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Description of Mitochondrial Gene Mutations in Pakistani Patients with Coronary Artery Disease: An Investigation of Genetic Susceptibility

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Research Article

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Abstract

Background: Mutations in mitochondrial DNA (mtDNA) were the important causes of cardiovascular diseases. However, little was known regarding the role of mitochondrial DNA (mt-DNA) mutations in coronary artery disease (CAD). To investigated the association between mitochondrial genes mutations and CAD in Pakistani population.

Methods: Approximately, 11 related CAD patients and 29 control subjects were recruited in this study; we performed PCR-RFLP to amplify mitochondrial genes and subsequently sequenced the PCR products. In addition, the pathogenicity scoring system was used to evaluate the deleterious roles of these genes mutations. We also used real-time PCR method to determine the mtDNA content in CAD patients carrying these mutations.

Results: Three mutations were identified by PCR-Sanger sequencing; these mutations included mt-ND4 12133C>T, mt-ND5 12372G>A and mt-CYB 15884G>C. These mutations were localized at the highly conserved nucleotides, may cause the failure in mt-DNA metabolism. Furthermore, CAD group showed a clear reduction in mitochondrial copy number by comparing with the controls.

Conclusions: Mutations in mt-DNA genes were the important causes of CAD, our findings provided novel insight into the pathophysiology of CAD that were manifested by mitochondrial dysfunction.

Keywords: Mt-DNA; Mutations; CAD; Copy Number; Mitochondrial Dysfunction

Introduction

Mitochondrial disorders lead to hearing impairment, heart diseases, muscle coordination losses, visual problems, muscle failing, neurological issues, growth reduction, dementia, respiratory disorders and learning disabilities [1]. Mitochondria are one of the unique cellular organelles having ability to perform cellular functions as well as produce energy in form of ATP [2]. Mitochondria is the only organelle that is control by its own and nuclear genome

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[3]. There are no introns present in human mitochondrial genome. Structurally, mitochondria have double stranded and circular genome that consist of 16569 base pairs [4]. Overall, mitochondria have 37 genes in which 2 genes are for rRNAs, 13 genes are for protein formation and 22 are coded for tRNAs. By nuclear genome, 1500 mitochondrial proteins are encoded approximately which contribute as the part of mitochondrial proteome [5]. The mitochondrial small genome is present in cells as many copies that is maternally inherited [6]. The mitochondrial genome is more susceptible to variation from 10% to 20% due to having limited repair acapabilities, no protective proteins and closely located with memebrane [7]. Mutations in mitochondrial genome lead to missing in metabolism of oxidative energy and other multiple disorders [8,9]. Some mutations are associated with disorders such as cancer, neurodegenerative diseases and aging [10]. Abnormal oxidative phosphorylation leads 15% to 25% diseases due to pathogenic mutations in mitochondrial DNA [11,12]. It has been identified that mutated tRNA molecules synthesis protein and make the mitochondrial genome become pathogenic [13,14]. There exist specific polymorphisms belonging to mitochondrial genes ND3 and CYTB, which are believed to be associated with high-altitude adaptation in the Tajiks population in Tibet native to China [15].

Mitochondrial genes mutations cause a wide range of disorders such as cardiomyopathy and encephalopathy [16,17]. Defects in blood circulatory system causes cardiac pathogenic conditions represented by cardiovascular diseases. Atherosclerosis, hypertension and coronary artery disease are rapidly growing pathologies [18]. Coronary artery disease is one of the most abundant cardiovascular diseases affecting 502,000 in USA and more than 1000,000 people in China annually [19,20]. The problematic associations like environmental factors, lifestyle and gene mutations promoted the disease pathology [21,22]. Whole genome wide study in European countries and central Asia identified numerous genetic loci that are associated with CAD [23,24]. Coronary Artery Disease is maternally inherited common disorder having association with changes in mtDNA encoded genes. A particular mutation 15928G>A has been accounted in 80% subjects with CAD [25]. We have a systematic mutation screening project for the mitochondrial DNA of subjects from Northern Pakistani families suffering from heart diseases and epilepsy [26]. The current study illustrates the study of a joint family of patients with CAD. The patients were selected having maternally transmitted CAD from the Clinic of Cardialogist in DHQ Hospitals, KP, Pakistan. This study was designed at the screening of mitochondrial protein coding genes for NADH dehydrogenase 4, NADH dehydrogenase 5 and cytochrome b (MT-ND4, MT-ND5 and MT-CYB).

