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PERSPECTIVE

The other, forgotten genome: mitochondrial DNA and mental disorders

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This paper summarizes recent research on mitochondrial DNA (mtDNA)—which might be described as the 'other, forgotten genome'. Recent studies suggest the possible pathophysiological significance of mtDNA in schizophrenia and neurodegenerative and mood disorders. Decreased activity of the mitochondrial electron transport chain has been implicated in both Parkinson's and Alzheimer's disease and while age-related accumulation of mtDNA deletions has been suggested as a possible cause, there is no concrete evidence that particular mtDNA polymorphisms are responsible. In schizophrenia, the activity and/or mRNA expression of complex IV are involved, but the direction of the alteration is not the same and there is no evidence linking schizophrenia with mtDNA. In bipolar disorder, there is some evidence of parent-of-origin effects and association with mtDNA polymorphisms but further investigation is needed to elucidate the role of mtDNA in mental disorders. *Molecular Psychiatry* (2001) **6,** 625–633.

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Introduction

The mitochondrion, one of the cytoplasmic organella, has its own genetic material: mitochondrial DNA (mtDNA).[1] Representative mitochondrial encephalomyopathies, such as CPEO (chronic progressive ophthalmoplegia)[2] and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)[3] caused by mutations of mtDNA, produce a variety of somatic symptoms. However, some cases are lacking in core symptoms of encephalomyopathy having only common physical symptoms despite the fact that they have the same mtDNA mutations. In other words: common diseases may occur in some patients as a result of subclinical mitochondrial encephalomyopathy caused by mtDNA mutation. And for this reason the pathophysiological involvement of mtDNA abnormalities is of clinical and research interest for mental disorders.

What is mitochondrial DNA?

Mitochondria are complex structures, widely distributed over the cytoplasm. Because these organella are separated from cytoplasm by the mitochondrial outer membrane and have their own genetic material, they are thought to be derived from bacteria that entered into symbiosis with eukaryotic cells billions of years ago. The principal function of the mitochondrion is to create a proton gradient between its inner and outer membrane via the electron transport chain, to produce adenosine triphosphate (ATP). Mitochondria also have enzyme systems involving the TCA cycle and lipid metabolism.[4]

Because the bcl-2 family, which regulates apoptosis, is expressed on the mitochondrial membrane, the role of mitochondria in regulating apoptosis has received much attention. While the apoptosis inhibiting factor, bcl-2, inhibits release of cytochrome *c* from mitochondria, the inducing factor, bax, enhances its release, and the released cytochrome *c* induces apoptosis itself through activation of caspases.[5]

Recent studies have also revealed the role that mitochondria play in regulating the intracellular calcium signaling system.[6] When the intracellular calcium level is increased by agonist stimulation, calcium is absorbed by mitochondria. Thereafter, mitochondria slowly release calcium to maintain slightly elevated levels. Fibroblasts of patients with MELAS[7] and hybrid cells containing mitochondria from patients with MERRF (myoclonic epilepsy with ragged red fiber)[8] show altered intracellular calcium response.

Characteristics of mitochondrial DNA

MtDNA as a genetic material has its own replication system separate from that of the nuclear genome. Although the whole mtDNA sequence made by Anderson *et al*[1] was 16569 bp in length, several errors and

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rare mutations were noted and a consensus sequence proposed.[9] MtDNA is also only inherited from the mother.

MtDNA encodes two ribosomal RNA genes (12S rRNA and 16S rRNA), 22 transfer RNA (tRNA), and 13 protein subunits of the electron transport chain (Figure 1).[10] These include seven subunits (ND1, ND2, ND3, ND4L, ND4, ND5 and ND6) of complex I (NADH:ubiquinone oxydoreductase), one subunit (Cyt b) of complex III (ubiquinol:cytochrome *c* oxidoreductase), three subunits (COI, COII, and COIII) of complex IV (cytochrome *c* oxidase), and two subunits (ATP6 and ATP8) of complex V (ATP synthetase).[1] Other subunits of mitochondrial proteins are encoded in the nuclear genome. In addition, there is a variable control region of 1100 bp containing the 'D-loop' which regulates replication. Most genes are encoded in the L (light)-strand, while the other strand, known as the H (heavy)-strand, also encodes several genes.

