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# Can a Genetic Test Predict the Development of Postoperative Atrial Fibrillation

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## Abstract

**Background:** Atrial fibrillation (AF) is the most common postoperative complication of cardiovascular surgery. In large cohorts, genetic variants in the 4q25 chromosome region have been associated with postoperative AF. However, the role of genetic testing in an individual patient to predict the development of AF has been understudied.

**Objectives:** To determine the role of genetic testing to predict postoperative atrial fibrillation in individual patients undergoing cardiac surgery.

**Patients and methods:** We prospectively genotyped 160 patients undergoing cardiac surgery using the deCODE-AF test, which measures two well validated SNP markers near the PITX2 gene on chromosome 4. These patients were followed during their hospitalization for the development of atrial fibrillation lasting more than 5 minutes.

**Results:** We studied 160 patients (109 men) with a mean age of 61.0 ± 11.5 years. Of these, 101 patients (70%) had off-pump surgery. All patients had some treatment to reduce the incidence of postoperative AF (metoprolol in 43, amiodarone in 38, atrial pacing in 39 and combination therapy in 40). Of the 160 patients, 143 had interpretable genetic data. Postoperative AF occurred in 23 patients (16%). Of those 23 patients, 3 had a positive genetic test. In the patients without AF, 37 of 120 had a positive genetic test. This yields a sensitivity of 16%, a specificity of 71%, a positive predictive value of 8% and a negative predictive value of 86%.

**Conclusion:** Genetic testing has a low sensitivity and positive predictive value in assessing the risk for postoperative AF in an individual patient. This supports a multifactorial etiology including inflammation, catecholamines, electrophysiological substrate and surgical techniques.

## Keywords

Atrial fibrillation, Coronary artery bypass grafts, CABG, Genetics

## Background

Nearly three million Americans have atrial fibrillation (AF) and this number is projected to rise to more than 10 million by the year 2050 [1]. AF is also the most common arrhythmia following cardiac surgery, presenting in 25-50% of patients [2]. The presence of post-operative atrial fibrillation (PoAF) is an independent risk factor for both morbidity and mortality [3,4]. PoAF increases the risk of stroke, congestive heart failure, and hemodynamic compromise [5-8]. Furthermore, patients who develop PoAF are more likely to have other post-operative complications, such as respiratory failure, a peri-operative myocardial infarction, and congestive heart failure [4]. In addition, PoAF has been associated with an increased length of hospital stay and to a greater frequency of inotropic and mechanical circulatory support, as well as increased ventilation time [4]. As a result, several pharmacological and non-pharmacological strategies have been utilized to reduce the incidence of PoAF [9].

The mechanism of PoAF is complex and not completely understood. Advancing age, valvular heart disease, atrial enlargement, pre-operative atrial arrhythmias and chronic lung disease are among the more commonly identified risk factors [10-13]. In population studies, positive genetic tests have been associated with a doubling of the risk of developing atrial fibrillation or atrial flutter [14]. PoAF may also be a genetic disorder with highly variable penetrance. A small study (110 patients) recently implicated the –174C/G polymorphism in the interleukin-6 (IL-6) gene as a risk factor for PoAF [15]. In large cohorts, genetic variants in the 4q25 chromosome region have also been associated with post-operative AF [16]. However, in a clinical setting, the role of genetic testing in an individual patient to predict the development of PoAF has been understudied.

## Objectives

The primary aim of this study was to examine the role of genetic testing to predict the development of PoAF in adult patients undergoing cardiac surgery. For this study, we used the deCODE-AF test- a DNA based test that screens for the presence of a SNP (single –nucleotide polymorphisms) that predisposes patients towards atrial fibrillation in population studies outside of the operating room. It measures two well-validated SNP markers (RS2200733 and RS10033464) near the PITX2 gene on chromosome 4. A positive genetic test is defined by the presence of either or both SNP markers (RS2200733 or RS100233464). In the non-operative setting, a positive test defines the subject's relative risk of having had or developing

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atrial fibrillation or atrial flutter by a factor of two compared with those with a negative test.