Materials and Methods

Patients and Families Enrollment

It was analytical and cross sectional study in which patients having CAD were diagnosed through ECG and X-ray and ECG via specialized doctors. The enrolled family members were informed about the aims and objectives of study. To contribute in investigation and data publication, the consent form was filled by family head member. A pedigree was constructed to capture the detaile information about cousin marriages and decease members. The details for each member of family about diseases and treatment were also recorded (Table 1 & Figure 1).

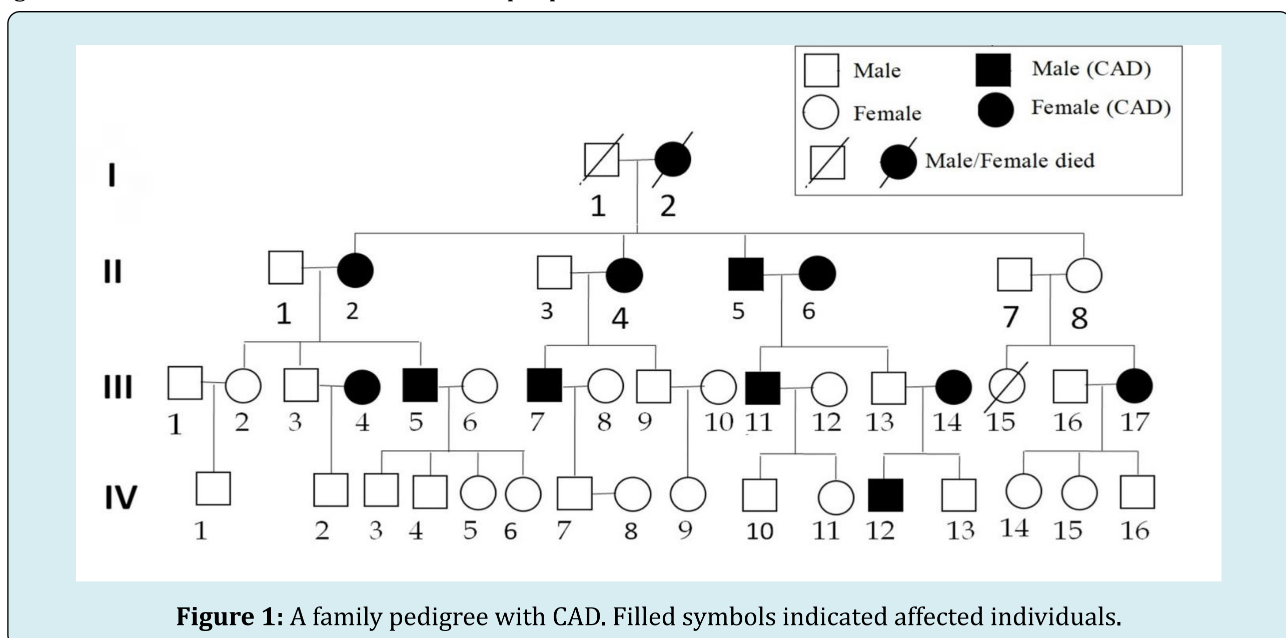

Figure 1: A family pedigree with CAD. Filled symbols indicated affected individuals.