Each cell contains many mitochondria and multiple copies of mtDNA are included in each mitochondrion. MtDNA evolved faster than nuclear DNA, and has large variation. Because it has no intron and no histone, and has a poor repair system, it is prone to somatic mutation. From this point of view mtDNA might be described as the 'weak point' of the human genome and may be associated with many neurodegenerative disorders and general medical diseases associated with aging.

MtDNA abnormality and its pathophysiology

Mitochondrial encephalomyopathy

Three diseases associated with and representative of mtDNA mutations are the mitochondrial encephalomyopathies such as MELAS and MERRF caused by point mutations in tRNA genes,[3] and CPEO caused by large-scale partial deletion.[2] The 4977-bp deletion is the most frequently seen in CPEO and for this reason is

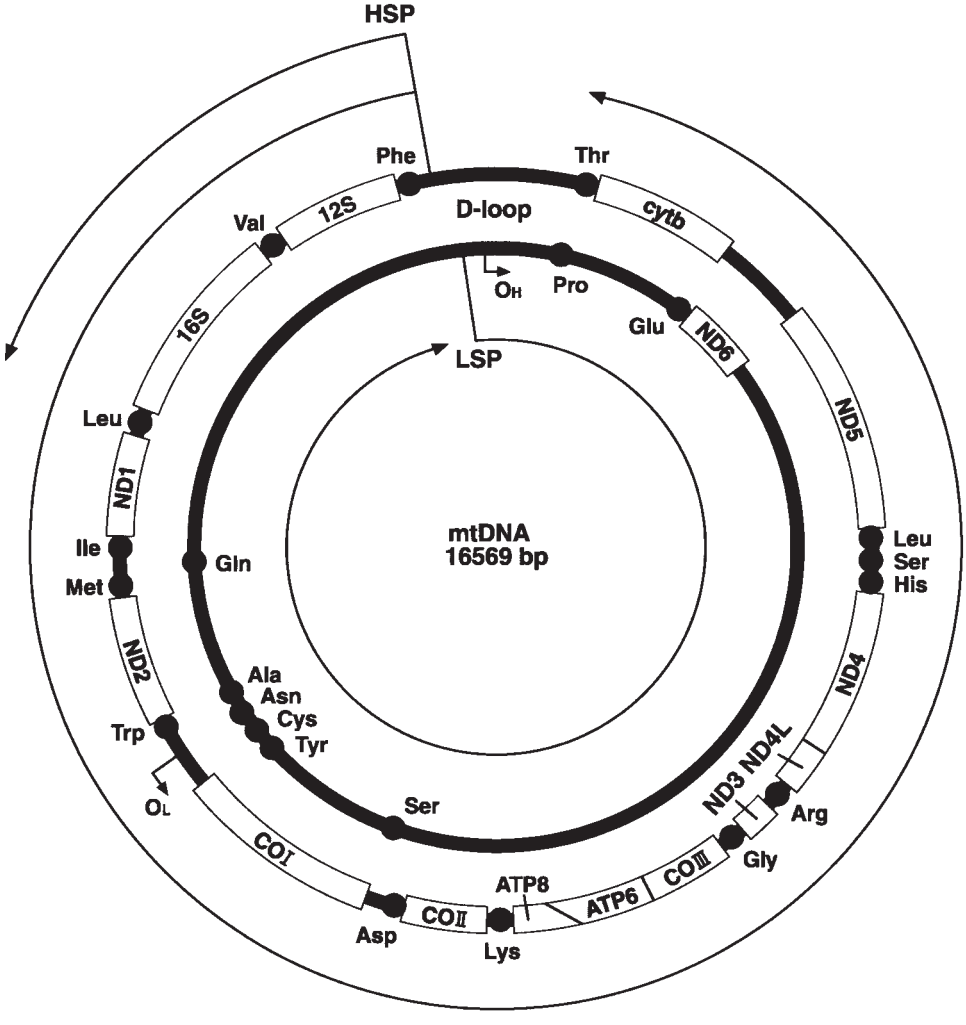

Figure 1 Distribution of genes in human mitochondrial DNA. ND1, ND2, ND3, ND4L, ND4, ND5, and ND6 are subunits of complex I. Cyt b is a subunit of complex III. COI, COII, and COIII are subunits of complex IV. ATPase6 and ATPase8 are subunits of complex V. 12SrRNA and 16SrRNA are ribosomal RNA genes. Twenty-two tRNA genes are shown as closed circles with three-letter abbreviations of amino acids. There are two forms each for Leu- and Ser-tRNAs. O_H and O_L indicate origin of replication of heavy (H) and light (L) strands. The outer circle represents the L-strand, while the inner represents the H-strand.

called the 'common deletion'. While MELAS and MERRF are maternally inherited, most cases of CPEO are sporadic without any family history. In either case, mutated mtDNA coexists with the wild-type and the ratio of mutated to wild-type mtDNA differs from tissue to tissue. This phenomenon called heteroplasmy causes variable presentation of the diseases.

The functional consequence of disease-related mtDNA mutations has been studied using the mitochondrial cybrid technique. When cells are cultured with a low concentration of ethidium bromide, replication of mtDNA but not nuclear DNA is inhibited and the cells finally lose their mtDNA. These cells, called ρ^0 (rho zero) cells, can be fused with platelets[11] or synaptosomes[12] taken from patients and which have mitochondria without nuclei that can be analyzed.

Common diseases

The discovery of maternally inherited diabetes and deafness (MIDD) associated with the 3243 mutation, a typical mutation of MELAS, facilitated a search for patients with common diseases caused by mtDNA mutations.

