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ORIGINAL RESEARCH

The Association of Mitochondrial tRNA^{Cys} G5783A Mutation with Major Depressive Disorder in Two Han Chinese Families

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Objective: In this study, we examined the genetic, medical, and molecular traits of two Han Chinese families with the tRNA^{Cys} G5783A mutation to investigate the relationship between mitochondrial DNA (mtDNA) mutations and major depressive disorder (MDD).

Methods: Clinical data and comprehensive mitochondrial genomes were collected from the two families. Variants were assessed for evolutionary conservation, allelic frequencies, and their structural and functional impacts. The study involved detailed mitochondrial whole genome analysis, as well as phylogenetic and haplotype analyses of the probands and other family members.

Results: We detailed the genetic, clinical, and molecular profiles of two Han Chinese families with MDD. These families exhibited a range of depression severities and notably low penetrance of MDD. Analysis of the mitochondrial genomes revealed a homoplasmic tRNA^{Cys} G5783A mutation. This mutation was found at a highly conserved cytosine at position 50 (C50) in the TΨC stem of tRNA^{Cys}, with a conserved coefficient of 100% across 17 species. Additionally, distinctive mtDNA polymorphisms associated with haplogroups H2 were identified.

Conclusion: The identification of the tRNA^{Cys} G5783A mutation in two unrelated individuals with depression strongly suggests that this mutation may play a role in the development of major depressive disorder (MDD). These Chinese families revealed low penetrances of MDD. Thus, the phenotypic tRNA^{Cys} G5783A mutation expression associated with MDD may be impacted by nuclear modifier gene(s) or environmental factors.

Keywords: major depressive disorder, mitochondrial DNA, tRNA, mutation, haplogroup, Chinese

Major depressive disorder (MDD) is a widespread mental health condition affecting approximately 185 million people globally.[1] There has been a notable increase in MDD cases worldwide following the COVID-19 pandemic.[2] MDD is defined by a continual state of depressed mood, lack of interest or enjoyment, and the presence of somatic and cognitive symptoms. Individuals diagnosed with MDD may experience a decline in their quality of life, influenced by social circumstances, and may also have difficulties in achieving desired results in their daily functioning.[3] MDD is the primary factor contributing to the number of years lost due to suicide. It significantly elevates the probability of suicide, raising the risk by over 20 times compared to those who do not have MDD.[4,5]

MDD is a complex condition that cannot be fully explained by any single biological or environmental factor. Instead, it appears to arise from the interplay of environmental, genetic, psychological, and biological variables.[3] The heritability of MDD is believed to be about 35%, as determined by research that focuses on families and twins. These studies have shown higher heritability than estimates from genome-wide association studies (GWAS) that focus solely on single-

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nucleotide polymorphisms (SNPs).[6] The outcomes imply that other genetic factors, like infrequent mutations, have a role in the risk of MDD.[7]

The global incidence of MDD is almost double in females compared to males and is rather stable throughout adulthood.[8] A significant incidence of depression was seen in mothers with predicted maternal inheritance,[9] with a moderate maternal bias in sensitivity to depression development. In addition to the fact that Mitochondrial DNA (mtDNA) is exclusively inherited via the maternal lineage.[10] In addition to the fact that mtDNA is exclusively inherited via the maternal lineage. Several research studies have investigated the association between MDD and mitochondria.[11–13]

As commonly understood, mitochondria are vital organelles within cells that serve as the principal generator of energy in the form of adenosine triphosphate (ATP).[14] Mitochondria, known as the cellular "powerhouse", have essential duties in supplying energy for every process within the cell and serving as a crucial mediator of several signaling mechanisms. The hypothesis of the "mitochondria theory of depression" is substantiated by an abundance of evidence that establishes a connection between symptoms of depression and MDD with uncommon mitochondrial diseases,[15] modified mitochondrial structure and activities, such as reduced generation of ATP,[16] and disturbed mitochondrial dynamics involving fusion, fission, and mitophagy.[17]

The association between illness and mtDNA mutations was first established in 1988.[18,19] Hence, mutations and polymorphisms in mtDNA may have an important function in several diseases in humans. Nevertheless, they do not always do this action in complete isolation. Individuals with Leber hereditary optic neuropathy (LHON) who have certain mtDNA mutations associated with LHON are more likely to develop the condition if they smoke cigarettes or consume large amounts of alcohol.[20] Despite the initial investigations being insufficiently powered and resulting in inconsistent results,[21] recent research has substantiated that prevalent polymorphic differences in mitochondrial DNA, frequently grouped into "haplogroups", modify our susceptibility to developing diseases such as Alzheimer's disease, Parkinson's disease, type II diabetes, and other late-onset disorders.[22–25]

