International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A Pilot Mitochondrial Genome-Wide Association on Migraine Among Saudi Arabians

Lubna Al Asoom[1], Johra Khan[2,3], Ahmad Al Sunni[1], Nazish Rafique[1], Rabia Latif[1], Majed Alabdali[4], Sayed AbdulAzeez[5], J Francis Borgio[5]

[1]Department of Physiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, 31541, Saudi Arabia; [2]Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Majmaah, 11952, Saudi Arabia; [3]Health and Basic Sciences Research Center, Majmaah University, Majmaah, 11952, Saudi Arabia; [4]Department of Neurology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, 31952, Saudi Arabia; [5]Department of Genetic Research, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam, 31441, Saudi Arabia

Correspondence: Lubna Al Asoom, Department of Physiology, College of Medicine, Imam Abdulrahman Bin Faisal University, P.O Box 2004, Dammam, 31541, Saudi Arabia, Tel +966505846344, Email lasoom@iau.edu.sa; Johra Khan, Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Majmaah, 11952, Saudi Arabia, Tel +966538077360, Email j.khan@mu.edu.sa

Background: Mitochondrial DNA (mtDNA) mutations have been reported in multiple neurological diseases and helped to explain the pathophysiology of these diseases. Similarly, variations in mtDNA might exist in migraine and can explain the effect of low ATP production in the neurons on the initiation of migraine attack. Therefore, in the current study we aim to explore the association of mtDNA mutations on migraine in the Saudi population.

Subjects and Methods: Over 1950 young Saudi female students were screened for migraine, among that a total of 103 satisfied the ICHD-3 criteria. However, 20 migraine cases confirmed in the neurology clinic and gave consent to participate in the study. Another 20 age-matched healthy controls were also recruited. Mitochondrial sequence variations were filtered from exome sequencing using NCBI GenBank Reference Sequence: NC_012920.1 and analysed using MITOMAP. Genes with significant single nucleotide polymorphisms (SNPs) were investigated by the gene functional classification tool DAVID and functional enrichment analysis of protein–protein interaction networks through STRING 11.5 for the most significant associated genes.

Results: Genome wide analysis of the mitochondrial sequence variations between the patients with migraine and control revealed the association of 30 SNPs ($p < 0.05$) in the mitochondrial genome. The highest significance ($p = 0.001033$) was observed in a coding SNP (rs1603225278) in the *CYTB* gene and rs386829281 in the region of origin of replication. Twenty-four significant SNPs were in the coding region of nine (*ND5, ND4, COX2, COX1, ND3, CYTB, COX3, ND2* and *ND1*) genes.

Conclusion: This is the first study to demonstrate the association of mtDNA variations with migraine in the Saudi population. The current findings will help to highlight the significance of mtDNA mutations to migraine pathophysiology and will serve as a reference data for larger national and international studies.

Keywords: mitochondrial DNA, Saudi Arabia, mtDNA variations, migraine, *CYTB* gene

Introduction

Mammalian mitochondrion is found to own a specific deoxyribonucleic acid (DNA) in its matrix. Mitochondrion DNA (mtDNA) is responsible for the transcription of essential proteins for the mitochondrial function.[1] As the paternal mtDNA is degraded upon fertilization, mtDNA is purely inherited from the maternal side.[2] Although mtDNA has double strands it is different in structure from the nuclear DNA.[3] Interestingly, it was found that mutations can occur in mtDNA as they do in the nuclear DNA and culminate in diseases. Furthermore, mtDNA is more vulnerable to mutations due to the lack of histone and the high exposure to oxygen free radicals in the mitochondria.[1] Mutations in mtDNA can lead to disturbances in the oxidative phosphorylation process and can affect the energy production process.[4] The first description of mtDNA mutation was reported in 1988 in patients with mitochondrial myopathy.[5] Later, multiple mutations were discovered and linked to specific diseases. Most mtDNA mutations are manifested by neurological symptoms such as

Received: 21 April 2022
Accepted: 6 July 2022
Published: 21 July 2022

myopathies, optic neuropathy, ophthalmoplegia, and myoclonic epilepsy which is seen in diseases such as Leber hereditary optic neuropathy (LHON) and Kearns–Sayre syndrome (KSS). Later, the study and identification mtDNA mutations helped to identify the pathophysiology of Alzheimer, Parkinson's, diabetes, and cancer.[6]

Migraine with its multiple types was proposed to be one of the neurological diseases that could be explained by mtDNA mutations. This is supported by the possible role of increased neuronal excitability, failure of the ATP synthesis and cerebral vascular abnormalities related to mitochondrial dysfunction on the pathophysiology of migraine.[7] In addition, the prominent maternal inheritance of migraine might also support the involvement of mtDNA mutations.[8] Studies that explore the pathophysiology of migraine with aura revealed some evidence for the involvement of mitochondrial dysfunction in the first stage of migraine attack. Similarly, a higher level of serum lactate was demonstrated in migraineurs during and between attacks that can further reflect the possible impairment of pyruvate metabolism in the Krebs cycle.[9] Studies from Finland[10] and Germany[11] on migraine patients reported associations with mitochondrial DNA variant. The Nord-Trøndelag Health Study (HUNT) is a single population-based cohort study conducted in Norway's Nord-Trøndelag County which revealed no significant association between the studied gene variations and migraine.[12] However, it is worth mentioning that, the study by Børte et al utilised a microarray of known variants.[12] Hence, a mitochondrial sequence-based study is needed to obtain all variants. Therefore, in the current study, we aim to identify the significant association of mitochondrial sequence variation using next generation-based sequencing analysis of mitochondrial sequence variation on migraine in the Saudi population and add a critical piece of information for studying migraine in humans.