About 1% of patients with diabetes mellitus (DM) had the 3243 mutation.[13] MtDNA mutations have also been found in patients with other common diseases such as cardiomyopathy, migraine, cluster headache, deafness, and so on.[14]

Neurodegenerative disorders

Since MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was found to cause Parkinson's disease via mitochondrial toxicity, mitochondrial dysfunction has been investigated in Parkinson's disease. While reduced complex I activity in the substantia nigra is a consistent finding, it remains unknown whether this is also observed in other brain regions or other tissues, and it is also the case for other mitochondrial electron transport chains. Although the reduction of complex I activity is thought to be caused by the accumulation of mtDNA deletions associated with aging,[15] this remains uncertain.[16]

It has also been postulated that mtDNA mutations may be a risk factor for Alzheimer's disease, partly because more mothers of patients with Alzheimer's disease had the disease.[17] Reduced activity of mitochondrial complex IV and reduced expression of ND4,[18] a subunit of complex I, have been reported for this disease postmortem. Although several mtDNA mutations/polymorphisms, such as 5460A,[19] 4336C,[20–22] and 3397G,[20] have been associated with Alzheimer's disease, these findings have not been replicated by later studies.[23–28] And although heteroplasmic mutations were found in platelets from patients with Alzheimer's disease,[29] this was later found to be an artifact produced by pseudogenes from the nuclear genome.[30–32] Although increased levels of deletion in brains postmortem were reported, again this was not confirmed in subsequent studies.[16]

Mitochondrial dysfunction has also been implicated in other neurodegenerative disorders such as ALS (amyotrophic lateral sclerosis)[5] and Huntington's disease.[33] All cybrids of these diseases show some functional abnormalities.[34–37]

Cybrid analysis is a powerful tool in studying the functional consequences of specific mtDNA mutations. However, its role in studies of neurodegenerative disorders is unclear and it is difficult to explain why these cybrids with mtDNA of platelets taken from patients have disease-specific abnormalities even though these diseases are not caused by specific mtDNA mutations.