Significantly, there is a correlation between the loss of mtDNA and depression, as well as decreased levels of antioxidants. This may be connected to the observed decrease in the creation of new mitochondria and the synthesis of antioxidants in individuals with depression.[26] Our earlier familial study indicated a potential link between MDD and mitochondrial ND1 T3394C mutations.[27] We also found two pedigrees associated with the mitochondrial ND6 T14502C mutation. The mitochondrial ND6 T14502C mutation may be associated with MDD.[28] This investigation aimed to characterize the medical, genetic, and molecular aspects of two Chinese families potentially inheriting MDD maternally. Molecular analysis identified the tRNA gene mutation G5783A in these families. Additionally, the study employed fragment polymerase chain reaction (PCR) to amplify the entire mitochondrial genome, followed by DNA sequencing, to better understand the impact of mitochondrial haplotypes on the expression of the G5783A mutation in these families.

Materials and Methods

Patients and Subjects

Two Han Chinese families (Figure 1) were recruited from the Psychiatric Clinic at Ningbo Kangning Hospital, Zhejiang Province. Structured clinical interviews were conducted to diagnose Major Depressive Disorder (MDD) in the probands, adhering to DSM-5 criteria.[29] A board-certified psychiatrist performed an additional diagnostic assessment to confirm the diagnosis. Exclusion criteria included substance-induced post-traumatic stress disorder (PTSD), psychotic disorders, eating disorders, and bipolar disorder. Following the explanation of the study's objectives and obtaining written informed consent, data were collected on age, gender, family history of MDD, history of suicide attempts, psychotic symptoms, and scores on the Hamilton Depression Rating Scale (HDRS).[30] Probands diagnosed with MDD scored at least 17 on the 17-item HDRS. MDD severity was classified based on HDRS scores as follows: normal ≤7; mild = 8–17; moderate = 18–24; severe >24.

The Ethics Committee at Ningbo Kangning Hospital approved the protocols requiring informed consent, blood samples, and clinical assessments from participating family members. Extensive interviews were conducted to document personal and familial MDD histories and other medical abnormalities. Additionally, 105 control DNA samples were obtained from the health screening clinic at the same hospital for mtDNA mutation screening. Control participants were