Materials and Methods

The protocol of the current study was written in concordance with the ethical considerations of human studies of the Declaration of Helsinki and it was reviewed and authorized (IRB number: IRB-2021-01-250) by the Institutional Review Board of Imam Abdulrahman Bin Faisal University. Young female candidates (n = 1950), with an age range of 18–30 years, were screened for migraine, among which a total of 103 satisfied the ICHD-3 criteria. Twenty migraine cases among the females who satisfied the ICHD-3 criteria were confirmed in the neurology clinic of the university hospital and were recruited upon receiving the consent from migraineurs in the campus of Imam Abdulrahman Bin Faisal University (IAU), Dammam, Saudi Arabia. Twenty healthy volunteer candidates who were age matched were enrolled as controls upon receiving the consent and had no complaints of headache.

The participants were first interviewed and the history of the disease was collected, including the severity of the headache on a scale of 1–10, number of attacks per month, the presence or absence of aura, other associated symptoms, use of medication, and possible precipitating factors such as stress, sleep deprivation, fasting or missed meal, physical activity, loud sounds, changes of weather or temperature, strong smell or lights, specific food articles, phases of menstrual cycle, family history of migraine, and past history (other chronic diseases). The aim and objectives of the study were also explained to them and then they signed informed consents for their participation in the study.

Analysis of Mitochondrial Sequence Variations

The DNA was extracted (QIAamp DNA Blood Mini Kit, Qiagen, Germany) from blood and the purity of the DNA was assessed by nanodrop, and concentration of the DNA was examined by qubit fluorometer. Agarose gel electrophoresis was used to check the DNA integrity. All the samples were then sequenced using paired end whole exome sequencing followed by quality screening. Good quality was considered when the sample depth mean was ≥7.5, the variant call rate of sample was ≥0.5, and the genotype quality of sample mean was ≥28. For good quality variants filtering, the following criteria like raw read depth ≥10, phred score quality ≥30, and mapping quality ≥30 were considered. One python package was utilized for quality assessment of samples, genotypes and variants. Similarly, the python package-based Hail standard was implemented for the entire pipeline analysis of genome-wide association. The p-value <0.05 was considered as significant. Mitochondrial sequence variations were filtered for further analysis using NCBI GenBank Reference Sequence: NC_012920.1 (mitochondrion of *Homo sapiens*, complete genome). Moreover, the mitochondrial sequence variations were analyzed for the mitomap frequency and gnomAD (genome aggregation database) frequency using MITOMAP.[13] Genes with significant single nucleotide polymorphisms (SNPs) were tested by the gene functional classification tool

DAVID[14] and functional enrichment analysis of protein-protein interaction networks using STRING 11.5.[15] The top nine associated genes functional annotation was done by STRING 11.5 (p-value <0.05). For the pathway enrichment using the enrichR server for genes and pathway involvement were performed by KEGG search and reactome pathway through DAVID and STRING 11.5.

Results

Age matched migraineurs (22.10±3.63) and the controls (21.86±1.75) were selected for the whole exome sequencing to identify the mitochondrial sequence variations. The controls and cases were not significantly different in the baseline characteristic such as age (p-value = 0.818), body weight (kg) (p-value = 0.115) and BMI (p-value = 0.095). Frequency of the most common precipitating factors among the migraineurs are presented in Figure 1. Among the migraineurs of the study 57.9%, 50% and 55%, were with aura, using pain killer and have positive family history of migraine, respectively.

A total of 189 (Table S1) mitochondrial sequence variations were retrieved from the exome sequence data. Genome wide analysis of the mitochondrial sequence variations between the patients with migraine and control revealed association of 30 SNPs (p<0.05) in the mitochondrial genome (Table 1). The highest significant (p = 0.001033) observed in a coding SNP (rs1603225278) in the *CYTB* gene. Twenty-four significant SNPs are in the coding region of nine different genes (*ND5, ND4, COX2, COX1, ND3, CYTB, COX3, ND2* and *ND1*) (Figure 2). A total of 7 SNPs (rs1603223919x, rs200044200, rs386829179, rs28359177, rs2854123, rs28359180 and rs193302971) were observed as significant in the *ND5* gene.

Networks of protein-protein interaction analysis and the functional enrichment of the genes (*ND5, ND4, COX2, COX1, ND3, CYTB, COX3, ND2* and *ND1*) with the significant SNPs revealed the most significant associated pathway, oxidative phosphorylation ($p = 2.55\times^{-12}$) in the Kyoto encyclopedia of genes and genomes pathway analysis of the significant genes (Figure 3; Table 2). Enrichment analysis of mitochondrial genes with significant variations associated with migraine individuals revealed the association of nervous system disease (p = 0.0083), brain disease (p = 0.0193), central nervous system disease (p = 0.0065), and Leber hereditary optic neuropathy ($p = 4.46\times10^{-11}$) (Table 2).

