Study to establish genetic association of cardiac conduction defect in Indian patients undergoing pacemaker implantation

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Introduction

The functional components of cardiovascular system can be broadly divided into the impulse-generating nodes and the impulse propagating His-Purkinje system. CCD is a disturbance of impulse conduction that can be permanent or transient depending on the anatomical or functional impairment.1 Historically, CCD was viewed purely as a structural disease of the heart in which macro or microscopically structural abnormalities in the conduction system underlie disruption of normal impulse propagation.2,3 In a substantial number of cases, however, conduction disturbances are found to occur in the absence of anatomical abnormalities. Familial background has been demonstrated to determine an individual’s predisposition to disease including the development of cardiac arrhythmias.4,5 Functional CCD is found to be a so-called primary electrical disease of the heart, a group of inherited diseases that result from functionally abnormal or absent, proteins encoded by mutated genes.6,7 The affected proteins are often cardiac ion channel proteins.

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Study to establish genetic association of cardiac conduction defect in Indian patients undergoing pacemaker implantation

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ABSTRACT

Background: The aim was to study the genetic association of cardiac conduction defects (CCDs) by evaluating single nucleotide polymorphism (SNP) in genes of SCN1B and KCNJ2 and to evaluate baseline characteristics between cases and controls.

Methods: Case group consisted of 81 individuals with diagnosis of conduction disturbances who underwent permanent pacemaker implantation. The control group consisted of 79 unrelated individuals above 18 years of age of the local population not having a present or past personal or family history (first degree relatives) of any cardiac ailment especially CCDs. Isolation of genomic deoxyribonucleic acid (DNA) from all samples was done, genomic DNA was checked to ensure the presence of intact DNA.

Results: SCN1B: SNP rs55742440 had no bearing on the protein except in producing a splice variant. SNP rs67701503 does not lie in the splice-site region, thus not having any significance in the regulation of the gene as well. NetGene2 analysis of SNP rs67486287 negates its presence in the splice site. KCNJ2:SNP rs199473653 leads to a missense amino acid change, resulting in homozygous GG variant found in almost equal frequency in both groups. SNP rs199473653 gene has not been reported as a disease causing mutation.

Conclusions: The alteration of nucleotide in SCN1B intron (SNP rs55742440, rs67701503, rs67486287) between cases and controls was found to have no odds of affecting the outcome of CCD. There was no variation or alteration in nucleotide bases of KCNJ2 (SNP rs786205813, rs199473653) between the groups.

Keywords: Genetic association, Cardiac conduction defect, Pacemaker implantation

INTRODUCTION

The functional components of cardiovascular system can be broadly divided into the impulse-generating nodes and the impulse propagating His-Purkinje system. CCD is a disturbance of impulse conduction that can be permanent or transient depending on the anatomical or functional impairment.1 Historically, CCD was viewed purely as a structural disease of the heart in which macro or microscopically structural abnormalities in the conduction system underlie disruption of normal impulse propagation.2,3 In a substantial number of cases, however, conduction disturbances are found to occur in the absence of anatomical abnormalities. Familial background has been demonstrated to determine an individual’s predisposition to disease including the development of cardiac arrhythmias.4,5 Functional CCD is found to be a so-called primary electrical disease of the heart, a group of inherited diseases that result from functionally abnormal or absent, proteins encoded by mutated genes.6,7 The affected proteins are often cardiac ion channel proteins.
involved in cardiac impulse formation. Disease of conduction block can occur at any level of the CCS and can manifest as sinoatrial exit block, atrioventricular (AV) block, infra-Hisian block or bundle branch block. Impaired conduction can be caused by ion channel defects that alter action potential shape or by defective coupling between cardiomyocytes. Inherited defects in cardiac conduction have been linked to mutations in SCN5A and SCN1B (both affect phase 0) and KCNJ2 (affects phase 3 and 4). As physicians, we seek to understand the root cause of human disease. Human genetics provides a unique tool for generating new hypotheses about the root causes of disease based on genome-wide searches in the human population that avoid prior assumptions about the underlying pathophysiologic processes.