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Sampling and PCR Amplification of Target DNA

Blood samples were extracted from patients and normal family members. DNA was extracted using Proteinase K and PCI based method. Nano drop and gel electrophoresis procedures were performed for the determination of quality and quantity of DNA and samples were kept at -20ºC. The following specific primers were used for mt-DNA genes amplification through PCR (Table 2). PCR reaction mixture (15µL) consisted of 1.5µL buffer, 3UTaq polymerase, 1µM dNTPs, 1mM MgCl2, 20 picomole forward and reverse primers, 7.2µL ddH2O and 20ng of DNA template. Thermocycler was adjusted at 95°C for 5 min followed by 35 cycles of denaturation at 95°C for 30s, annealing at 52°C for 1 min, extension at 72°C for 1 min. The final extension time of 7min was adjusted at 72°C.

Subjects	Gender	Age (Years)	Observation	Diagnosis	Systolic/Diastolic mm/Hg	LVD	RVD
II-1	M	90	N	N	130/85	45	20
II-2	F	80	CAD	X-ray, ECG	140/90	55	30
II-3	M	85	N	N	135/80	40	18
II-4	F	72	CAD	X-ray, ECG	140/90	52	26
II-5	M	75	CAD	X-ray, ECG	130/85	50	29
II-6	F	82	CAD	X-ray, ECG	140/90	53	28
II-7	M	70	N	N	145/95	40	12
II-8	F	78	N	N	130/90	38	15
III-1	M	62	N	N	125/83	39	13
III-2	F	59	N	N	122/81	37	16
III-3	M	63	N	N	140/90	42	15
III-4	F	58	CAD	X-ray, ECG	110/70	50	30
III-5	M	60	CAD	X-ray, ECG	125/82	55	29
III-6	F	56	N	N	120/90	50	20
III-7	M	50	CAD	X-ray, ECG	150/90	49	20
III-8	F	51	N	N	135/95	46	18
III-9	M	48	N	N	140/85	43	20
III-10	F	45	N	N	130/90	38	25
III-11	M	35	CAD	X-ray, ECG	140/90	52	25
III-12	F	30	N	N	135/85	47	18
III-13	M	30	N	N	130/90	41	17
III-14	F	27	CAD	X-ray, ECG	130/70	49	30
III-15	M	40	N	N	130/85	45	12
III-16	F	38	CAD	X-ray, ECG	150/95	50	26
IV-1	M	19	N	N	120/80	35	18
IV-2	M	25	N	N	120/85	37	20
IV-3	M	26	N	N	120/90	45	13
IV-4	M	24	N	N	120/80	39	12
IV-5	F	21	N	N	130/85	41	15
IV-6	F	19	N	N	120/90	47	14
IV-7	M	25	N	N	130/80	46	10

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IV-8	F	20	N	N	120/85	40	18
IV-9	F	16	N	N	120/80	39	20
IV-10	M	22	N	N	125/80	37	25
IV-11	F	20	N	N	120/80	47	24
IV-12	M	15	CAD	X-ray, ECG	130/90	48	25
IV-13	M	13	N	N	120/80	39	16
IV-14	F	23	N	N	125/80	40	12
IV-15	F	20	N	N	120/85	43	9
IV-16	M	18	N	N	120/80	42	13

Table 1: Clinical and biochemical data for pedigrees of a Pakistani family.

Target gene Primer IDsize	Primer sequence (5'-3')	Product
mt-DNAND4MT-13F	TTTACCACAACACAATTGGG	525bp
MT-13R	GCTCAGTGTCAGTTCGAGATA	
mt-DNACYBMT-21F	ATCGGAGGACAACCAGTAAGC	320bp
MT-21R	TGATGGGTGAGTCAATACTTGG	

Table 2: Primers for mt-DNA genes PCR amplification.