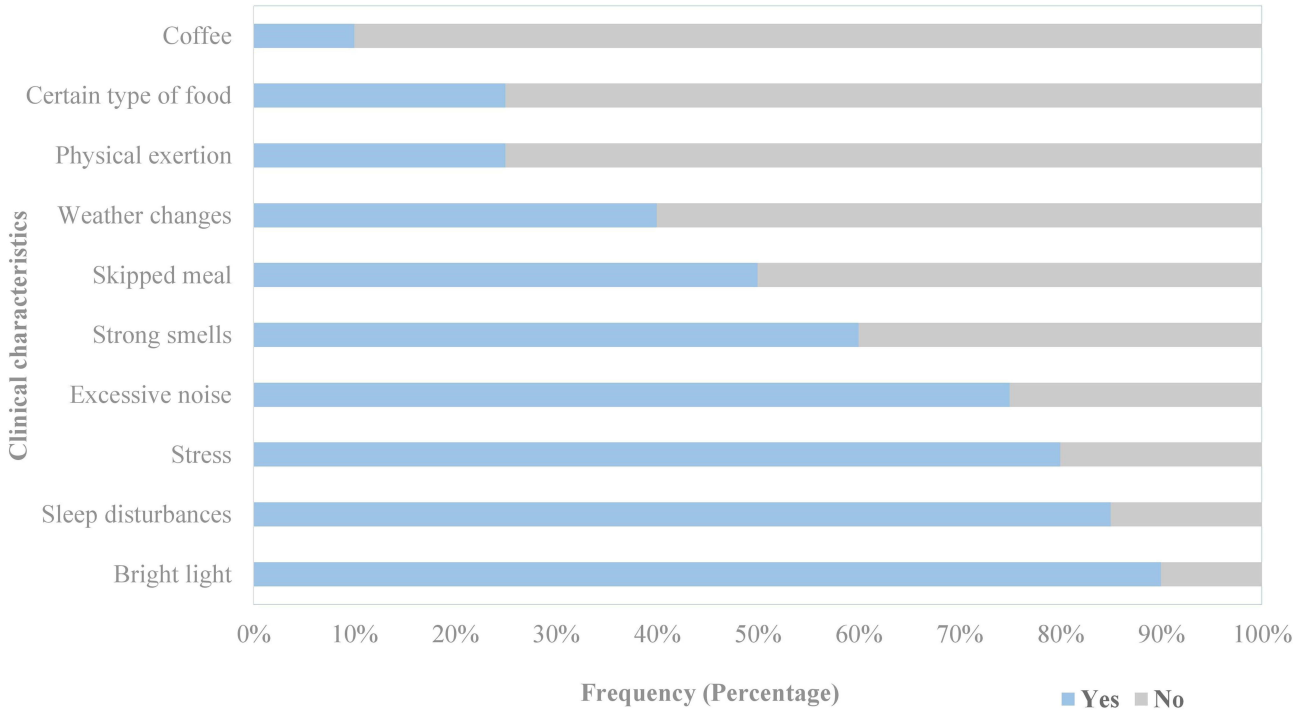

Figure 1 Precipitating possible factors of migraine attack and frequency in the migraine participants from Saudi Arabia.

Table 1 List of Mitochondrial Sequence Variations Associated with Migraine

S. No	Locus Contig	Locus Position	Existing Variation (SNP ID)	Alleles	Associated Allele	Gene	*p*-value
1	chrM	15433	rs1603225278	["C", "T"]	T	*CYTB*	0.001033
2	chrM	16220	rs386829281	["A", "G"]	G		0.001033
3	chrM	10217	rs1556423786	["A", "G"]	G	*ND3*	0.010229
4	chrM	12834	rs1603223919	["A", "G"]	G	*ND5*	0.010229
5	chrM	13135	rs200044200	["G", "A"]	A	*ND5*	0.010229
6	chrM	15317	rs2853507	["G", "A"]	A	*CYTB*	0.010229
7	chrM	8152	rs1603221312	["G", "A"]	A	*COX2*	0.010229
8	chrM	16301	rs879194775	["C", "T"]	T		0.026534
9	chrM	10115	rs3899188	["T", "C"]	C	*ND3*	0.03179
10	chrM	1018	rs2856982	["G", "A"]	A		0.03179
11	chrM	11386	rs1556423940	["T", "C"]	C	*ND4*	0.03179
12	chrM	11944	rs3087901	["T", "C"]	C	*ND4*	0.03179
13	chrM	13395	rs386829179	["A", "G"]	G	*ND5*	0.03179
14	chrM	13590	rs28359177	["G", "A"]	A	*ND5*	0.03179
15	chrM	13650	rs2854123	["C", "T"]	T	*ND5*	0.03179
16	chrM	13803	rs28359180	["A", "G"]	G	*ND5*	0.03179
17	chrM	13934	rs193302971	["C", "T"]	T	*ND5*	0.03179
18	chrM	16209	rs386829278	["T", "C"]	C		0.03179
19	chrM	16354	rs878897391	["C", "T"]	T		0.03179
20	chrM	2789	rs28358581	["C", "T"]	T		0.03179
21	chrM	3594	rs193303025	["C", "T"]	T	*ND1*	0.03179
22	chrM	5196	rs1603219826	["T", "C"]	C	*ND2*	0.03179
23	chrM	7175	rs28358874	["T", "C"]	C	*COX1*	0.03179
24	chrM	7256	rs1556423258	["C", "T"]	T	*COX1*	0.03179
25	chrM	7274	rs879089638	["C", "T"]	T	*COX1*	0.03179
26	chrM	7771	rs368038563	["A", "G"]	G	*COX2*	0.03179
27	chrM	8206	rs28358883	["G", "A"]	A	*COX2*	0.03179
28	chrM	9221	rs367578507	["A", "G"]	G	*COX3*	0.03179
29	chrM	9530	rs879237361	["T", "C"]	C	*COX3*	0.03179
30	chrM	11467	rs2853493	["A", "G"]	G	*ND4*	0.041918