**METHODS**

This study had focused on the genetic association of various kind of conduction abnormalities, complete heart block, AV block, sick sinus syndrome (SSS) and bifascicular heart block (BFHB/TFHB) by evaluating single nucleotide polymorphism in genes of SCN1B (rs55742440, rs67701503 and rs67486287) and KCNJ2 (rs786205813 and rs199473653).

This study was approved from institutional ethics committee of Gauhati medical college and hospital (no. MC/190/2007/PT-I/144). This observational case control study was conducted in the department of cardiology, Gauhati medical college and hospital (GMCH), Guwahati from April 2017 to October 2018. Case group consisted of 81 individuals, greater than 18 years of age with diagnosis of conduction disturbances resulting due to SSS, left bundle branch block (LBBB), BFHB, TFHB, Mobitz type 2 block, various other kinds of AV blocks or complete heart block (CHB) who underwent permanent pacemaker implantation. Control group consisted of sex and age-matched healthy unrelated volunteers/staff from the hospital.

**Inclusion criteria**

Patients of age greater than 18 years, presenting with or without symptoms, with ECG or Holter monitoring findings, suggestive of first, second and third-degree AV block or CHB, BFHB or TFHB, SSS, high-degree AV block, subjects who were already implanted pacemaker in past for the conduction abnormalities of CHB, SSS, BFHB, or TFHB were included in the study.

**Exclusion criteria**

Conduction defect due to myocardial infarction or ischemia congenital complete heart block, congenital structural heart disease (cyanotic or acyanotic), conduction disorder occurring post cardiac surgery, conduction disorder due to metabolic causes like dyselectrolytemia, hypothyroidism, side effect of drug or due to connective tissue disorder, conduction disorder associated with neuromuscular disorder were excluded from the study.

The control group consisted of 79 unrelated individuals above 18 years of age of the local population not having a present or past personal or family history (first-degree relatives) of any cardiac ailment, especially CCDs. Isolation of genomic DNA from all samples was completed within 4 weeks from the time of sample collection. Genomic DNA was checked to ensure the presence of intact DNA. Extracted DNA samples were quantified in a nano drop.

**RESULTS**

The case group comprised 81 individuals of age 58.66±13.42 years, while control group had 79 individuals of age 54.02±11.75 years. In the case group, maximum CCDs were observed between 51 and 60 years of age, representing 27.10% of total cases. The youngest individual who were implanted permanent pacemaker for the diagnosis of complete heart block aged 23 years. Approximately 74.07% of individuals in the case group were males and 25.93% were females.

In the control group, 69.62% were males and 30.38% were females. Males were more commonly affected by CCDs as compared to females than the study population and subsequently pacemaker implantation rates were higher in males.

The most common conduction abnormality was found to be CHB, comprising 64.19% of cases. Male-to-female ratio of CHB in this study was 2.5:1. The least common variety of cardiac conduction disorder among the study population was RBBB with first-degree AV block and BFHB involving the posterior fascicle that comprised 1.23% of the cases.

Approximately 92.5% cases were symptomatic on presentation. The most common symptom at presentation among the cases was syncope that was well described by the patient or accompanying attendant as single or multiple episodes of loss of consciousness associated with fall and self-recovery. Syncope was present in 59.25% of cases. Approximately 3.7% of cases presented without any symptoms and were incidentally diagnosed.

Amongst cases 34.56% had diabetes mellitus (DM) and 56.79% had hypertension against controls in which DM and hypertension was present in 12.65% and 37.97% respectively. Hypertension was most frequent co existent condition amongst both cases and controls. In our study there is statistically significant difference between groups with respect to presence of DM and hypertension. These conditions were found more in cases as compared to controls.
**Table 1:** TC characteristics in the study groups.

| Base pair | Cases | Controls | The two-sided p value is 0.9188 and is considered not significant |
|-----------|-------|----------|---------------------------------------------------------------|
| TG+       | 58    | 55       | Percentage of confidence interval is 0.7444 to 1.478. Chi-square statistics with Yates correction=0.01040. |
| TG-       | 23    | 24       | The OR is 1.08; hence, this does not affect odds of outcome. |

