

# Bipolar Disorder as a Mitochondrial Disease

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Relapse, recurrence, and psychosis are common features in bipolar disorder (BD), affecting all aspects of an individual's life with repercussions for the overall economy. BD is further compounded by the lack of measurable biological markers because current diagnosis relies largely on subjectively documenting mood and behavior. Without a thorough understanding of the underlying target biology of BD, the diagnosis, management, prevention, and treatment of this debilitating condition will remain an unsolved challenge, inflicting continued substantial burden on health care costs.

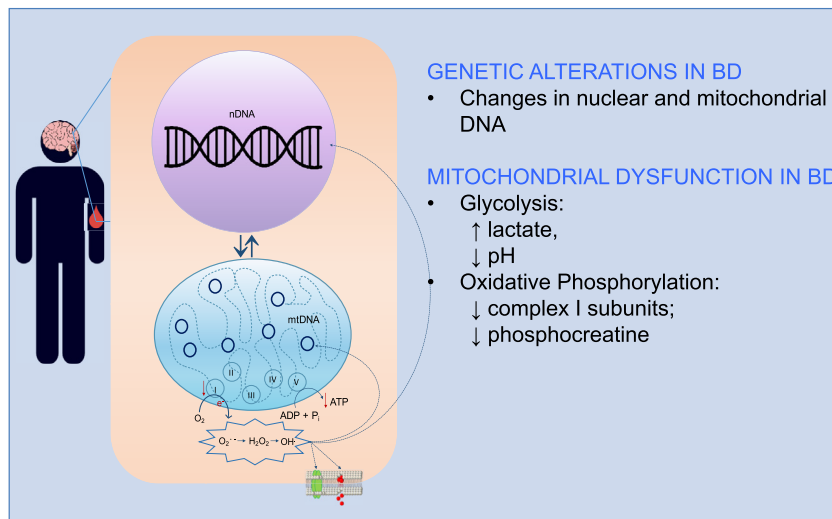
Studies from our laboratory and others point to the role of mitochondrial and energy metabolism (1). Some of the earliest and most direct evidence for mitochondrial dysfunction in BD has come from magnetic resonance spectroscopy studies showing higher levels of lactate in the brain (2) and cerebrospinal fluid (3), and lower levels of adenosine triphosphate and phosphocreatine in the brain of patients with BD. Indeed, lactate levels are critical to diagnosing a wide variety of mitochondrial diseases. Intriguingly, individuals with mitochondrial disease commonly present with psychiatric symptoms (4).

Moreover, complex I dysfunction is the most frequent cause of human mitochondrial disorders and a major source of cellular reactive oxygen species. Mutations in the core complex I subunits can sometimes be so severe and lethal that individuals carrying the mutations never reach adulthood. For example, mutations in the mitochondrial complex I *NDUFV1* gene (1268C>T) are associated with complex I deficiency resulting in truncation of 91% of the mature *NDUFV1* protein and leading to early severe phenotypes with death less than 2 years after birth (5). In other cases, mutations in nuclear or mitochondrial DNA may produce slight functional consequences that while not lethal may lead to noticeable symptoms (if any) that can impact an individual's quality of life, like those seen in BD. Specifically, mutations in the mitochondrial DNA 3644T>C (the region encoding mitochondrial complex I subunit ND1) is associated with BD, which causes decreased complex I activity and decreased mitochondrial membrane potential in trans-mitochondrial cybrids (cell lines transfected with mutant mitochondria that harbor the same nuclear DNA) (6). Likewise, several single nucleotide polymorphisms in other nuclear DNA-encoded mitochondrial complex I genes, such as *NDUFV2* (-3188C>T and -602G>A) are associated with BD (7), yet functional consequences of these single nucleotide polymorphisms remain to be fully explored. Moreover, a recent study using young neurons derived from induced pluripotent stem cells of BD shown changes on expression of multiple mitochondria genes and smaller mitochondrial size and higher membrane potential. This lends further support to a heritable defect in mitochondria being present in patients with BD.