Discussion

The present study aimed to identify the significant association of mitochondrial gene variations and migraine in Saudi candidates using next generation-based whole sequencing analysis of mitochondrial DNA. Successfully, we were able to

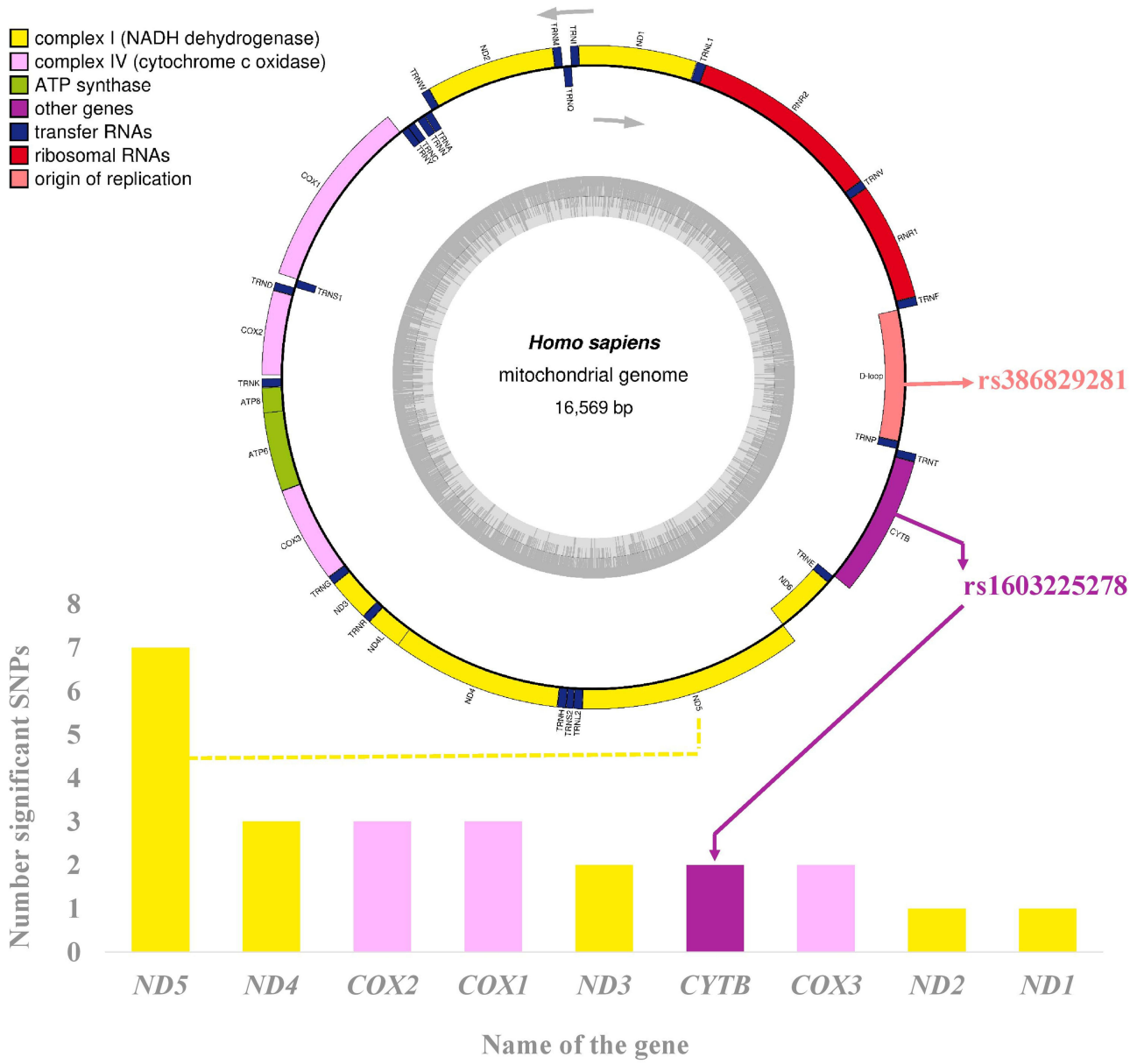

Figure 2 Name of the genes in the mitochondrial and number of significant sequence variations. Dark pink histogram indicates the gene with the most significant SNP (rs1603225278) in the *CYTB* gene. The second most significant SNP, rs386829281 in the region of origin of replication. Arrow with ash colour indicates direction of the transcription. Mitochondrial genome map was constructed using OGDRAW (OrganellarGenomeDRAW).[16]