**Table 2:** TT characteristics in the study groups.

| Base pair | Cases | Controls | The two-sided p value is 0.9537, considered not significant by chi square method |
|-----------|-------|----------|--------------------------------------------------------------------------------|
| TC+       | 09    | 10       | Chi square statistics with Yates correction=0.003369                             |
| TC-       | 72    | 69       | OR is 0.8625; hence, this SNP is associated with lower odds of outcome.          |

**Table 3:** TT characteristics in the study groups.

| Base pair | Cases | Controls | The two-sided p value by Chi-square is 0.8174 and hence is considered not significant. |
|-----------|-------|----------|--------------------------------------------------------------------------------------|
| TT+       | 08    | 06       | Chi-square statistics with Yates correction=0.1081                                   |
| TT-       | 73    | 73       | OR is 1.06; hence, this SNP is not associated with odds of outcome.                  |

**Table 4:** GC characteristics in the study groups.

| Base pair | Cases | Controls | The two-sided p value is 0.7423 and is considered not significant. |
|-----------|-------|----------|-------------------------------------------------------------------|
| GC+       | 06    | 08       | Chi-square statistics with Yates correction=0.1081.                |
| GC-       | 75    | 71       | OR is 0.71; hence, this SNP is associated with lower odds of outcome.|

**Table 5:** Alterations in nucleotide of SCN1B SNP rs67701503.

| Base pair | Cases | Controls | The two-sided p value is 0.7830 and is considered not significant. |
|-----------|-------|----------|-------------------------------------------------------------------|
| AC+       | 16    | 18       | Chi-square statistics with Yates correction=0.07585.               |
| AC-       | 65    | 61       | OR is 0.8341; hence, this SNP is associated with lower odds of outcome.|

**Table 6:** Alterations in nucleotide of SCN1B SNP rs67701503.

| Base pair | Cases | Controls | The two-sided p value is 0.7830 and is considered not significant. |
|-----------|-------|----------|-------------------------------------------------------------------|
| CC+       | 65    | 61       | Chi-square statistics with Yates correction=0.07585.               |
| CC-       | 16    | 18       | OR is 1; hence, this SNP is not associated with odds of outcome.    |

**Table 7:** Alteration in SCN1B SNP rs67486287.

| Base pair | Cases | Controls | The two-sided p value is 0.8330 and is considered not significant. |
|-----------|-------|----------|-------------------------------------------------------------------|
| CG+       | 71    | 69       | Chi-square statistics with Yates correction = 0.4445.              |
| CG-       | 10    | 10       | OR is 1.02; hence, this SNP does not affect odds of outcome.       |

**Table 8:** Alteration in nucleotide of KCNJ2 SNP rs786205813.

| Base pair | Cases | Controls |
|-----------|-------|----------|
| T+        | 81    | 79       |
| T-        | 00    | 0        |
Alteration of nucleotide in SCN1B SNP rs55742440. SNP rs55742440 (NM_001037.4 (SCN1B): c.448+181T>C) has been shown in databases to produce a variant T>C (Table 1-4).

After applying Chi square, the two-sided p value is 0.9188 and is considered not significant.

Alterations in the nucleotide of SCN1B SNP rs67701503 SNV rs67701503 (NM_001037.4 (SCN1B): c.448+296C>A) is also an intron variant (SO:0001627) producing a variant C>A (Table 5 and 6).

Alteration in SCN1B SNP rs67486287 (G>C). SNP rs67486287 (NM_001037.4:c.448+301G>C) is an intron variant (SO:0001627) that might result in a missense change from amino acid arginine to threonine at codon location 250 as shown in genomic view in the transcript variant (Table 7 and 8).

**Alteration in nucleotide of KCNJ2 SNP rs78620581 C>T**

KCNJ2 rs199473653 A>G. SNP rs199473653 (NM_000891.2(KCNJ2):c.245G>A ) is a coding sequence variant causing a change in the transcript at location 245 (Table 9 and 10).

No variation or alteration in the nucleotide bases of KCNJ2 SNP was observed between cases and controls.

**DISCUSSION**

In this study, the mean age of the cases is 58.66±13.42 years. This is in concordance with an Indian study conducted by Ashraf et al.\(^9\) The mean age among males was 62±16 years and females were 62±15 years. The most commonly affected age group was 51-60 years comprising 27.10% of cases.