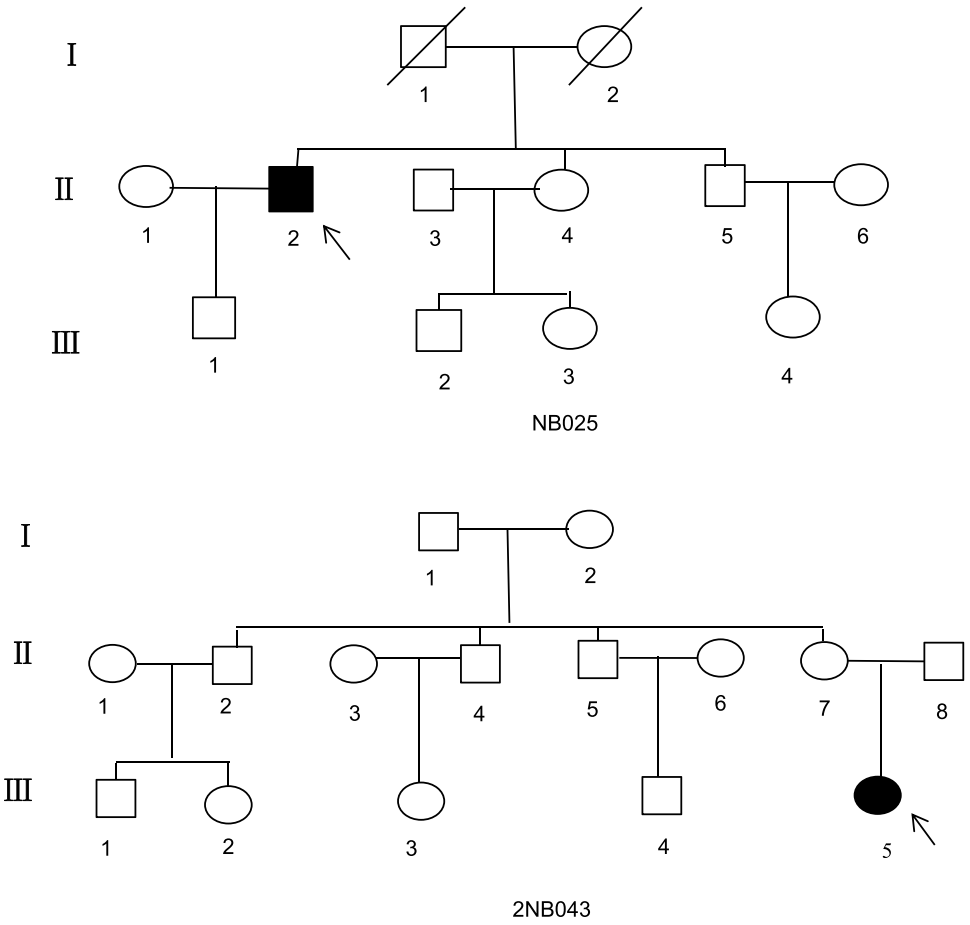

Figure 1 Two Chinese pedigrees with MDD. Roman numerals are used to represent different generations. Patients are indicated by filled symbols. The arrow denotes the probands.

interviewed to ensure they had no significant psychiatric disorders in their medical history and were not currently using psychotropic medications. At the time of study entry, all participants were confirmed to be in good health, free of chronic conditions, without acute infections, and not pregnant.

Mutational Analysis of the Mitochondrial Genome

Genomic DNA was isolated from whole blood samples using Puregene DNA isolation kits (Gentra Systems). PCR amplification of the entire mitochondrial genomes from both probands was conducted using 24 overlapping fragments with sets of light (L)- and heavy (H)-strand oligonucleotide primers, as previously described.[31] The PCR fragments were purified and sequenced using the Big Dye Terminator Cycle Sequencing Kit on an ABI 3700 automated DNA sequence. The resulting sequences were then compared to the revised Cambridge Reference Sequence (GenBank accession number: NC_012920).[32] The Seqweb program GAP (GCG) was used to align DNA and protein sequences. This method was also applied to analyze blood samples from 105 normal controls.

Phylogenetic and Haplogroup Analyses

Seventeen vertebrate mtDNA sequences were used in the interspecific analysis, including *Macaca mulatta, Trachypithecus obscurus, Macaca Sylvanus, Papio hamadryas, Colobus guereza, Pan troglodytes, Nycticebus coucang, Pan paniscus, Gorilla gorilla, Chlorocebus aethiops, Lemur catta, Homo sapiens, Pongo abelII, Hylobates lar, Pongo pygmaeus, Cebus albifrons*, and *Tarsius baucanus*. Conservation was assessed by comparing mtDNA sequences across

17 vertebrate species. The mtDNA sequences from both Chinese probands with the $tRNA^{Cys}$ G5783A mutation were classified into Asian mitochondrial haplogroups according to the mitochondrial haplogroup nomenclature.[33]

Statistical Analysis

Statistical analysis was carried out using the unpaired, two-tailed Student's *t*-test contained in Excel. For each independent in vitro experiment, at least three technical replicates were used, and a minimum number of three independent experiments were performed to ensure adequate statistical power. Correlation analysis was performed using the curve fitting routine in the GraphPad Prism package. Differences were considered significant at a $P<0.05$.

Results

Clinical Presentation

Proband II-2 from family NB025, a 66-year-old woman as detailed in Table 1, reported experiencing depression and sought treatment at the Psychiatric Clinic of Ningbo Kangning Hospital. She scored 24 on the Hamilton Depression Rating Scale (HDRS) and did not have a history of suicide attempts, consistent with typical MDD symptoms. No additional abnormalities were found during the psychiatric evaluation, and her medical history was otherwise unremarkable. The family is from Zhejiang Province in eastern China. However, no cases of MDD were identified among her five other matrilineal relatives.

Proband III-5 from the 2NB043 pedigree, a 16-year-old, sought treatment at the Psychiatric Clinic of Ningbo Kangning Hospital. Diagnosed with Major Depressive Disorder (MDD) two years prior, she scored 24 on the Hamilton Depression Rating Scale (HDRS) and had a history of suicide attempts, reflecting typical MDD characteristics. Her medical records showed no other significant health issues. The family is from Zhejiang Province in eastern China, and no MDD cases were found among her other matrilineal relatives.

