Mitochondrial Variation in Brain: Aging, Gender, and Psychiatric Disorders

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**Background:** Mitochondria provide energy for brain cells by the process of oxidative phosphorylation. Mitochondrial abnormalities and deficiencies in oxidative phosphorylation have been reported in individuals with schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD).
Mitochondria provide energy for brain cells by the process of oxidative phosphorylation. Mitochondrial abnormalities and deficiencies in oxidative phosphorylation have been reported in individuals with schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD).
Protein abnormalities in dorsolateral prefrontal cortex in schizophrenia and bipolar disorder using 2-dimensional gel electrophoresis.

4 of 15 proteins found to be differentially expressed in schizophrenia are associated with metabolic or mitochondrial function.

25 of the 51 significantly differentially expressed proteins in bipolar disorder were associated with metabolic or mitochondrial function.

Pennington et al, 2008, Molecular Psychiatry
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Brain area</th>
<th>Differences compared with healthy controls</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD II^a</td>
<td>Frontal lobe</td>
<td>↓ CP in BP II in all psychiatric states</td>
<td>118</td>
</tr>
<tr>
<td>BD^a</td>
<td>Frontal lobe</td>
<td>↓ CP in left frontal lobe of patients in depressive state; ↓ CP in right frontal lobe in manic and euthymic states</td>
<td>119</td>
</tr>
<tr>
<td>BD^b</td>
<td>Frontal lobe</td>
<td>= ATP; higher right to left ratio of PC (euthymic)</td>
<td>120</td>
</tr>
<tr>
<td>BD^c</td>
<td>Occipital lobe</td>
<td>↓ CP after photic stimulation in nonresponders to lithium</td>
<td>121</td>
</tr>
<tr>
<td>BD^a</td>
<td>Frontal lobe</td>
<td>↓ Intracellular pH in euthymic patients, also drug-free; pH normal in manic or depressive states</td>
<td>122–124</td>
</tr>
<tr>
<td>MDD^d</td>
<td>Frontal lobe</td>
<td>= ATP; ↓ CP, more in severely than mildly depressed patients</td>
<td>122</td>
</tr>
<tr>
<td>MDD^d</td>
<td>Frontal lobe</td>
<td>↓ ATP</td>
<td>125</td>
</tr>
<tr>
<td>MDD^e</td>
<td>Basal ganglia</td>
<td>↓ ATP</td>
<td>126</td>
</tr>
</tbody>
</table>

^aSome patients treated with Li and/or other drugs.
^b1-week medication free period before examination.
^cTreated with lithium.
^dSome patients treated with antidepressants and/or other drugs.
^eUntreated.
↑ increase; ↓ decrease; = no change.
For other abbreviations, see text.

Table 7
Top-Regulated Pathway/GO Terms in the Meta-Analysis

<table>
<thead>
<tr>
<th>Functional grouping</th>
<th>Representative terms</th>
<th>No. of genes</th>
<th>% Reg. (p &lt; 0.01)</th>
<th>↓</th>
<th>↑</th>
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<tbody>
<tr>
<td>Energy metabolism</td>
<td>Oxidative phosphorylation</td>
<td>109</td>
<td>47%</td>
<td>51</td>
<td>0</td>
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<tr>
<td>Protein turnover</td>
<td>Proteasome</td>
<td>31</td>
<td>71%</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ubiquitin-conjugating enzyme activity</td>
<td>57</td>
<td>44%</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>RNA Processing</td>
<td>mRNA splicing</td>
<td>62</td>
<td>42%</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Intracellular protein transport</td>
<td>235</td>
<td>36%</td>
<td>84</td>
<td>1</td>
</tr>
<tr>
<td>Stress response</td>
<td>Heat shock protein activity</td>
<td>34</td>
<td>41%</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>MHC antigen response</td>
<td>MHC class-II receptor activity</td>
<td>15</td>
<td>80%</td>
<td>12</td>
<td>0</td>
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<tr>
<td>Metallothionein</td>
<td>Metallothionein</td>
<td>11</td>
<td>45%</td>
<td>0</td>
<td>5</td>
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</tbody>
</table>

Notable literature gene sets

<p>| | | | | | |</p>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendrocyte/myelin</td>
<td>Oligodendrocyte/myelin</td>
<td>19</td>
<td>16%</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Dopamine related</td>
<td>Dopamine receptor activity</td>
<td>5</td>
<td>0%</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Serotonin related</td>
<td>Serotonin receptor activity</td>
<td>13</td>
<td>0%</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GABA related</td>
<td>GABA-A receptor activity</td>
<td>22</td>
<td>5%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Synapse related</td>
<td>Synapse</td>
<td>28</td>
<td>29%</td>
<td>8</td>
<td>0</td>
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</table>

