Increased Levels of Circulating Cell-Free mtDNA in Plasma Predicts Severity of Depressive Symptoms in Bipolar Disorder

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Methodological question

The methodological question being addressed is whether patients with bipolar disorder (BD) show circulating cell-free mtDNA abnormalities and its association with the severity of depressive symptoms in BD.

Background

Bipolar disorder (BD) is a severe and chronic psychiatric disorder that affects approximately 1-4% of the world population. The pathophysiological pathways responsible for BD remain elusive, likely due to multifactorial etiology involving the interaction between multiple genetic, neurochemical, and environmental factors. The mitochondrial dysfunction hypothesis has been corroborated by several studies showing that BD patients present an atypical mitochondrial metabolism, abnormal mitochondrial morphology and dynamics, and mitochondrial DNA (mtDNA) damage. The amount of mtDNA released by a cell is a marker of mitochondrial health. Circulating cell-free mitochondrial DNA (ccf-mtDNA) levels reflect dysregulation homeostasis in place of cellular stress, apoptosis, or bioenergetic compromise. Furthermore, a recent surge of investigators looking at ccf-mtDNA as a potential biomarker in psychiatric conditions has been increasingly growing in interest, mainly in the context of mitochondrial dysfunction.

Aims: (1) we evaluated whether the ccf-mtDNA levels were different between individuals with BD compared to healthy controls (HCs), and (2) we evaluated the association between BD symptomatology with peripheral ccf-mtDNA levels.

Methods

In this study, 112 subjects were enrolled at the Center of Excellence in Mood Disorders at UTHealth, including 65 BD type I (BD-I) and 47 HCs. All subjects underwent a comprehensive clinical interview and diagnosis of BD according to the DSM-IV-TR. Mood symptoms were assessed with the Montgomery Asberg Depression Scale (MADRS), Young Mania Rating Scale (YMRS). Quantitative analysis of the plasma levels of ccf-mtDNA was performed using a real-time polymerase chain reaction (rtPCR).

Results

Table 1. Characteristics of the sample and comparison of socio-demographics and clinical variables between participants

	All participants 112 (100%)	BD-I 65 (58%)	Healthy control 47 (42%)	*p* value
Sex, n (%)				0.391
Female	79 (70.5%)	47 (59.5%)	32 (40.5%)	
Male	33 (29.5%)	18 (54.5%)	15 (45.5%)	
Age, mean ± SD	34.5 ± 10.2	34.9 ± 10.2	33.9 ± 10.2	0.418
Ethnic, n (%)				0.268
Hispanic or Latino	22 (19.6%)	10 (15.4%)	12 (25.5%)	
Non-Hispanic or Latino	88 (78.6%)	54 (83.1%)	34 (72.3%)	
Unknown	2 (1.8%)	1 (1.5%)	1 (2.1%)	
Race, n (%)				0.068
White or Caucasian	35 (31.3%)	26 (40.0%)	9 (25.7%)	
Hispanic or Latino	18 (16.1%)	7 (10.8%)	11 (23.4%)	
African American	38 (33.9%)	19 (29.2%)	19 (40.4%)	
American Indian or Alaskan	1 (0.9%)	1 (1.5%)	0	
Asian	10 (8.9%)	4 (6.2%)	6 (12.8%)	
Hawaiian or Pacific Islander	1 (0.9%)	1 (1.5%)	0	
More than one race	9 (8.0%)	7 (10.8%)	2 (4.3%)	
BMI, mean ± SD	29.7 ± 8.1	31.1 ±8.7	27.8 ± 6.8	0.040
Smoking, n (%)				<0.001
No	94 (83.9%)	48 (73.8%)	46 (97.9%)	
Yes	18 (16.1%)	17 (26.2%)	1 (2.1%)	
Psychotropic medication, n (%)				<0.001
No	55 (49.1%)	8 (14.5%)	47 (100%)	
Yes	57 (50.9%)	57 (87.7%)	0	
MADRS, mean ± SD	8.58 ± 10.77	14.77 ± 10.61	0.28 ± 0.90	<0.001
YMRS, mean ± SD	4.09 ± 6.45	6.83 ± 7.35	0.36 ± 0.82	<0.001

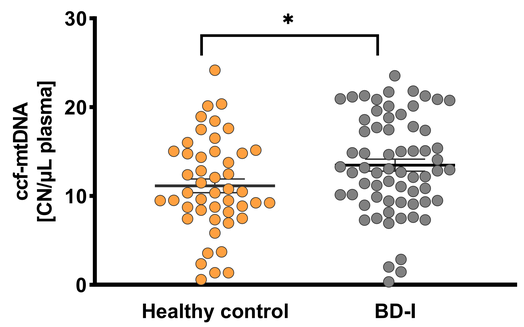

Figure 1. Plasma circulating cell-free mitochondrial DNA (ccf-mtDNA). Data were presented as mean ± standard error of the mean and were analyzed with univariate generalized models with adjustment for sex, age, BMI, smoking status, and current medication status. * Different from the healthy control, p < 0.05.

Disclosure
The authors have no conflicts of interest to disclose.

Table 2. Summary of univariate ANOVA on cell-free circulating mitochondrial DNA (ccf-mtDNA) in plasma from healthy controls (HC) and patients with bipolar disorder type I (BD-I)

Source of variation	MTND4		
	df	F	Sig.
Age	1	0.045	0.832
Sex	1	0.503	0.480
BMI	1	0.363	0.548
Psychotropic medication	1	0.770	0.382
Smoking status	1	1.635	0.204
HC vs. BD-I	1	4.053	**0.047**

Table 3. Results of multiple linear regression on cell-free circulating mitochondrial DNA (ccf-mtDNA) in plasma from healthy controls (HC) and patients with bipolar disorder type I (BD-I)

Dependent	Independent	b	SE	t	p value
MADRS	Sex	1.850	1.955	0.946	0.346
R^2= 0.363	Age	0.069	0.086	0.800	0.426
	BMI	0.079	0.109	0.728	0.468
	Psychotropic medication	10.554	1.821	5.796	**<0.001***
	Smoking status	-0.750	2.533	-0.296	0.768
	MTND4	0.410	0.154	2.654	**0.009***
YMRS	Sex	1.654	1.307	1.265	0.209
R^2= 0.205	Age	-0.009	0.058	-0.159	0.874
	BMI	-0.078	0.073	-1.070	0.287
	Psychotropic medication	5.142	1.218	4.222	**<0.001***
	Smoking status	-2.011	1.694	-1.187	0.238
	MTND4	-0.013	0.103	-0.129	0.898

Conclusions

These preliminary results indicate that elevated levels of ccf-mtDNA are observed in BD-I subjects compared to HCs. In addition, that levels of ccf-mtDNA is associated with the severity of depressive symptoms among BD-I subjects. Thus, our results provide further evidence that mitochondrial dysfunction may be proximal to the pathogenesis of BD. Further studies are needed to investigate the potential role of bioenergetics in disease progression, prognosis, and response to treatment.

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