Detection of Mutations by Sequence Analysis

The PCR products were analyzed by 1% agarose gel electrophoresis. Purified PCR products were commercially analyzed for nucleotide sequences from biological technology department of TSINGKE Chengdu (China)http://foreign.macrogen.co.kr/eng/. Further alignment studies were carried out through online DNA analysis tools like NCBI Blast and Ugene. The nucleotide sequences obtained were compared with rCRS sequence.

Cross-Validation Of Deleterious Effect of Mutations by Computational Tools

PON-mt-tRNA, a multi-factorial probability-based prediction tool, was used for classification of newly observed human mt-tRNA mutations. It integrates machine learning prediction together with evidence of biochemistry, histochemistry, and segregation, to compute the posterior probability of pathogenicity. This method displayed high performance with Accuracy and Matthews Correlation Coefficient (MCC) of 1.00 and 0.99, respectively. It accepts input as the comma separated single query with mitochondrial genome location, reference nucleotide, and new nucleotide; output score ranges from 0 to 1, following increasingly deleterious pattern. Variations are classified into five classes that is, variants of uncertain significance, neutral, likely neutral, likely pathogenic, and pathogenic. Mitochondrial tRNA Informatics Predictor (MitoTIP, Philadelphia, PA, http:// journals. plos. org/ ploscompbiol/ article? id=10.1371/ journal.pc bi.1005867), is another tool for predicting pathogenicity of novel mitochondrial tRNA variants, which was effectively employed in our analysis to have combinatorial optimization of in silico predictions. MitoTIP is based on multiple sources of information for prediction of the likelihood that novel single nucleotide variants in tRNA encoding sequences would cause disease [27,28]. Upon query, the predictive algorithm incorporates an estimation of the importance of a position across all known mitochondrial tRNAs using data from publically available databases (like MITOMAP and GenBank); the output ranges from−5.9 to 21.8 (Supplementary data).

Secondary Structure Prediction of Mutated Genes

"RNA structure web server is a tool to predict secondary structures of mutated genes with lowest free energy and base pair probabilities. The server to predict secondary structure combines separate prediction and analyzed algorithms which is, finds structures with most predictable accuracy, expects a lowest free energy structures, calculates the function separately and pseudo knot (if any) prediction. DNA sequence takes by server and generates an extremely possible, annotated cluster of secondary structures, opening with the minimum free energy structure and including furthers with different probabilities of accuracy. Three mutant sequences (m.12133C>T, m.12372G>A and m.15884G>C) were submitted to the server for comparative structure analysis.

Prediction of Secondary and 3D Structures

For the prediction of mitochondrial genes secondary structure, the RNA fold web server was used. The generated 2D structures were used in dot-bracket format for the generation of normal and mutant sequence 3D structures using the automated RNA structure 3D Modeling server (RNA

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Composer) was used for the prediction of mitochondrial genes 3D.

Results

Subjects

In present study 40 individuals were selected from the family. All the diagnosed patients had signs of hypertension and CAD in their family history.

Genes and Mutations

We identified three mutations in CAD patients after mtDNA genes analysis and indicate three point mutations including m.12133C>T, m.12372G>A, and m.15884G>C (Figure 2). The mutations m.12133C>T and m.12372G>A are heteroplasmic while m.15884G>C representing homoplasmic condition.

Validation by in Silico Predictive Tools

All the three variants were reported to be deleterious by MitoTIP server. The difference in the degree of predicted deleteriousness is due to the fact that both tools work on different algorithms/principles and consider diverse factors. However, the computational predictive tools strongly support that the mutations show different types of variation (Table 3).