Mitochondrial DNA variations have been demonstrated to be associated with phenotype, treatment response, and biochemical changes in BD. Indeed, our group recently sequenced mitochondrial DNA from 224 patients with BD, and the data suggest a higher risk of psychosis with the U haplogroup and variation in the ND4 gene implicated in electron transport chain energy regulation (8). Mitochondrial DNA 10398A mutation has been shown to be associated with better response to lithium treatment in patients with BD (9). The same mutation has been also associated with higher fasting glucose and lower glucose utilization in the prefrontal cortex. Many genetic studies have also searched for risk genetic variants in the nuclear DNA using genome-wide association studies. No specific mutations in mitochondria have been identified in patients with BD. *CACNA1C*, a calcium channel, *ANKK3*, a gene involved in regulation of neuronal function, and *ZNF804A*, a gene involved in myelin transcription, are among the most significant findings from genome-wide association studies in BD. The exact role of these genes in BD is not yet fully understood, and whether mutation on these genes increases the susceptibility of mitochondrial dysfunction in patients with BD has not been studied.

Beyond imaging data and DNA mutations, evidence for mitochondrial complex I dysfunction also exists at the messenger RNA and protein levels. A systematic review of microarray studies demonstrated decreased gene expression of the core electron-transferring complex I subunits (*NDUFV1*, *NDUFS8*, and *NDUFS7*) in postmortem prefrontal cortex and hippocampus, specifically from subjects with BD. Lower levels of these core subunits may increase the rate of electron leakage from complex I, resulting in increased reactive oxygen species concentration. Indeed, *NDUFS7* protein levels were found to be decreased in the prefrontal cortex of subjects with BD, which correlated with decreased complex I activity (10).

Given the strength of biochemical and imaging data supporting mitochondrial dysfunction in BD, why don't genetic studies in BD point to mitochondrial dysfunction in BD? One major reason may be that two human genomes (nuclear and mitochondrial DNA) are involved in making mitochondrial proteins and controlling mitochondrial function. These two genomes are inherited independently—unlike the nuclear genes, mutations in the mitochondrial DNA are inherited from the maternal parent, and the number of mitochondria carrying the mutations, called heteroplasmy, can differ from person to person. Genetic variations in either genome and the interaction between nuclear and mitochondrial single nucleotide polymorphisms can affect the production of mitochondrial proteins and overall mitochondrial function. A majority of mitochondrial proteins are encoded by nuclear DNA, and therefore protein quality control mechanisms are needed to ensure proper



**Figure 1.** Bipolar disorder (BD) as a mitochondrial disease. ADP + P, adenosine diphosphate plus phosphate; ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; nDNA, nuclear DNA.

folding, degradation, and import of mitochondrial proteins into the mitochondria. Timely removal of damaged mitochondria is crucial for healthy cellular metabolism. An open question is how mutation in either nuclear or mitochondrial DNA affects these quality control processes involved in regulating mitochondrial protein integrity and function. A second major reason may be the complexity of nuclear and mitochondrial DNA communication and interaction. Even the seemingly complex I dysfunction (being most common in humans) is difficult to diagnose because it is associated with a wide range of functional and clinical presentations.

Great progress has been made in the investigation of mitochondrial genetics and function in BD (Figure 1); however, this field continues to grow. Understanding how mutations in the nuclear and mitochondrial DNA affect mitochondrial protein integrity and function will allow us to understand whether BD shares a common pathology with mitochondrial disease and to define whether mitochondrial dysfunction is casual or consequence of the illness. Identifying the clear association between mitochondrial genetics and BD will allow for the identification of at-risk groups. Furthermore, understanding the biochemical effects of any identified mutations will open the window to development of clinical relevant biomarkers and therapeutics that will effectively treat this chronic and debilitating illness.

**Acknowledgments and Disclosures**

This study was supported by Canadian Institute of Health Research Grant No. MOP-133439, Ontario Mental Health Foundation Grant No. 498567, and Ministry of Research and Innovation of Canada Grant No. ERA-14-10-022 (to ACA) and Canadian Institute of Health Research Grant No. MOP-484414 (to LTY).

The authors report no biomedical financial interests or potential conflicts of interest.

**Article Information**

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Received Sep 20, 2017; accepted Sep 20, 2017.

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