Aging

MtDNA, damaged by active oxygen, produces free radicals, which further attack mtDNA. This cycle is thought to be part of the biochemical background of aging.[38] On the basis of postmortem studies it has also been reported that mtDNA 4977-bp deletions increased with age in brains postmortem.[39] More recently, a T414G transversion was found to increase with age in human fibroblast mtDNA.[40]

Tanaka *et al*[41] sequenced the whole mtDNA genome in 11 healthy Japanese subjects more than 100 years old and compared these sequences with those of control subjects. They reported that the 5178A polymorphism was significantly more frequent in these centenarians and it is possible that a higher rate of 5178A may be associated with the higher life expectances of the Japanese. De Benedictis *et al* also report a relationship between mtDNA and longevity in Caucasians.[42]

MtDNA studies in mental disorders

Schizophrenia

Neuroimaging studies Phosphorus-31 magnetic resonance spectroscopic (^{31}P-MRS) studies suggest decreased levels of adenosine triphosphate (ATP) in the basal ganglia and temporal lobes of patients with schizophrenia.[43]

Mode of inheritance There is some evidence to suggest higher maternal transmission of schizophrenia.[44–46] The reason for this is unclear and may reflect mitochondrial inheritance or differences in opportunity between the sexes for finding partners.[47]

Comorbidity with mitochondrial disease Patients with MELAS sometimes demonstrate delusions and hallucinations due to delirium[48–51] or schizophrenia-like symptoms.[52–59] Of these, delusions and hallucinations due to delirium[48–51] can be regarded as directly related to neuronal dysfunction due to MELAS. Two of the 3243 mutation cases without any central nervous system symptoms except for schizophrenia,[58,59] and four patients with MELAS who demonstrated schizophrenia long before onset of MELAS have been reported.[52–55] These six cases, however, may represent occasional comorbidity of MELAS and schizophrenia in view of the high rate of schizophrenia in the general population. The finding by Odawara *et al* that none of

the 300 unselected schizophrenic patients had the 3243 mutation supports this view.[60]

To clarify the relative risk of schizophrenia in patients with the 3243 mutation, the incidence of schizophrenia should be examined in large numbers of patients with the 3243 mutation.

Postmortem biochemical and mRNA studies Two groups—at the Institute of Psychiatry in the UK and at Uppsala University in Sweden—have studied mitochondrial function extensively in schizophrenia. Whatley and colleagues at the Institute of Psychiatry examined mRNA extracted postmortem from the frozen brains of patients with schizophrenia and depression.[61] They isolated five cDNAs present at abnormal levels in the frontal cortex of schizophrenic patients and found that all the sequences encode mitochondrial transcripts. Three of the cDNAs showing reduced expression in schizophrenia were derived from 16s rRNA, and two demonstrating increased expression were 12s rRNA and COII (cytochrome *c* oxidase subunit II). Of these, increased levels of COII mRNA were confirmed in the frontal cortex of eight schizophrenic patients and five controls.[62] Increased COII was even more prominent in two drug-free schizophrenic patients, and the antipsychotic drug flupenthixol was found to decrease COII expression in experimental animals, suggesting that it was not drug-related. However, contrary to expectation, the activity of cytochrome *c* oxidase in the frontal cortex of patients with schizophrenia post-mortem did not show any alteration. However, the sensitivity of cytochrome *c* oxidase to azide and the sensitivity of NADH-cytochrome *c* reductase to rotenone was decreased in brains of schizophrenic patients.[63]

