative patients with HCM (7).

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In the present Supplement we include sentences like: "The desmoplakin protein connects desmin to the Armadillo repeat proteins, plakoglobin and plakophilin-2." Just what is the clinician to make of these unfamiliar terms, especially considering that at the moment we cannot specifically treat these mutations? There was a time before antibiotics when some physicians knew the names of disease-causing bacteria named *Pseudomonas aeruginosa* and *Staphloccocus aureus*. This was a time when these bacterial names were as unfamiliar as "KVLQT1 (KCNQ1), found at locus 11p15.5, the cause of long QT1". Bacterial names have become familiar with the development of antibiotics and long familiarity with their syndromes. One would expect that same familiarity will develop with the disease-causing mutations of inherited heart disease.

The future of therapeutics based on genotype analysis in inherited heart disease is difficult to foresee. One avenue of research in HCM has been the observation that genotype-positive, phenotype-negative mice with HCM can be prevented from developing HCM phenotype by pharmacologic intervention (8, 9). A clinical trial is currently proceeding in genotype-positive offspring using diltiazem to prevent or retard the development of HCM phenotype.

It is possible now to prevent offspring from inheriting genetic disease by Preimplantation Genetic Diagnosis or Screening (PGD). In this advanced and expensive procedure, embryos conceived through in vitro fertilization are tested by cell biopsy and genetic analysis. Only those embryos that are genetically normal are implanted (10). In this way, parents who know they are gene positive can avoid transmitting their mutant gene to the next generation. One wonders if this technology will find application in the inherited causes of sudden death.

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