Furthermore, there is no substantiated evidence suggesting that any individuals from these families exhibited additional identifiable factors associated with MDD. Comprehensive family medical histories revealed no other medical conditions, such as diabetes, hearing loss, or vision problems.

mtDNA Analysis

To elucidate the molecular basis of MDD, we analyzed mitochondrial genome mutations in the probands. PCR amplification revealed that the G5783A mutation occurs at a highly conserved cytosine at position 50 (C50) of the TΨC stem of tRNACys, near the 5′ end of OriL (positions 5721–5798), encompassing 37 bp of the 3′ end anti-sense strand of the $tRNA^{Cys}$ gene.[34–36]

While the $tRNA^{Cys}$ G5783A mutation was consistent among subjects, they exhibited different mtDNA polymorphisms. The mitochondrial genomes displayed multiple nucleotide changes (Table 2), including 15 variants in the D-loop, 2 in the 12S rRNA gene, 3 in the 16S rRNA gene, 1 in the tRNA gene, 12 silent variants, and 5 missense mutations in polypeptide-encoding genes: A8860G (Thr112Ala) in ATP6, A10750G (Asn94Ser) in ND4, A12361G (Thr9Ala) in ND5, C14766T (Thr7Ile), and A15326G (Thr194Ala) in CYB. Of these, 26 mutations were present in both probands. Phylogenetic analysis of RNA and polypeptide variants, compared with sequences from 17 other organisms, identified 8 mutations with high evolutionary conservation (≥ 75%) in both probands. Except for $tRNA^{Cys}$ G5783A, the other 7 mutations were also common in control subjects. The $tRNA^{Cys}$ G5783A mutation showed 100% evolutionary conservation (Figure 2) and was absent in 105 non-associated Chinese control subjects. Based on mitochondrial haplogroup nomenclature, the mtDNA from the NB025 and 2NB043 pedigrees was classified into the Eastern Asian haplogroup H2.

Table 1 Summary of Clinical Molecular Data for Two Probands Carrying the $tRNA^{Cys}$ G5783A Mutation

Subject	Gender	Age of Test (Years)	Age of Onset (Years)	First Episode	History of Suicide Attempts	Psychotic Symptoms	HDRS	Level of Depression	mtDNA Haplogroup
NB025-II-2	M	66	59	Y	N	N	24	Moderate	H2
2NB043-III-5	F	16	14	Y	Y	N	24	Moderate	H2

Table 2 mtDNA Mutations in Two Chinese Pedigrees with MDD

Gene	Position	Replacement	Conservation[a] (%)	CRS[b]	NB025	2NB043	Previously Reported[c]
D-loop	73	A to G		A	G	G	Yes
	152	T to C		T	C		Yes
	263	A to G		A	G	G	Yes
	309	C to CCT		C	CCT	CCT	Yes
	310	T to C		T	C	C	Yes
	328	A to G		A		G	Yes
	489	T to C		T		C	Yes
	515	A to G		A	G		Yes
	16129	G to A		G	A	A	Yes
	16182	A to C		A	C	C	Yes
	16183	A to C		A	C	C	Yes
	16187	C to A		C		A	Yes
	16189	T to C		T	C	C	Yes
	16223	C to T		C		T	Yes
	16261	C to T		C	T		Yes
12S rRNA	750	A to G	100.0	A	G	G	Yes
	1438	A to G	100.0	A	G	G	Yes
16S rRNA	2363	A to G	94.1	A	G	G	Yes
	2706	A to G	88.2	A	G	G	Yes
	3106	CN to C	5.9	CN	C	C	Yes
ND2	4703	T to C	17.6	T	C	C	Yes
	4769	A to G	47.1	A	G	G	Yes
	5093	T to C	47.1	T	C	C	
	5141	C to T	94.1	C		T	Yes
$tRNA^{Cys}$	5783	G to A	100.0	G	A	A	Yes
CO1	5894	A to G	5.9	A	G		Yes
	7028	C to T	70.6	C	T	T	Yes
CO2	7984	G to A	5.9	G	A		Yes
	8270	CACCCCCTCT to C	35.3	CACCCCCTCT	C	C	Yes
ATP6	8860	A to G(Thr112Ala)	82.4	A	G	G	Yes
ND4	10750	A to G(Asn94Ser)	88.2	A	G		Yes
	11719	G to A	5.9	G	A	A	Yes
ND5	12361	A to G(Thr9Ala)	64.7	A	G	G	Yes
	13158	A to G	94.1	A	G	G	Yes
	13269	A to G	47.1	A	G	G	Yes
CYTB	14766	C to T(Thr7Ile)	76.5	C	T	T	Yes
	15326	A to G(Thr194Ala)	82.4	A	G	G	Yes
	15337	C to T	47.1	C	T		Yes

Notes: [a]Conservation of amino acids for polypeptides or nucleotides for RNAs in 17 different species. [b]CRS, Cambridge reference sequence. [c]See online mitochondrial genome databases http://www.mitomap.org and http://www.genpat.uu.se/mtDB/.