Cavelier and colleagues[64] at Uppsala University examined cytochrome oxidase activity in the brains of schizophrenic patients postmortem and compared them with those of patients with Alzheimer's disease. Activity was significantly decreased in caudate (63%) and frontal cortex (43%) in schizophrenic patients compared with controls. However, average levels of mtDNA 4977 deletion did not differ significantly between schizophrenic patients and controls, and COX activity in schizophrenic patients did not correlate with levels of mtDNA 4977 deletion. No age-related accumulation of mtDNA deletions was found in schizophrenic patients in contrast to controls and patients with Alzheimer's disease. In a subsequent study, Prince and colleagues[65] examined the effects of haloperidol and fluphenazine on the activity of the mitochondrial electron transport chain and found that these typical antipsychotics decreased complex I activity in rat brain while increasing complex IV activity. Methamphetamine (MAP) and phencyclidine (PCP), both of which cause schizophrenic symptoms, decrease COX activity in many brain regions. Both clozapine and fluphenazine inhibit the effects of MAP and PCP on complex IV activity.[66] They further examined regional differences of mitochondrial electron transport chain activity in brains of schizophrenic patients postmortem. Complex IV activity was reduced in the caudate and increased in the putamen and nucleus accumbens of schizophrenic patients.[67] Subsequently, they found increased COX activity in the putamen to be significantly associated with cognitive dysfunction when assessed antemortem.[68] They concluded that increased COX levels in the putamen are related to cognitive dysfunction.

Both of these studies suggest that altered activity of complex IV and/or expression of COII, a subunit of complex IV, may be related to the pathophysiology of schizophrenia. However, these two lines of study are not consistent with each other since activity of complex IV was unchanged[63] or decreased[64] in the frontal lobes, while mRNA expression of complex IV increased in the frontal lobes,[62] putamen,[67] and nucleus accumbens[67] and decreased in the caudate.[67] Furthermore, antipsychotics decreased COII expression, while increasing COX activity.[65]

Electron microscopic studies Electron microscopic investigation has revealed that mitochondria are significantly decreased in the axonal terminal in the caudate and putamen.[69] This is more significant for drug-free patients than patients under treatment, indicating that it may not be due to the effects of drugs. Hyperplasia of mitochondria in the presynaptic terminals has been reported in the substantia nigra.[70]

MtDNA polymorphisms Lindholm *et al*[71] at Uppsala sequenced the whole mitochondrial genome in two patients with schizophrenia showing marked decrease of complex IV activity in brains postmortem and two probands with schizophrenia in families showing maternal inheritance. They found five missense mutations in protein coding regions and compared the frequencies in 81 patients and 259 controls. Two polymorphisms, 14793G and 15218G, both of which cause amino acid substitution of Cyt b, were more frequently and significantly seen in schizophrenia. When geographical distribution was examined, however, there was no significant association in Northern Sweden while a significant association was found in Southern Sweden. They concluded that there is no association between these polymorphisms and schizophrenia. Gentry *et al* also reported that the 14793 polymorphism, as well as other candidate mtDNA polymorphisms (5460 and 1309), was not associated with schizophrenia for both Caucasians and African-Americans.[72]

Mood disorders

Neuroimaging studies Increased incidence of white matter hyperintensity (WMHI) lesions detected by magnetic resonance imaging is the most consistent neuroimaging finding in bipolar disorder and late-onset major depression.[73] WMHI, a nonspecific finding frequently indicating ischemic change, is also reported in mitochondrial encephalopathy.[74]

Using phosphorus-31 magnetic resonance spec-

troscopy (^{31}P-MRS), the authors report that intracellular pH was decreased in the frontal lobes of patients with bipolar disorder.[75] However, the effects of drugs could not be ruled out. Although this finding was replicated in drug-free patients, the number of drug-free subjects ($n = 7$) was too small to draw a definite conclusion.[76]

Using ^{31}P-MRS, the authors also report that phosphocreatine (PCr) decreased in the frontal lobes in bipolar depression.[77] In major depression, decreased ATP in the frontal lobes[78] and basal ganglia[79] has also been reported. However, these ^{31}P-MRS findings in mood disorders are not similar to those observed in mitochondrial encephalopathies, ie, decreased PCr and normal pH.[74]

Photic stimulation ^{31}P-MRS studies show no significant difference between bipolar disorder and controls. However, when patients were divided with regard to lithium response, significantly lower levels of PCr after photic stimulation (PS) in the occipital lobe was shown in lithium-resistant bipolar disorder.[80] Patients with MELAS showed a different response, ie, prominent decrease of PCr during PS,[81] while patients with CPEO without CNS involvement showed similar findings to lithium-resistant bipolar disorder, ie, decrease of PCr after PS.[82]

