Screening of the I_{to} regulatory subunit Klf15 in patients with early-onset lone atrial fibrillation

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INTRODUCTION

Several studies have associated mutations in genes encoding potassium channels and accessory subunits involved in cardiac repolarization with susceptibility of atrial fibrillation (AF). The majority of mutations identified display a gain-of-function consequence on potassium currents and this, by shortening the cardiac action potential, function as a substrate for re-entry wavelets in the atria and thereby susceptibility to AF (Nattel, 2002). Gain-of-function mutations in KCNQ1 which encodes the α-subunit of I_{Ks} (Chen et al., 2003; Hong et al., 2005; Otway et al., 2007; Das et al., 2009; Abraham et al., 2010; Bartos et al., 2011, 2013), in KCNH2 encoding the β-subunits/regulatory units of I_{Ks}/I_{to} (Yang et al., 2009; Pilsbry et al., 2010; Chung et al., 2011), in KCNJ8 encoding Kir2.1 and Kir6.1 respectively, in KCNA5 encoding Kv1.5 and in ABCC9 encoding K_{ATP} channel (Xia et al., 2005; Olson et al., 2007; Yang et al., 2009; Christophersen et al., 2012; Delaney et al., 2012; Mann et al., 2012). In a recent Nature paper by Jeyaraj et al. (2012) the Krüppel-like factor 15 (Klf15) was found to transcriptionally control rhythmic expression of KChIP2, a critical subunit required for generating the transient outward potassium current (I_{to}), and that deficiency or excess of Klf15 increased the susceptibility of arrhythmias. On this basis we hypothesized that mutations in Klf15 could be associated with AF. A total of 209 unrelated Caucasian lone AF patients were screened for mutations in Klf15 by direct sequencing. No mutations in the lone AF cohort were found. In one patient we found a synonymous variant (c.36C>T). In NHLBI GO Exome Sequencing Project (ESP) the variant was present in 31 of 4269 Caucasian individuals and in 3 of 2200 African Americans. In our cohort Klf15 was not associated with lone AF.

Keywords: lone AF, Klf15, ESP, genetics, mutation

MATERIALS AND METHODS

A total of 209 patients were included from eight hospitals in the Copenhagen region of Denmark. Patient records from all in and outpatient activity in the past 10 years with the diagnosis AF were identified and read. Only lone AF patients were included in this study. ECG and clinical information was collected in order to reduce the possibility of undiagnosed heart disease. All patients were Caucasian. The study was approved by the local ethics committee (KF 01313322) and conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients. Gene analyses were performed using fluorescence-based real-time PCR (ABI PRISM 7900 Sequence Detection System, Applied Biosystems, CA, USA). Primers are available on request.

RESULTS

Clinical characteristics of the AF cohort who fulfilled the inclusion criteria are listed in Table 1. We found no mutations in Klf15 in our AF cohort. In one patient we found a synonymous variant c.36C>T. In NHLBI GO Exome Sequencing Project (ESP) the variant was present in 31 of 4269 Caucasian individuals and in 3 of 2200 African Americans (Andreasen et al., 2013; Exome Variant Server, 2013).

DISCUSSION

This is the first study to examine the genetic variation in Klf15 in a lone AF cohort. Klf15 encodes the Krüppel-like factor 15 and have...
Table 1 | Clinical characteristics of the lone AF population (n = 209).

| Characteristic                  | Value (Mean ± SD) |
|--------------------------------|-------------------|
| Median age of onset, years     | 51 (46–57)        |
| Male gender, %                 | 82                |
| Height, cm                     | 173 ± 7           |
| Weight, kg                     | 89 ± 17           |
| BMI, kg/m²                     | 26.7 ± 4.6        |
| Blood pressure, mmHg           | 131 ± 13          |
| Systolic                        | 78 ± 9            |
| Heart rate, beats/min          | 69 ± 20           |
| Family history of AF           | 35%               |
| First degree relatives with AF | 31%               |

All numbers are reported as mean ± standard deviation unless otherwise noted. IQR, interquartile range.

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