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Association study of polymorphisms in the autosomal mitochondrial complex I subunit gene, NADH dehydrogenase (ubiquinone) flavoprotein 2 (*NDUFV2*), and bipolar disorder

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Summary

The mitochondrial dysfunction hypothesis of bipolar disorder (BPD) was proposed based on a maternal inheritance pattern in family-based studies (McMahon *et al.*, 1995). For the BPD linkage signal around human chromosome 18p11.2, Gershon *et al.* (1996) found a parent-of-origin effect only when maternal *and* paternal inheritance was considered. An *autosomally* encoded mitochondrial protein imported into mitochondria to perform important functions might explain this finding. *NDUFV2*, encoding the 24 kDa subunit of mitochondrial complex I, is one such gene found within the aforementioned BPD linkage region.

Single nucleotide polymorphisms (SNPs) in *NDUFV2* showed nominally significant associations with BPD in various ethnic populations (Washizuka et al., 2003; Xu et al., 2008; Zhang et al., 2009). To replicate or extend these findings, we studied three SNPs in *NDUFV2* (Chr18:9,102,675-9,134,336; build GRCh37:Feb2009:hg19): −3188C>T (rs2377961, Chr18:9,099,554) and −602G>A (rs1156044, Chr18:9,102,140) in the promoter, and +86C>T (rs906807, Chr18:9,117,867), a missense (A29V) SNP in exon 2, using the National Institute of Mental Health (NIMH) Caucasian control (no psychiatric or chronic neurological disease history) and BPDI (ascertained by DSM-IV criteria) populations. Informed consent was obtained from all individuals according to Institutional Review Board (IRB) requirements. 741 control and 569 BPDI individuals were genotyped using the Taqman® Genotyping Assay system (Applied Biosystems, Inc., Foster City, CA). Individuals with “undetermined” genotypes at any locus, representing 1.5% of control and 6.0% of BPDI samples, were removed from further analysis. Thus, 730 control and 535 bipolar individuals were included in our data analyses.

All SNPs were in Hardy-Weinberg equilibrium (rs2377961, BPDI p=0.140, Controls p=0.281; rs1156044, BPDI p=0.494, Controls p=0.794; rs906807, BPDI p=0.408, Controls p=0.889). rs2377961 was in strong LD with rs1156044 (D’=0.843, r^2=0.288) and rs906807 (D’=0.832, r^2=0.325), and rs1156044 was in strongest LD with rs906807 (D’=0.914,

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r^2=0.721). There were no statistically significant associations between genotypes and BPDI at rs2377961 (X^2=3.873; *p*=0.144), rs906807 (X^2=4.711; *p*=0.095) or rs1156044 (X^2=5.798; *p*=0.055). Neither allele at rs2377961 (X^2=0.572; *p*=0.449) showed association with BPDI; however, the "A" allele at rs1156044 (X^2=5.362; *p*=0.021) and "C" allele at rs906807 (X^2=4.173; *p*=0.041) were nominally associated with BPDI. Notably, association of the "A" allele at rs1156044 agrees with a study of a smaller Caucasian population (Xu et al., 2008), but is opposite the trend observed for BPDII in a Japanese population (Washizuka et al., 2003). While our findings may bolster those of Xu *et al.* (2008), statistical significances of the allelic associations in the present study were not upheld after Bonferroni correction (α=0.0167 for 3 tests).

Washizuka *et al.* (2003) found association of a "CTGT" promoter haplotype in *NDUFV2* with BPD, where "G" is rs1156044. Haplotype (rs1156044-rs906807) analysis of our data revealed no statistically significant association of the "GT" (X^2=2.765; *p*=0.096) or "AT" (X^2=1.259; *p*=0.262) haplotypes, but the "AC" haplotype showed statistical significance (X^2=7.033; *p*=0.008) after Bonferroni correction (α=0.0125 for 4 haplotype comparisons). However, after 10,000 permutations of our data, no associations remained statistically significant (lowest permutation adjusted *p*-value=0.064 for the "AC" haplotype). Thus, we cautiously conclude that the "AC" haplotype in *NDUFV2* may be associated with BPDI in this Caucasian population.

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References

Gershon ES, Badner JA, Detera-Wadleigh SD, Ferraro TN, Berrettini WH. Maternal inheritance and chromosome 18 allele sharing in unilineal bipolar illness pedigrees. Am J Med Genet. 1996; 67:202–207. [PubMed: 8723048]

McMahon FJ, Stine OC, Meyers DA, Simpson SG, DePaulo JR. Patterns of maternal transmission in bipolar affective disorder. Am J Hum Genet. 1995; 56:1277–1286. [PubMed: 7762550]

Washizuka S, Kakiuchi C, Mori K, Kunugi H, Tajima O, Akiyama T, et al. Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet. 2003; 120B:72–78. [PubMed: 12815743]

Xu C, Li PP, Kennedy JL, Green M, Hughes B, Cooke RG, et al. Further support for association of the mitochondrial complex I subunit gene NDUFV2 with bipolar disorder. Bipolar Disord. 2008; 10:105–110. [PubMed: 18199248]

Zhang J, Li X, Wang Y, Ji J, Yang F, Feng G, et al. Association study on the mitochondrial gene *NDUFV2* and bipolar disorder in the Chinese Han population. J Neural Transm. 2009; 116:357–361. Epub 2009 Feb 5. [PubMed: 19194776]