Mode of inheritance It has also been observed that patients with manic-depressive illness more frequently have affected mothers than fathers, and more often have affected maternal relatives.[83] An explanation is X-linked dominant inheritance and higher prevalence rate in females. The non-Mendelian gender-related pattern of inheritance is now referred to as 'parent-of-origin effect (POE)'. McMahon *et al*[84] suggest this might be caused by mitochondrial inheritance. It is still unknown whether POE is involved in bipolar disorder,[85–88] and even if it is, DNA methylation might also explain the phenomenon. Linkage to chromosome 18, limited to paternally transmitted pedigrees, has also been reported, suggesting involvement of genomic imprinting, rather than mitochondrial inheritance.[89] And a segregation analysis suggested multifactorial inheritance in maternally inherited pedigrees and a single major gene in paternally transmitted pedigrees.[90]

Comorbidity with mitochondrial diseases Depression frequently shows comorbidity with general disorders including mitochondrial encephalomyopathy[91–101] and there are several reports suggesting a pathogenetic role for mtDNA mutation in mood disorders.[95,99]

Suomalainen *et al*[95] report a family with CPEO caused by multiple deletions of mtDNA. The proband shows severe retarded depression for many years, and the onset of CPEO noted after a long history of depression. Autopsy revealed greater deletion in the brain than muscles. Several other affected family members also had depression. In this family, depression may be regarded as a symptom of mitochondrial encephalopathy. However, 'multiple deletion' of mtDNA is not a primary abnormality of mtDNA but is autosomally inherited. The authors examined the 4977-bp deletion in leukocytes of patients with mood disorders by quantitative PCR and found increased deletion in two patients.[98,102] However, the increased levels of deletion in leukocytes were not maternally inherited and did not co-segregate with depression in these two families, suggesting no pathogenetic role.[102]

Depression is one of the symptoms of Wolfram syndrome characterized by diabetes mellitus, optic atrophy, and deafness. Although this is an autosomal recessive inherited disease, interaction with mtDNA is suggested because certain symptoms resemble those of mitochondrial disorders and multiple deletions of mitochondrial DNA (mtDNA) have been reported.[103] Non-affected carriers of this gene have an estimated 26-fold increased risk of psychiatric hospitalization.[104] Because the gene involved, WFS1/wolframin,[105,106] is located at 4p16 where linkage with bipolar disorder has been suggested,[107] mutations of WFS1 have been sought in patients with bipolar disorder without Wolfram syndrome. Of several newly identified missense mutations, only one (Ala559Thr) was associated with affective disorder,[108] while others were not linked with the disease in a bipolar family linked to 4p16,[109] or associated with bipolar disorder.[110,111] Recently, WFS/wolframin was found to be localized in the endoplasmic reticulum, which argues against its role in mitochondrial function.[112] There is another locus for Wolfram syndrome at 4q22–24,[113] although the significance of the gene for bipolar disorder has not been examined.

Suzuki *et al*[99] performed psychiatric evaluation of 15 patients with mitochondrial DM and found that nine had mental disorders, of which four had mood disorders and one schizophrenia. However, this report is limited by the small number of patients and lack of robust diagnostic procedure. There is no evidence indicating the 3243 mutation is a risk factor for mood disorders.

MtDNA in the postmortem brain Using Southern blot analysis of postmortem specimens Stine *et al*[114] found no mtDNA deletions in seven patients with bipolar disorder and nine who committed suicide. The authors measured the common deletion using quantitative PCR[115] and found a marginal increase for bipolar disorder compared with controls. However, the levels of deletion were at most 0.6%, which cannot impair energy metabolism. Unlike schizophrenia, no postmortem biochemical studies have been reported for bipolar disorder.