Discussion

This study conducted a clinical, genetic, and molecular analysis of two Chinese families with MDD. Both probands experienced moderate depressive episodes with initial symptoms. Sequence analysis of their complete mitochondrial genomes revealed distinct mtDNA polymorphisms and the identical $tRNA^{Cys}$ G5783A mutation in these pedigrees.

Mitochondrial tRNA mutations account for over half of the documented pathogenic mtDNA mutations.[37] These tRNAs have specific secondary and tertiary structures, including stems, loops, the amino acid acceptor stem, and the anticodon loop, which are crucial for their function and stability (Figure 3). In mitochondrial protein synthesis, each amino acid is typically carried by a single mitochondrial tRNA, such as $tRNA^{Cys}$. A single nucleotide substitution can disrupt or destabilize the tRNA's secondary and tertiary structures, impairing its function.[38,39] The G5783A mutation we identified

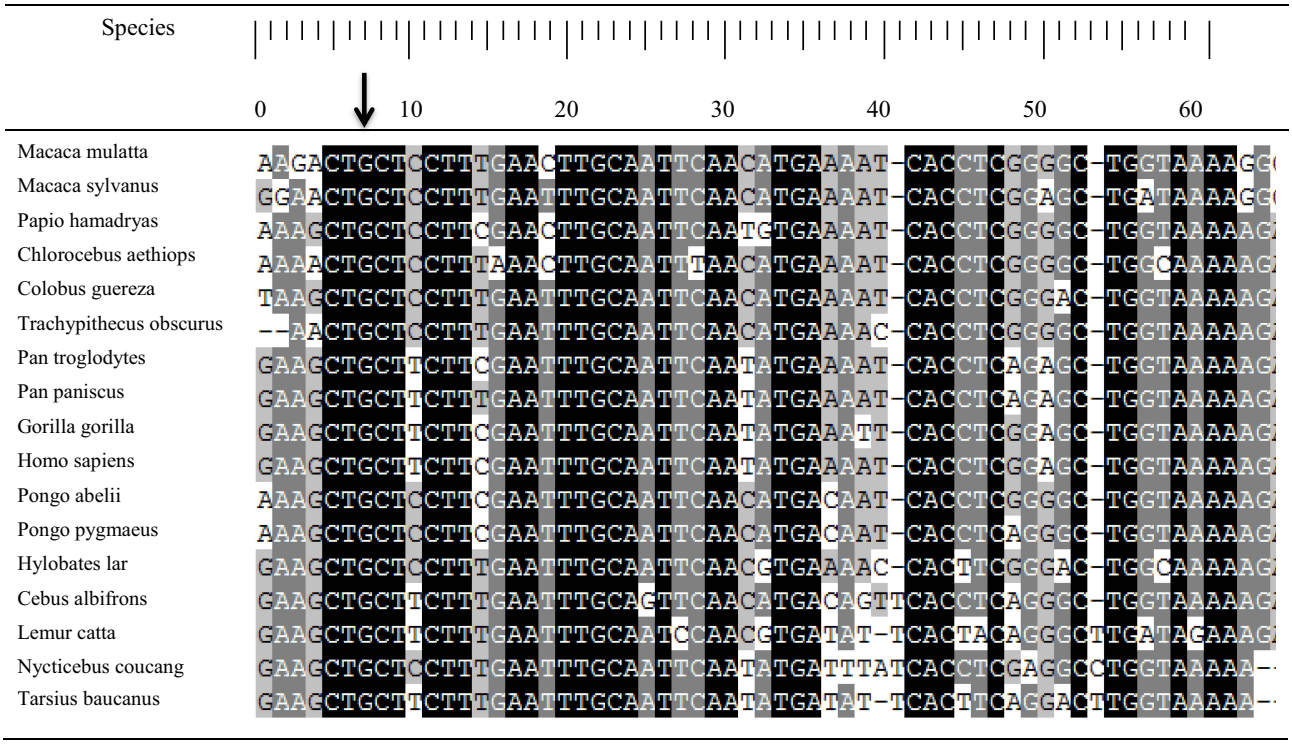

Figure 2 Conservation of amino acids for polypeptides or nucleotides for partial $tRNA^{Cys}$ in 17 different species. The black arrow indicates mitochondrial nucleotides at position 5783 for 17 different species.