The initial discovery of these genetic risk markers for atrial fibrillation was made by decodes scientists in 2007 [14]. To identify genetic variants conferring the risk of AF in the general population, the deCODE AF test study group conducted a genome-wide analysis of more than 300,000 SNPs across the entire genome among 5,000 Icelandic AF patients and healthy controls. Alleles of the same two SNPs, RS2200733 and RS100233464, both located near the PITX2 gene on chromosome 4q25, were found to be significantly more common in AF patients than in control subjects. These findings were then validated in studies of more than 18,000 patients with all forms of AF and controls, including cohorts from Iceland, Sweden, the Massachusetts General Hospital, and, for the strongest of the variants, a cohort of Han Chinese from Hong Kong. deCODE's findings have subsequently been confirmed by several groups in other cohorts in addition to the discovery of additional risk markers that are also included in the deCODE AF™ test [14,17-25].

## Patients and Methods

### Description of study cohort

For this study, 160 adult patients, who were in sinus rhythm, and scheduled for coronary artery bypass graft surgery (CABG), valve surgery, or both were selected to participate in this study. This study was approved by the Institutional Review Board at The George Washington University. In addition, informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

### Data and end-point collection

All patients underwent continuous electrocardiographic monitoring for at least seven days after their surgery, or until hospital discharge, if sooner, by the use of a centralized cardiac telemetry system equipped with arrhythmia and rate detection alarm triggers. The electrocardiographic data was stored for 24 hours and 2 blinded cardiologists reviewed all of the electrocardiographic data on a daily basis. Patients were excluded from the trial if they had a preoperative history of atrial fibrillation or had used a class I or III anti-arrhythmic agent in the past 6 months.

The primary endpoint of this study was the occurrence of atrial fibrillation lasting longer than 5 minutes or for any length of time requiring treatment as a result of symptoms or hemodynamic compromise. Prophylactic strategies to reduce the incidence of postoperative atrial fibrillation were directed by the cardiac surgical team. As a result, subjects could receive amiodarone, a beta blocker or atrial pacing, since this is the standard of care at our institution.

### Genotyping

Patients enrolled in the study were genotyped using the deCODE-AF test (deCODE Genetics, Reykjavik, Iceland) by swabbing their buccal mucosa at some point during their post-operative hospital course. The swabs were collected, sealed, and shipped to the deCODE Diagnostics Laboratory to undergo testing for genetic variants on chromosome 4q25.

### Statistical analysis

Continuous variables were summarized as means ± standard deviation. Continuous variables were compared by using the student t test. A p value of <0.05 was considered to indicate statistical significance. A chi-squared test was performed on the genetic data.

## Results

For this study, we enrolled 160 patients (109 men), with a mean age of 61.0 ± 11.5 years (range=44 – 76 years). Of the 160 patients studied, 17 patients were excluded from the study due to uninterpretable genetic data leaving only 143 patients in our cohort. Importantly, these 17 patients were not different than the other 143 subjects studied. Of these 143 patients, 101 patients (70%) had off-pump surgery, and 70% were men. As shown in Table 1, all patients had some treatment to reduce the incidence of postoperative AF (metoprolol in 43, amiodarone in 38, atrial pacing in 39 and a combination of therapies in 40).