demonstrate a significant association of 30 different SNPs allocated mainly in nine genes (*ND5, ND4, COX2, COX1, ND3, CYTB, COX3, ND2* and *ND1*). The most significant association was in gene: *CYTB* (p = 0.001033), while the highest number of associated SNPs was demonstrated in gene *ND5*. These mitochondrial genes are responsible for encoding important proteins in the respiratory electron transfer chain in the mitochondria. *Mt-CYTB* which is the most significantly associated gene is responsible for encoding cytochrome b which is part of complex III.[17] *Mt-ND* genes including *ND1, ND2, ND3, ND4*, and *ND5* are genes responsible for encoding essential components of complex I which is NADH dehydrogenase.[18] Mt-*COX1*, mt-*COX2* and mt-*COX3* genes encode cytochrome c oxidase which is a subunit of complex IV.[19] Mutations in these mitochondrial genes are reported earlier in multiple neurological and muscular diseases like MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), mitochondrial encephalomyopathy, mitochondrial myopathy,[20] Leber hereditary optic neuropathy,[21] and muscle weakness.[22] The link between neurological and muscular symptoms and the mitochondrial mutations can be explained by the absolute reliance of these

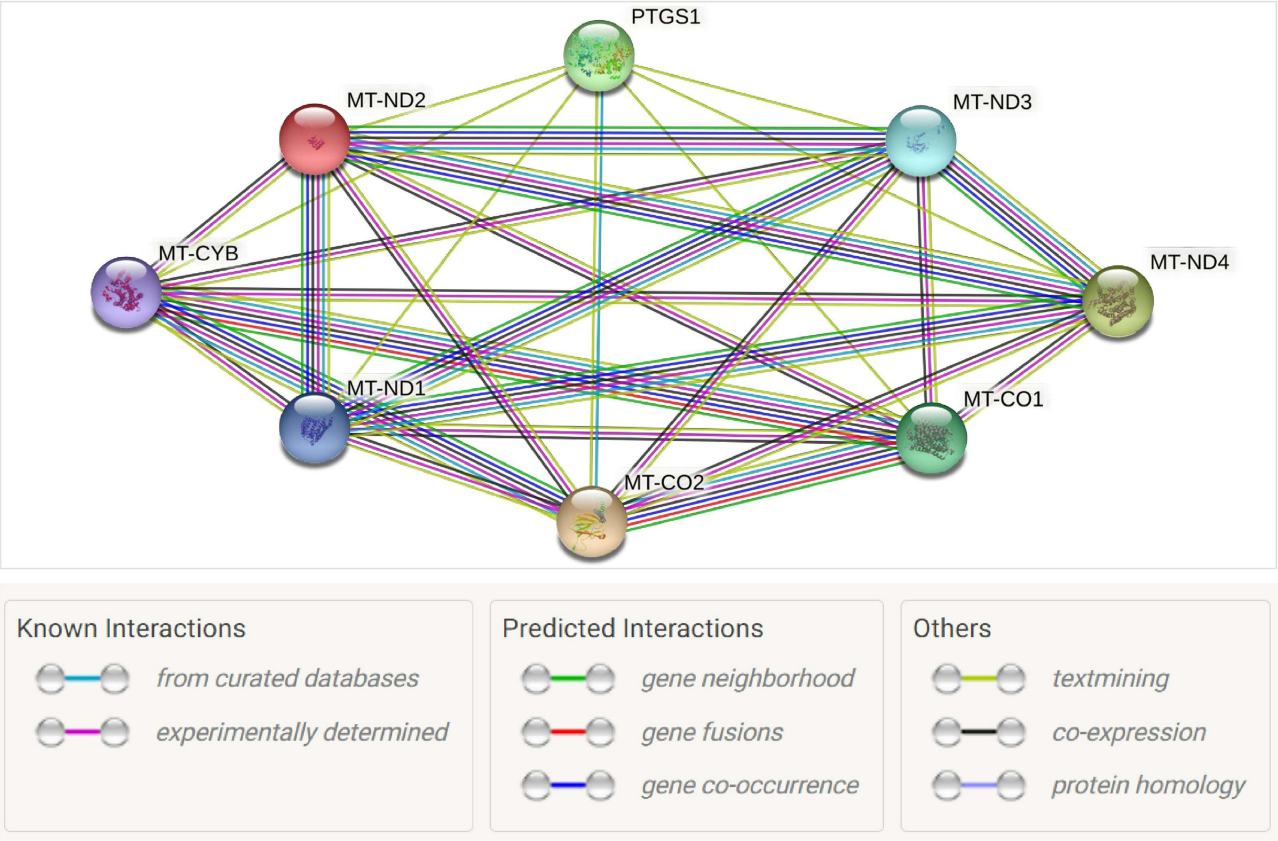

Figure 3 Functional enrichment analysis through protein-protein interaction networks (STRING 11.5) of mitochondrial genes with significant variations associated with migraine.

tissues ie nervous and muscular tissue on the aerobic metabolism and the oxidative phosphorylation system of the mitochondria. Therefore, any disturbance in the machinery of energy production particularly in the respiratory electron transfer chain can be manifested by neurological and muscular symptoms.