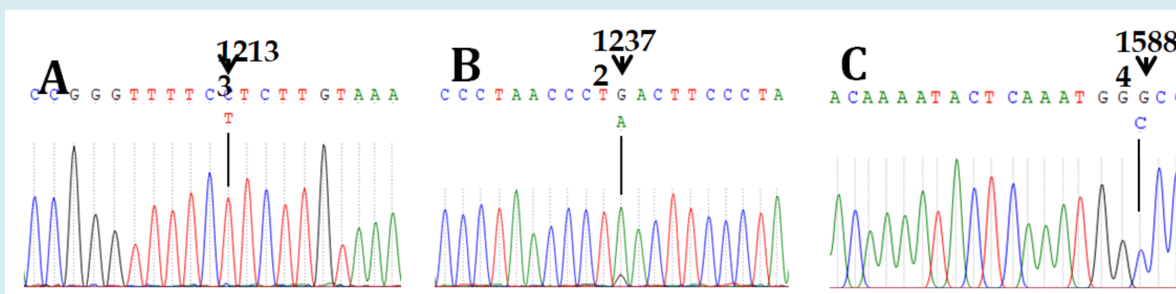

Figure 2: Computational predictive tools strongly support that the mutations show different types of variation.

Locus	rCRS Position	Query Position	rCRS NT	Query NT	Mut Type
ND4	12133	110	C	T	Transition
ND5	12372	350	G	A	Transition
Cytb	15884	93	G	C	Transversion

Table 3: List of mutations identified in CAD patients and their pathogenicity predictions by MitoTIP and PON-mt-tRNA.

Predicted RNA Secondary Structures of Mitochondrial Genes

The harmful impact of the varients nucleotide could be understood by particular RNA secondary structures. Two to three structures generated by RNA structure Webserver and one of them was selected with free minimum energy. Three mutant models that are m.12133C>T, m.12372G>A and m.15884G>C were observed (Figure 3), with disruptive confirmation that could possibly change the role of mt-DNA genes which lead to pathogenic phenotype.

Discussion

CAD is the most abundant type of heart diseases disturbing approximately 25% individuals and the primary death cause worldwide [29]. It leads to heart failure, myocardial infarction and rapid loss that is recorded 64% in women and 50% in men [30-32]. CAD has been linked with a combined or quantitative impact of multifactorial ecological conditions, hereditary factors or nuclear factors and psychological status [33-36]. Numerous risk factors having linked with CAD include serum lipids, diabetes, blood ceramides, lifestyle and hypertension [37]. Studies on the family history and genetic has an established association with CAD that may enhance the chances of occurrence from 40% to 60%. CAD developed primarily by contribution of genetic factors [38,39]. Mitochondrial DNA mtDNA4977 deletion, 16189T>C, 15928G>A and T16519C have been associated with CAD [40-43]. Equally, several tRNA pathogenic mutations have been identified having contribution in CAD patients [44-46]. We have evaluated a family with history of CAD for mitochondrial gene mutations (Figure 1). Total 40 individuals were recruited in the study after signing the consent forms, 11 of these subjects were diagnosed for CAD (Table 1). Three genes mt-ND4, mt-ND5 and mt-CYB were PCR amplified and fragment size was confirmed for each by agarose gel electrophoresis. Purified PCR product was commercially analyzed for nucleotide sequences and mutations in the above gene sequences were detected. We found mutations m.12133C>T, m.12372G>A and m.15884G>C position in the mitochondrial genes – mt-ND4, mt-ND5 and mt-CYB respectively (Figure 2). None of

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these mutations was detected in the healthy subjects from this family.

Conclusions

Our findings suggest an association of coronary artery disease with mitochondrial genes mutations that are different from normally published pathogenic mutations. The effect of known mutations on RNA secondary structure that was estimated by online biological softwares. Disruptive structure of mutants confirmed through in silico studies which lead to mitochondrial dysfunction or pathogenic effect. The prediction studies by software based on computer have strongly maintained the pathogenicity level of known mutations signifying an in vivo confirmation.

Ethical Statement

This study was approved by Ethical Committee of Institution and Board of Advanced Studies and Research at Hazara University, Mansehra 21300, Pakistan according to the notification number F.No.73/Ittl/ORlClB C2016/.

Conflicts of Interest

The authors have no competing interests to declare.

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