**Table 1:** Baseline clinical characteristics of the study population dependent on the results of genetic testing

| **Demographics** | | | |
|---|---|---|---|
| | **Positive Genetic Test (n=40)** | **Negative Genetic Test (n=103)** | **p value** |
| Atrial fibrillation (n) | 3 | 20 | 0.08 |
| No Atrial fibrillation (n) | 37 | 83 | |
| **Demographics** | | | |
| Age (years) | 60 + 13 | 63 + 11 | 0.22 |
| Females (n) | 12 | 40 | 0.3 |
| **Medical History** | | | |
| Prior Myocardial Infarction (n) | 16 | 34 | 0.43 |
| LV ejection fraction <40% (n) | 8 | 17 | 0.62 |
| Hypertension (n) | 23 | 81 | 0.01 |
| Diabetes (n) | 16 | 33 | 0.37 |
| Asthma/COPD (n) | 3 | 19 | 0.10 |
| Stroke/TIA (n) | 5 | 9 | 0.34 |
| **Preoperative Therapies** | | | |
| Statin (n) | 29 | 65 | 0.28 |
| β blocker (n) | 26 | 66 | 0.75 |
| ACE inhibitor (n) | 17 | 49 | 0.58 |
| Digoxin (n) | 0 | 1 | 0.72 |
| Metoprolol (n) | 12 | 27 | 0.65 |
| Amiodarone (n) | 7 | 26 | 0.32 |
| Atrial Pacing (n) | 8 | 26 | 0.51 |
| Combination (n) | 13 | 24 | 0.26 |
| **Form of Surgery** | | | |
| Coronary Bypass (n) | 32 | 82 | 0.58 |
| Valve Surgery (n) | 7 | 15 | 0.66 |
| Both (n) | 1 | 6 | 0.37 |
| Off Pump (n) | 27 | 66 | 0.70 |

In our cohort, 23 patients (16.1%) developed PoAF. In the 23 patients who developed postoperative atrial fibrillation, the initial ventricular rate was 123 ± 22bpm and the duration of each episode was 244 ± 66 minutes. Fifteen patients had spontaneous termination of their atrial arrhythmia, while 8 patients underwent electrical cardioversion.

Of the 23 subjects with PoAF, three had a positive genetic test (13 %). In the 120 patients without PoAF, 37 had a positive genetic test (30%). Therefore, in the 40 subjects with a positive genetic test for atrial fibrillation, only 8% developed PoAF. In contrast, in the 103 subjects with a negative genetic test, 19.4% developed PoAF. This yielded a sensitivity of 16%, a specificity of 71%, a positive predictive value of 8% and a negative predictive value of 86% (Figure 1).

## Discussion

The goal of this study was to examine the role of genetic testing to predict the development of post-operative atrial fibrillation in patients undergoing cardiac surgery. Specifically, two well-validated SNP markers (RS2200733 and RS10033464) near the PITX2 gene on chromosome 4q were measured. In population studies, positive genetic tests for these two SNP markers have been associated with a doubling of the risk of developing atrial fibrillation or atrial flutter [14]. In addition, in large databases, genetic testing has also been predictive of the development of post-operative atrial fibrillation. Body and colleagues reported results in a cohort of 959 patients undergoing coronary artery bypass surgery with or without valve surgery, and replicated these SNP markers in a validation cohort. The authors of this large study genotyped 45 SNP markers encompassing the 4q25 locus [16]. They found additive odds ratios for the 7 associated 4q25 SNP's ranged between 1.57 and 2.17. However, our results suggest that a positive genetic test for atrial fibrillation does not predict the development of post-operative atrial fibrillation in an individual patient.