Few studies in the literature have focused on studying the association of mtDNA mutations and migraine. One study has identified a mutation in the mitochondrial transfer RNA (m.3243A>G) in a group of subjects. Further analysis of the same cohort showed that the subjects of this mutation (m.3243A>G) have higher prevalence of migraine.[23] Similarly, studies of diseases with mitochondrial mutations demonstrated a higher incidence of migraine in these patients.[24] Studying the mitochondrial mutations, as is the case with other neurological diseases, can help in understanding the pathophysiology of migraine. Some studies proposed that the alteration of the energy production that resulted from abnormal oxidative phosphorylation and a deranged respiratory electron transfer chain can lower the level of ATP in the involved neurons. In migraine, particularly migraine with aura, a lower ATP level of the affected neurons can reduce the threshold for the cortical spreading depression (CSD) and can culminate in the initiation of the aura.[25] Another supportive evidence is that imaging techniques in migraineur patients revealed disturbances in the mitochondrial function in certain areas of the brain.[26] Mitochondrial DNA variations from Arab ancestries have reported for its association with obesity,[27] however there were no studies from the Arab population, specifically from Saudis on the neurological diseases.[28] On an international level the HUNT study in Norway's Nord-Trøndelag County revealed no significant association using a microarray of known variants between these specific variants and migraine in the Norwegian population; furthermore, the study excluded samples not passing quality control for nuclear genotypes, in addition to samples with low call rate and closely maternally related.[12] Hence, this study is the first to study the association of mtDNA mutations on migraine in Arab ancestries, specifically from the Saudi population and it adds a valuable piece of knowledge to the Saudi genome project. It further encourages large studies to confirm the current found mutations.

Table 2 Enrichment Analysis of Mitochondrial Genes with Significant Variations Associated with Migraine

Pathway ID	Pathway Description	Observed Number of Gene Count	Background Gene Count	Strength	False Discovery Rate	Matching List of Proteins in the Network
Kyoto encyclopedia of genes and genomes (KEGG) pathway						
hsa00190	Oxidative phosphorylation	7	130	2.12	2.55E-12	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa04714	Thermogenesis	7	229	1.87	6.09E-11	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa05012	Parkinson disease	7	240	1.85	6.09E-11	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa05020	Prion disease	7	265	1.81	8.31E-11	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa05016	Huntington disease	7	298	1.76	1.49E-10	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa05010	Alzheimer disease	7	355	1.68	3.93E-10	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa05014	Amyotrophic lateral sclerosis	7	352	1.69	3.93E-10	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa01100	Metabolic pathways	8	1447	1.13	5.20E-08	MT-CO1,MT-CYB,PTGS1,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
hsa04723	Retrograde endocannabinoid signaling	4	145	1.83	1.11E-05	MT-ND1,MT-ND4,MT-ND2,MT-ND3
hsa04260	Cardiac muscle contraction	3	87	1.93	0.00024	MT-CO1,MT-CYB,MT-CO2
hsa04932	Non-alcoholic fatty liver disease	3	148	1.7	0.001	MT-CO1,MT-CYB,MT-CO2
Reactome Pathway						
HSA-611105	Respiratory electron transport	7	101	2.23	1.77E-11	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
HSA-6799198	Complex I biogenesis	4	55	2.25	2.24E-05	MT-ND1,MT-ND4,MT-ND2,MT-ND3
HSA-1430728	Metabolism	8	2089	0.97	5.96E-05	MT-CO1,MT-CYB,PTGS1,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
WikiPathways						
WP111	Electron transport chain: OXPHOS system in mitochondria	7	103	2.22	2.03E-12	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
WP623	Oxidative phosphorylation	4	60	2.21	6.30E-06	MT-ND1,MT-ND4,MT-ND2,MT-ND3
WP4324	Mitochondrial complex I assembly model OXPHOS system	3	56	2.12	0.00084	MT-ND1,MT-ND4,MT-ND2

(*Continued*)

https://doi.org/10.2147/IJGM.S371707 DovePress

Table 2 (Continued).