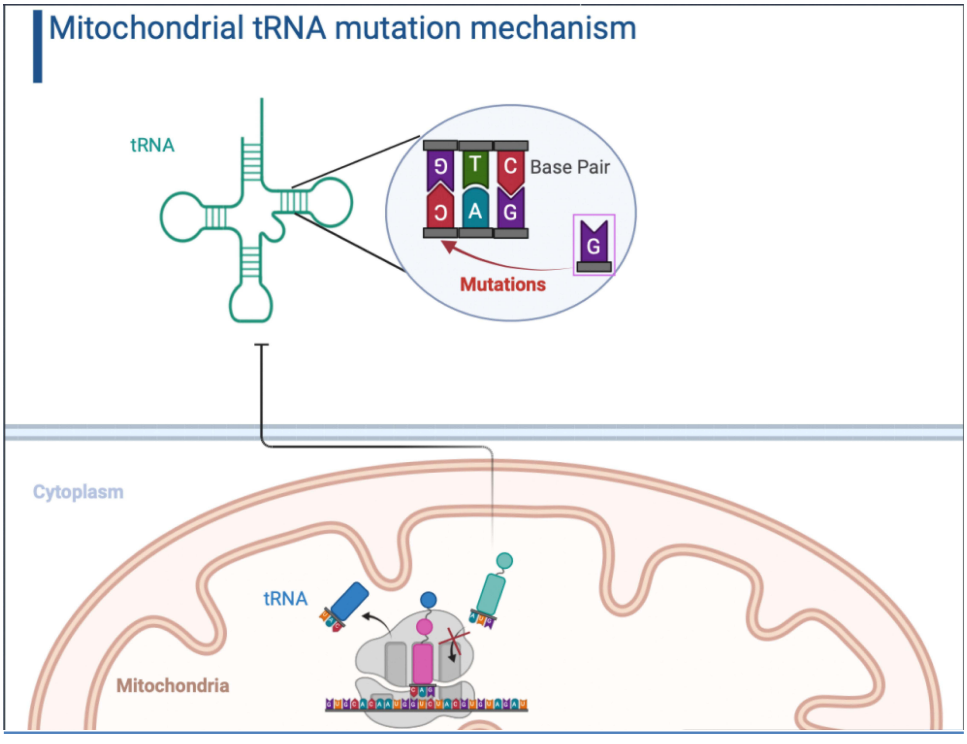

Figure 3 Mitochondrial tRNA mutation mechanism.

in the structurally critical T-arm stem region of $tRNA^{Cys}$ (Figure 4) contributes to the known repertoire of tRNA gene mutations. The patient carrying this mutation exhibited a multisystemic disorder with symptoms including myopathy, neurosensory hearing loss, renal failure, cardiomyopathy, hepatomegaly, and both endocrine and exocrine dysfunctions.

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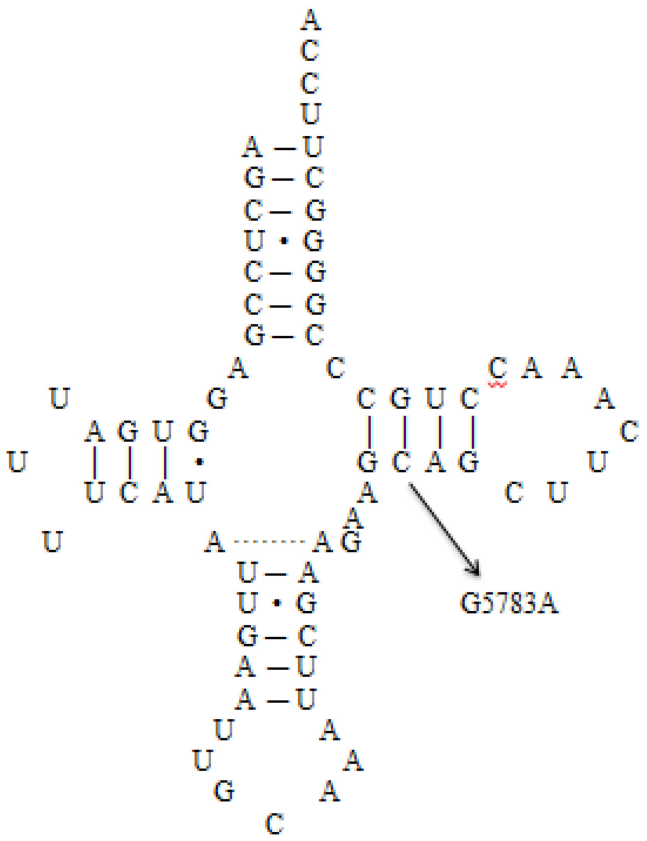