In a study by Shenthar et al the gender distribution for overall CIED implants was 64% males and 36% females. The gender distribution (male:female) in bradycardia pacemakers, ICD and CRT was 65:35, 85:15 and 70:30, respectively.\(^10\) In line with the other studies in the present study, the males are more commonly affected than females. Approximately 60% of cases were males and 55% of controls were males. In the present study, male-to-female ratio in cases and controls was 2.8:1 to 2.29:1, respectively.

LBBB was the commonest conduction defect in both the sexes in the research done by Ashraf et al with 27.7% in males and 31.5% in females.\(^9\) The results of our study are in concordance to the study by Jain et al. In both the studies, complete heart block was the most common CCD in both the sexes. In a study published by Jain et al out of 312 patients, 82.05% patients were suffering from acquired AV block, in which 68.26% had CHB and 13.78% had symptomatic, high-grade AV block.\(^11\) Approximately 16.02% patients were having SSS. In this study, acquired AV block is the most common indication for pacemaker implantation.

In a study by Kanse et al 91% of patients were symptomatic at presentation. The most commonly presenting symptoms were syncope, light headedness, palpitation and dyspnea, in 59.9%, 62.2%, 56.7% and 56.7% of patients, respectively.\(^12\) Approximately 92% patients were symptomatic at presentation in a study by Jain et al (2018) and syncope (68.26%) was the most common symptom were comparable with previous studies. In concordance with the background research, the present study had 92.5% cases symptomatic on presentation, with syncope being the most common presentation, found in 59.25% of patients. Dyspnea was the second most common presentation.

The association of diabetes mellitus has been shown with right bundle branch block.\(^13\) Jeong et al studied 14,540 Korean adults and found that age, gender, hypertension and DM are independently associated with RBBB.\(^14\) Analyzing 14,500 EKGs, Garcia et al found a high prevalence of bi-fascicular block (37.5%) in DM patients.\(^15\) Direct evidence involving the increased prevalence of high-degree AV block in DM patients was published by Podlaha et al. They studied 258 patients retrospectively. Second or third-degree AV block was present in 48.8% patients. Diabetes mellitus was found in 49.2% versus that of 38.4% of the age and sex-matched control group.\(^16\) In our study, the prevalence of DM was statistically significantly higher in cases as compared to the controls. Approximately 34.5% of cases were diabetics as compared to 12.6% controls.

In the present study, hypertension was present in 56.79% of cases as opposed to 37.97% of controls. This finding was in concordance with the study by Ashraf et al which also showed that majority of the patients were hypertensive.\(^9\)

Refsgaard et al published results regarding SCN1B. A total of 28 sequence variants were identified using variant analysis, seven in SCN1B, three in SCN2B, two in SCN3B, two in SCN4B, four in FHL1 and ten in LMNA. The identified variants were listed. Three of the variants

| Base pairs | Cases | Controls |
|-----------|-------|----------|
| G×       | 81    | 79       |
| G-       | 00    | 0        |

Table 10: Alteration in nucleotide of KCNJ2 SNP rs199473653.
were novel. All novel variants were positioned in flanking introns and did not affect a canonical splice site. One non-synonymous variant was identified (FHL1 p.D275N). No disease-causing mutations were identified.\textsuperscript{17}

Watanabe et al screened the four beta-subunit genes (SCN1B-SCN4B) for mutations and reported 2 mutations in SCN1B (R85H, D153N) and 2 mutations in SCN2B (R28Q, R28W). Functional analysis of the mutant $\beta1$ and $\beta2$ subunits demonstrated altered channel gating and a reduction in a indicating a loss-of-function effect.\textsuperscript{18}

Xia et al reported a novel missense mutation in the KCNJ2 gene in a Chinese AF kindred. KCNJ2 encodes the Kir2.1 channel that underlies the inward rectifier potassium current; IK1.A valine-to-isoleucine mutation (V93I) was identified, resulting in a gain-of-function effect with increased potassium current amplitudes, in both the inward and outward directions. Enhanced inward rectifier currents have been demonstrated to promote AF by accelerating and stabilizing atrial rotors that maintain arrhythmia.\textsuperscript{19}