Pathway ID	Pathway Description	Observed Number of Gene Count	Background Gene Count	Strength	False Discovery Rate	Matching List of Proteins in the Network
WP4919	Neuroinflammation	2	13	2.58	0.0067	MT-CO1,MT-CO2
WP4396	Nonalcoholic fatty liver disease	3	155	1.68	0.0098	MT-CO1,MT-CYB,MT-CO2
WP4922	Mitochondrial complex IV assembly	2	35	2.15	0.0282	MT-CO1,MT-CO2
Disease gene association						
DOID:705	Leber hereditary optic neuropathy	5	11	3.05	4.46E-11	MT-CO1,MT-CYB,MT-ND1,MT-ND4,MT-ND2
DOID:700	Mitochondrial metabolism disease	7	173	2	8.57E-11	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2,MT-ND3
DOID:0060536	Mitochondrial complex i deficiency	4	41	2.38	1.23E-06	MT-ND1,MT-ND4,MT-ND2,MT-ND3
DOID:1398	Parasitic infectious disease	4	62	2.2	4.46E-06	MT-CO1,MT-CYB,MT-ND1,MT-CO2
DOID:3652	Leigh disease	4	72	2.13	7.04E-06	MT-ND1,MT-ND4,MT-ND2,MT-ND3
DOID:883	Parasitic helminthiasis infectious disease	3	31	2.37	9.70E-05	MT-CO1,MT-ND1,MT-CO2
DOID:0050251	Coenurosis	2	2	3.39	0.00029	MT-CO1,MT-ND1
DOID:1495	Cystic echinococcosis	2	4	3.09	0.00068	MT-CO1,MT-ND1
DOID:3687	MELAS syndrome	2	4	3.09	0.00068	MT-ND1,MT-ND4
DOID:331	Central nervous system disease	5	1107	1.04	0.0065	MT-CO1,MT-ND1,MT-CO2,MT-ND4,MT-ND2
DOID:3762	Cytochrome-c oxidase deficiency disease	2	22	2.35	0.0083	MT-CO1,MT-CO2
DOID:850	Lung disease	3	172	1.63	0.0083	MT-CO1,MT-CYB,MT-ND1
DOID:863	Nervous system disease	6	2132	0.84	0.0083	MT-CO1,MT-CYB,MT-ND1,MT-CO2,MT-ND4,MT-ND2
DOID:10652	Alzheimers disease	2	35	2.15	0.0169	MT-ND1,MT-ND2
DOID:0080000	Muscular disease	3	254	1.46	0.0193	MT-CO1,MT-ND1,MT-ND4
DOID:114	Heart disease	3	257	1.46	0.0193	MT-CO1,MT-CYB,MT-ND1
DOID:936	Brain disease	4	739	1.12	0.0193	MT-CO1,MT-ND1,MT-CO2,MT-ND4

Further studies among Arab ancestries with a large sample size and haplotyping analysis may confirm the possible association of the significant impact on the pathways of migraine development. Even though the small sample size in the study is one of the notable limitations, the current pilot study opens an avenue for large confirmatory studies.

Conclusion

Our present study demonstrated the significant association of 30 SNP variants in 9 genes: *CYTB, COX1, COX2, ND1, ND2, ND3, ND4, ND5*, and *COX3* with Saudi migraineurs, which should be further confirmed. The most significant SNP variant was located in the *CYTB* gene, while the highest number of associated SNP variants with migraine were found in *ND5*. The mutated variants are responsible for encoding essential proteins that constitute important subunits in the respiratory electron transfer chain, and therefore play a significant role in the energy production and ATP synthesis by the mitochondria in the neurons. The current study's findings are the first in this population and require larger scale studies to confirm the association.

Data Sharing Statement

All data will be available on reasonable request from the corresponding author.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) at Imam Abdulrahman Bin Faisal University. IRB approval number: IRB-2021-01-250.

Acknowledgments

The authors thank the Dean, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, for her continuous support and encouragement. The authors thank Mr. Ranilo, M. Tumbaga, and Mr. Horace T. Pacifico for their assistance.

Funding

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number (IFP-2020-46).

Disclosure

The authors declare no conflicts of interests in this work.

References

1. Yan Y, Duanmu D, Zeng Z, Liu L, Song S. Mitochondrial DNA: distribution, mutations, and elimination. *Cells*. 2019;8(4):379. doi:10.3390/cells8040379
2. Sharma P, Sampath H. Mitochondrial DNA integrity: role in health and disease. *Cells*. 2019;8(2):100. doi:10.3390/cells8020100
3. Basu U, Bostwick AM, Das K, Dittenhafer-Reed KE, Patel SS. Structure, mechanism, and regulation of mitochondrial DNA transcription initiation. *J Biol Chem*. 2020;295(52):18406–18425. doi:10.1074/jbc.REV120.011202
4. Fontana GA, Gahlon HL. Mechanisms of replication and repair in mitochondrial DNA deletion formation. *Nucleic Acids Res*. 2020;48(20):11244–11258. doi:10.1093/nar/gkaa804
5. Holt IJ, Harding AE, Morgan-Hughes JA. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. *Nature*. 1988;331(6158):717–719. doi:10.1038/331717a0
6. Greaves LC, Reeve AK, Taylor RW, Turnbull DM. Mitochondrial DNA and disease. *J Pathol*. 2012;226(2):274–286. doi:10.1002/path.3028
7. Yorns WR, Hardison HH. Mitochondrial dysfunction in migraine. *Semin Pediatr Neurol*. 2013;20(3):188–193. doi:10.1016/j.spen.2013.09.002
8. Stuart S, Griffiths LR. A possible role for mitochondrial dysfunction in migraine. *Mol Genet Genomics*. 2012;287(11–12):837–844. doi:10.1007/s00438-012-0723-7
9. Sparaco M, Feleppa M, Lipton RB, Rapoport AM, Bigal ME. Mitochondrial dysfunction and migraine: evidence and hypotheses. *Cephalalgia*. 2006;26(4):361–372. doi:10.1111/j.1468-2982.2005.01059.x
10. Finnilä S, Autere J, Lehtovirta M, et al. Increased risk of sensorineural hearing loss and migraine in patients with a rare mitochondrial DNA variant 4336A>G in tRNAGln. *J Med Genet*. 2001;38(6):400–405. doi:10.1136/jmg.38.6.400
11. Zaki EA, Freilinger T, Klopstock T, et al. Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. *Cephalalgia*. 2009;29(7):719–728. doi:10.1111/j.1468-2982.2008.01793.x
12. Børte S, Zwart JA, Skogholt AH, et al. Mitochondrial genome-wide association study of migraine - the HUNT Study. *Cephalalgia*. 2020;40(6):625–634. doi:10.1177/0333102420906835