MtDNA polymorphisms Three groups from the UK, Japan, and USA have been studying mtDNA polymorphisms in bipolar disorder. Kirk *et al*[116] sequenced the whole mitochondrial genome in 25 patients with bipolar disorder and demonstrated differences in the mitochondrial genetic distances within the bipolar and control groups. They determined these by making all the pairwise comparisons possible of mtDNA haplotypes in the bipolar or control groups and found that

the bipolar group had fewer closely related haplotypes than controls, suggesting selection against certain haplotypes in the bipolar cases. However, no concrete evidence indicating a certain mitochondrial haplotype increases vulnerability to bipolar disorder has been reported.

The authors searched for mtDNA polymorphisms associated with bipolar disorder using heteroduplex analysis and SSCP (single strand conformation polymorphism). Of the nine evolutionary conserved mutations/polymorphisms genotyped in 135 patients with bipolar disorder and 187 controls,[117] the only base substitution that exists in polymorphic frequency, G10398A, was significantly associated with bipolar disorder (10398A: 33% in bipolar disorder, 22% in controls). The authors also report the 5178C polymorphism as being significantly associated with bipolar disorder.[118] Both 5178C and 10398A cause amino acid substitutions in complex I (ND2 or ND3). The C/A haplotype of these polymorphisms is more frequently seen in patients with bipolar disorder (33%) compared with controls (16%) with an odds ratio of 2.4.[117] While the 5178A genotype is not seen in Caucasians, the G10398A polymorphism frequently is.

McMahon *et al*[119] sequenced the whole mitochondrial genome in nine unrelated probands selected from large pedigrees with exclusive maternal transmission of bipolar disorder. Of these, 15 variants of possible pathological significance were assayed in 92 patients and 63 controls classified into major groups comprising the European mtDNA haplotype structure (haplogroup). There was no significant difference in haplogroup frequencies between patients with bipolar disorder and controls. Although four variants (709, 1888, 10398 and 10463) had odds ratios higher than 2 or lower than 0.5, they concluded that there was no association between variants with bipolar disorder. Despite the negative findings, it is still intriguing that the largest difference found for the 10398 polymorphism (10398A: 78% in bipolar and 64% in controls) was similar to that in our study. The 10398A genotype might therefore be a risk factor for bipolar disorder although the effect is small. The authors proposed the mitochondrial dysfunction hypothesis for bipolar disorder in accordance with these findings.[120]

Other topics

Niculescu *et al*[121] identified a series of candidate genes for bipolar disorder and psychosis by analyzing gene expression profiles after methamphetamine treatment in rat brain by GeneChip. The largest increase was found for NDUFS8 at 11q15, a nuclear-encoded subunit of complex I. The finding may suggest that mitochondrial protein may be a candidate molecule for the pathophysiology of bipolar disorder and psychoses.

Methodological problems

Research of mtDNA in mental disorders involves various methodological problems that are not an issue in studying nuclear genes.

Firstly, a linkage study cannot be applied because transmission of mtDNA is simple and occurs without recombination. Secondly, association studies are hampered by large inter-ethnic differences. Thirdly, it is difficult to prove the pathophysiological significance of certain mtDNA mutations. Because the usual transfection experiments cannot be used, the cybrid method is used to examine the functional consequence of mtDNA mutation.[11] However, it remains uncertain if this method can be viewed as a 'gold standard', because ρ^0 cells still have mitochondrial membrane potential.[122] Fourthly, mutations can be missed in peripheral blood cells when the mutation is heteroplasmic and localized in the brain. Contamination by nuclear genes needs to be considered when heteroplasmic mutations are examined.[30–32] Fifthly, the mtDNA polymorphism is a non-specific genetic risk factor. Recently, it has been suggested that depressive symptoms are elevated in the preclinical phase of Alzheimer's disease[123] and patients with mood disorders have a higher risk of dementia.[124] Although the contribution of different mitochondrial polymorphisms to Alzheimer's disease and bipolar disorder are described in the literature, they might be duplicating each other.

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