In 2004, Ellinor et al screened a COHORT of 141 patients with lone AF for KCNQ1 mutations and failed to identify any mutations. In a subsequent study, the same group screened 96 unrelated probands with familial AF for mutations in the KCNJ2 and KCNE1-5 genes and once again found no evidence of causal mutations.\textsuperscript{20}

Multiple transcript variants encoding different isoforms have been found for this gene. SNP rs55742440 (NM_001037.4 (SCN1B):c.448+181T>C) has been shown in databases to produce a variant $T>C$. This changed the amino acid from leucine to proline producing tight turns and changes in main chain conformations. But in the present study, sequence was producing a variant from $T>G$ and mostly in heterozygous condition. This changed the amino acid in the protein from hydrophobic leucine to polar arginine. This should theoretically result in a change in the protein assembly. But this alteration lied in the intronic region and bears no resemblance to a splice variant of either the donor or acceptor site (as observed by NetGene2 software online). Thus, the sequence ontology of this alteration should have no effect on the protein, except in producing a splice variant which again is not being supported profusely by the data available online. Hence, the variant was benign and further studies are recommended in this context.

SNP rs67701503 (NM_001037.4 (SCN1B):c.448+296C>A) was also an intron variant (SO: 0001627), resulting in C>A. This variant was predicted to be benign by multiple algorithms, and/or has population frequency not consistent with disease. This variant was also located downstream of the coding region and did not lie in the splice-site region, thereby not having any significance in the regulation of the gene as well.

SNP rs67486287 (NM_001037.4:c.448+301G>C) was an intron variant (SO:0001627) that might produce a missense variant changing amino acid arginine to threonine at codon location 250, as shown in genomic view in a transcript variant. But this was insignificant as it lied in the intronic region and the NetGene2 analysis negates its presence in the splice site. Hence, this variant can best be summed up as a benign variant.

SNP rs199473653 (NM_000891.2 (KCNJ2):c.245G>A) is a coding sequence variant, resulting in a change in the transcript at location 245, that is transition from G>A (missense; c.245G>A), leading to a change in amino acid from arginine to glutamine (sequence ontology: SO:0001583) at codon 82 (p.Arg82Gln) in KCNJ2 protein. The arginine residue is highly conserved, and there was a small physicochemical difference between arginine and glutamine. It was very rare in general population databases and experimental studies using an animal cell model have shown that it resulted in the creation of non-functioning K+ channels (PMID: 16217063, 22589293). In summary, this was a rare variant that had been reported in individuals and families affected with ATS and have been shown to cause a deleterious effect on channel function. Hence, this variant had been classified as pathogenic.

In the present study COHORT, only homozygous GG variants have been found in almost equal frequency in the healthy controls as well. The allele variant of arginine at position 82 had been shown to be pathogenic in various types of studies. This general prediction was being shown through in silico analysis of the variation that lied in the helical structure of transmembrane part of protein. As there was almost no change in the healthy versus patient group for this particular variant, it can be stated that rs199473653, in the present study, was not affecting the KCNJ2 function. Any variation observed in patients may be attributed to the presence of any other variants that affect other parts of the channel protein. The study can further be validated by larger number of samples and inclusion of associated variants at regulatory points.
In summary, while Ile79Thr was a good candidate for a disease-causing mutation, with the clinical and molecular information available currently, we cannot unequivocally determine the clinical significance of this variant. The variant was found in LQT panel(s).

CONCLUSION

In total 81 cases of CCDs were studied, of which 21.70% cases belonged to the age group of 51-60 years, with the mean age of cases being 58.66±13.42 years and male to female ratio being 2.8:1. The mean age of controls was 54.02±11.75 years, with similar male to female ratio being 2.8:1. The mean age of cases being 58.66±13.42 years and male to female ratio being 2.8:1. The mean age of controls was 54.02±11.75 years, with similar male to female ratio. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases. The most common symptom was syncope, which was complete heart block, which comprised 64.19% of cases.

This study paved way for future studies focusing on exonic regions and inclusion of analysis of SCN1A gene.

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