13. Ruiz-Pesini E, Lott MT, Procaccio V, et al. An enhanced MITOMAP with a global mtDNA mutational phylogeny. *Nucleic Acids Res*. 2007;35 (Databaseissue):D823–D828. doi:10.1093/nar/gkl927
14. Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc*. 2009;4(1):44–57. doi:10.1038/nprot.2008.211
15. Szklarczyk D, Morris JH, Cook H, et al. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. *Nucleic Acids Res*. 2017;45(D1):D362–D8. doi:10.1093/nar/gkw937
16. Greiner S, Lehwark P, Bock R. OrganellarGenomeDRAW (OGDRAW) version 1.3.1: expanded toolkit for the graphical visualization of organellar genomes. *Nucleic Acids Res*. 2019;47(W1):W59–W64. doi:10.1093/nar/gkz238
17. Meunier B, Fisher N, Ransac S, Mazat JP, Brasseur G. Respiratory complex III dysfunction in humans and the use of yeast as a model organism to study mitochondrial myopathy and associated diseases. *Biochim Biophys Acta*. 2013;1827(11–12):1346–1361. doi:10.1016/j.bbabio.2012.11.015
18. Liu C, Fetterman JL, Liu P, et al. Deep sequencing of the mitochondrial genome reveals common heteroplasmic sites in NADH dehydrogenase genes. *Hum Genet*. 2018;137(3):203–213. doi:10.1007/s00439-018-1873-4
19. Mani S, Rao SN, Kumar MVK. G6036A substitution in mitochondrial COX I gene compromises cytochrome c oxidase activity in thiamine responsive Leigh syndrome patients. *J Neurol Sci*. 2020;415:116870. doi:10.1016/j.jns.2020.116870
20. Nesti C, Meschini MC, Meunier B, et al. Additive effect of nuclear and mitochondrial mutations in a patient with mitochondrial encephalomyopathy. *Hum Mol Genet*. 2015;24(11):3248–3256. doi:10.1093/hmg/ddv078
21. Rezvani Z, Didari E, Arastehkani A, et al. Fifteen novel mutations in the mitochondrial NADH dehydrogenase subunit 1, 2, 3, 4, 4L, 5 and 6 genes from Iranian patients with Leber's hereditary optic neuropathy (LHON). *Mol Biol Rep*. 2013;40(12):6837–6841. doi:10.1007/s11033-013-2801-2
22. Ronchi D, Cosi A, Tonduti D, et al. Clinical and molecular features of an infant patient affected by Leigh Disease associated to m.14459G > A mitochondrial DNA mutation: a case report. *BMC Neurol*. 2011;11(1). doi:10.1186/1471-2377-11-85
23. Nesbitt V, Pitceathly RD, Turnbull DM, et al. The UK MRC mitochondrial disease patient cohort study: clinical phenotypes associated with the m.3243A>G mutation–implications for diagnosis and management. *J Neurol Neurosurg Psychiatry*. 2013;84(8):936–938. doi:10.1136/jnnp-2012-303528
24. Guo S, Esserlind AL, Andersson Z, et al. Prevalence of migraine in persons with the 3243A>G mutation in mitochondrial DNA. *Eur J Neurol*. 2016;23(1):175–181. doi:10.1111/ene.12832
25. Bron C, Sutherland HG, Griffiths LR. Exploring the hereditary nature of migraine. *Neuropsychiatr Dis Treat*. 2021;17:1183–1194. doi:10.2147/NDT.S282562
26. Sprenger T, Borsook D. Migraine changes the brain: neuroimaging makes its mark. *Curr Opin Neurol*. 2012;25(3):252–262. doi:10.1097/WCO.0b013e3283532ca3
27. Al Asoom LI, Al Afandi DT, Al Abdulhadi AS, Rafique N, Chathoth S, Al Sunni AA. Protective association of single nucleotide polymorphisms rs1861868-FTO and rs7975232-VDR and obesity in Saudi Females. *Int J Gen Med*. 2020;23:235–241. doi:10.2147/IJGM.S251466
28. Borgio JF. Heterogeneity in biomarkers, mitogenome and genetic disorders of Arab population with special emphasis on large-scale whole-exome sequencing. *Arch Med Sci*. 2021. doi:10.5114/aoms/145370