Figure 4 The secondary structure of $tRNA^{Cys}$.

The commonly used criteria for assessing mutation pathogenicity include: (a) occurrence in less than 1% of controls; (b) evolutionary conservation; and (c) potential structural and functional impact.[40] Several factors support the deleterious role of the 5783G>A mutation: it is absent in 105 normal controls, it is a heteroplasmic mutation, its conservation coefficient is 100% across 17 species, it affects a crucial T-arm stem region of $tRNA^{Cys}$, and it aligns with mitochondrial proliferation and mtDNA amplification. Additionally, all four respiratory chain complexes showed significantly reduced activity in muscle biopsies, indicating widespread mitochondrial dysfunction due to impaired tRNA function.[41]

Although both families displayed typical clinical symptoms of MDD, there were differences in psychotic symptoms and age of onset. The penetrance rates in these families were 16.7%. This study highlights a low penetrance of MDD among the two Chinese families with the $tRNA^{Cys}$ G5783A mutation, suggesting that the $tRNA^{Cys}$ G5783A mutation alone may not fully account for the clinical phenotype.,[42] Similar to other mutations, it alone is insufficient to induce the clinical phenotype. Thus, the expression of the $tRNA^{Cys}$ G5783A mutation likely necessitates additional modifying factors, such as nuclear background, environmental influences, and mitochondrial haplotypes. Notably, research has shown that mitochondrial haplotypes can impact the penetrance and expressivity of primary mtDNA mutation-related MDD.[43] In this study, both the NB025 and 2NB043 pedigrees were classified under the Eastern Asian H2 haplotypes, suggesting that H2 haplotypes carrying the G5783A mutation may influence the likelihood of developing MDD.

There were some limitations to this study. First, the penetrance rates in these families of MDD were low, and the two families were only one patient with MDD. Secondly, the study of the G5783A mutation was not verified by other matrilineal relatives in the two families, although the mitochondrial genome was not recombinant. Finally, this study did not test the mitochondrial function of two first probands. Additionally, the role of mtDNA epigenetics in MDD development remains underexplored, necessitating further research to clarify its contribution to disease etiology and therapeutic strategies. In conclusion, the $tRNA^{Cys}$ G5783A mutation might represent a mitochondrial gene mutation linked to MDD. Nuclear modifier genes or environmental factors may influence the phenotypic expression of the MDD-

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associated $tRNA^{Cys}$ G5783A mutation in these Chinese individuals. Our findings could offer new insights into the pathophysiological mechanisms of MDD and provide valuable data for therapeutic approaches and interventions.

Conclusion

In this study, we report the clinical, genetic and molecular characterization of two Chinese families with MDD. Identifying the $tRNA^{Cys}$ G5783A mutation in two individuals with no genetic relation who exhibit symptoms of depression provides compelling evidence that this mutation may be implicated in MDD development. The two Chinese pedigrees that carried the $tRNA^{Cys}$ G5783A mutation did not exhibit any functionally significant mutations in their mtDNA. Nonetheless, there was a low penetrance of MDD among the two Chinese families with the $tRNA^{Cys}$ G5783A mutation. Therefore, the phenotypic expression of the $tRNA^{Cys}$ G5783A mutation related to MDD may be influenced by the nuclear modifier gene (s) or environmental factors.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Committee of Ningbo Kangning Hospital (NBKNYY-2022-LC-29). All participants received verbal and written information about the study and provided written consent to participate in this study. All procedures carried out in studies conformed to the 1964 helsinki Declaration and its subsequent amendments or similar ethical standards.

Consent for Publication

Informed consent was obtained from the patients to publish their case details and accompanying images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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