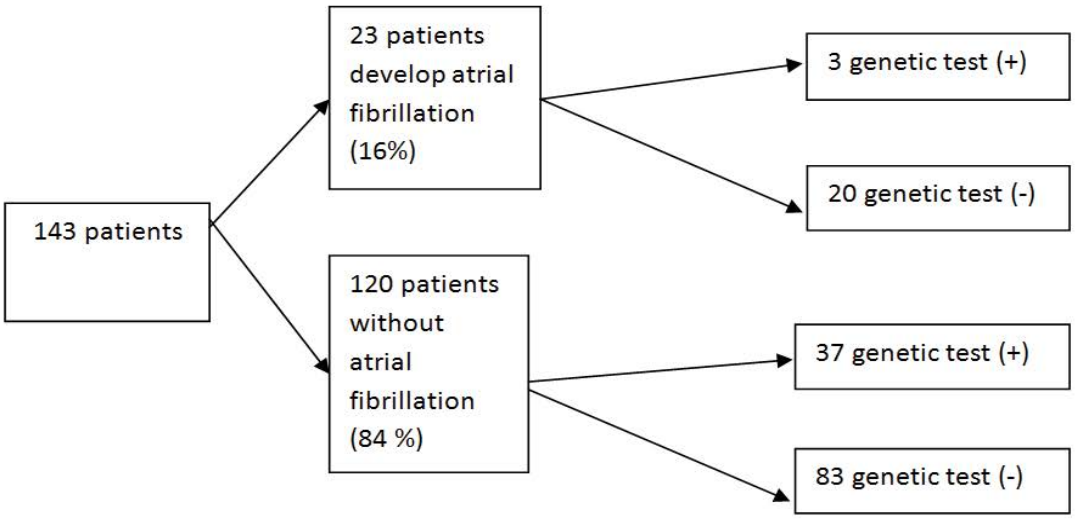


**Figure 1:** Results of genetic testing

The mechanism which allows these SNP variants (RS2200733 and RS100233464) to result in postoperative atrial fibrillation is unclear. However, these SNP's lie upstream from a gene (PITX2) that could plausibly play a role in the pathogenesis of atrial fibrillation. The PITX2 gene is thought to be critical in the development of the human left atrium, pulmonary venous system and in the suppression of left atrial pacemaker cells in early development [26,27]. Thus, these variants could lead to atrial fibrillation in adulthood.

In our study, genetic testing had a low sensitivity and positive predictive value in assessing the risk of developing postoperative AF in an individual patient. This supports a multifactorial etiology including inflammation, catecholamines, electrophysiological substrate and surgical techniques. Clinical factors can also be used to predict postoperative atrial fibrillation, such as age, the performance of valve surgery, hypertension, CHADS2 score, infections, dehydration, and medication use.

However, on a clinical level, these results display shortcomings that can be analyzed from two standpoints. In our small-scale study, of the 16% of patients who developed postoperative AF, only three (13%) of these patients had a positive genetic test, characterizing them as insignificant. Furthermore, a positive genetic test was discovered in 30% of patients that did not develop postoperative AF, thus giving a positive predictive value of only 8% and a negative predictive value of 86%. On an individual level, this suggests that genetic testing cannot be utilized to predict the development of postoperative atrial fibrillation.

## Limitations

The main limitation in this study is the administration of prophylactic treatment for AF in all patients. Therapies used prophylactically to prevent the development of post-operative atrial fibrillation included metoprolol, amiodarone, and atrial pacing. By doing so, the results of genetic testing may have potentially been skewed. In other words, patients with a positive genetic test may not have developed AF as a result of atrial pacing, metoprolol or amiodarone administration. Of note, the results of genetic testing were not different when differing therapeutic strategies were analyzed. It should also be noted that administration of these drugs is standard protocol for patients in most hospitals in the United States.

In conclusion, two SNP markers (RS2200733 and RS1003346) near the PITX2 gene on chromosome 4q have proved to be well-validated and statistically significant in predicting the development of atrial arrhythmias in a large population based cohort. Genetic testing may also play a role in examining the risk of post-operative atrial fibrillation in a large database. However, genetic testing does not appear to play an important role in the prediction of post-operative atrial arrhythmias in an individual patient about to undergo cardiac surgery.

## Disclosures

None of the four authors have any conflicts of interest. Although there was no funding for this study, deCODE Diagnostic Laboratory performed the genetic testing free of charge. However, they received blinded genetic material in the mail and returned the results with an assigned alpha-numeric code. The authors had full control of the design of the study, methods used, outcome parameters and results, analysis of data and production of the written report. None of the article contents are under consideration for publication in any other journal or have been published in any journal.

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