Table 2
Summary of Study Characteristics in Meta-Analysis Studies

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<tr>
<th>Study ID</th>
<th>Samples</th>
<th>Controls</th>
<th>Bipolar</th>
<th>Collection*</th>
<th>Region</th>
<th>Array type</th>
<th>Probe sets</th>
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<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>34</td>
<td>32</td>
<td>A</td>
<td>Frontal BA46</td>
<td>Affy hgu133A</td>
<td>22283</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>29</td>
<td>11</td>
<td>C</td>
<td>Frontal BA46/10</td>
<td>Affy hgu133A</td>
<td>22283</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>35</td>
<td>32</td>
<td>A</td>
<td>Frontal BA46</td>
<td>Affy hgu133A</td>
<td>22283</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>14</td>
<td>14</td>
<td>C</td>
<td>Frontal BA6</td>
<td>Affy hgu133 2.0+</td>
<td>54681</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>26</td>
<td>30</td>
<td>A</td>
<td>Frontal BA46</td>
<td>Affy hgu133 2.0+</td>
<td>54681</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>28</td>
<td>24</td>
<td>C</td>
<td>Cerebellum</td>
<td>Affy hgu95Av2</td>
<td>12453</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>34</td>
<td>33</td>
<td>A</td>
<td>Frontal BA46</td>
<td>Affy hgu133A</td>
<td>22283</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>40</td>
<td>18</td>
<td>C</td>
<td>Frontal BA46/10</td>
<td>Affy hgu95Av2</td>
<td>12453</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>10</td>
<td>11</td>
<td>C</td>
<td>Cerebellum</td>
<td>Affy hgu95av2</td>
<td>12453</td>
</tr>
<tr>
<td>10</td>
<td>71</td>
<td>36</td>
<td>35</td>
<td>A</td>
<td>Frontal BA46</td>
<td>Codelink human 20K</td>
<td>19907</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>35</td>
<td>35</td>
<td>A</td>
<td>Frontal BA46</td>
<td>cDNA</td>
<td>14369</td>
</tr>
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<td>12</td>
<td>23</td>
<td>12</td>
<td>11</td>
<td>C</td>
<td>Frontal BA8/9</td>
<td>Affy Hgu95Av2</td>
<td>12453</td>
</tr>
</tbody>
</table>

*A = Array collection; C = Neuropathology Consortium collection.
Gene groups related to energy shuttles and oxidative metabolism, as well as certain amino acid metabolic pathways, exhibit reduced expression in schizophrenia.

Table 2. Ranking of metabolic genes according to Z load scores

<table>
<thead>
<tr>
<th>Rank</th>
<th>Gene name</th>
<th>Gene group (category)</th>
<th>UniGene Hs ID</th>
<th>GEMs present</th>
<th>GEMs decrease</th>
<th>Average Z</th>
<th>Z load</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antizyme inhibitor</td>
<td>Omithine–polyamine (iv)</td>
<td>223014</td>
<td>9</td>
<td>7</td>
<td>2.49</td>
<td>17.43</td>
</tr>
<tr>
<td>2</td>
<td>Crystallin, μ</td>
<td>Omithine–polyamine (iv)</td>
<td>924</td>
<td>10</td>
<td>7</td>
<td>2.22</td>
<td>15.53</td>
</tr>
<tr>
<td>3</td>
<td>Ornithine aminotransferase</td>
<td>Omithine–polyamine (iv)</td>
<td>75485</td>
<td>5</td>
<td>4</td>
<td>3.13</td>
<td>12.53</td>
</tr>
<tr>
<td>4</td>
<td>Translocase of inner mitochondrial membrane 17</td>
<td>Mitochondrial–translocases (vii)</td>
<td>20716</td>
<td>9</td>
<td>6</td>
<td>2.06</td>
<td>12.33</td>
</tr>
<tr>
<td>5</td>
<td>Ubiquitin-specific protease 14</td>
<td>Ubiquitin (vii)</td>
<td>75981</td>
<td>9</td>
<td>5</td>
<td>1.87</td>
<td>9.33</td>
</tr>
<tr>
<td>6</td>
<td>Glutamic-oxaloacetic transaminase 2, mitochondrial</td>
<td>Malate shuttle (i), aspartate–alanine (iv)</td>
<td>170197</td>
<td>10</td>
<td>6</td>
<td>1.39</td>
<td>8.33</td>
</tr>
<tr>
<td>7</td>
<td>3-Oxoacid CoA transferase</td>
<td>Ketone body (iii)</td>
<td>177584</td>
<td>10</td>
<td>5</td>
<td>1.59</td>
<td>7.93</td>
</tr>
<tr>
<td>8</td>
<td>ATP synthase, mitochondrial F1 complex, α</td>
<td>ETC V (i)</td>
<td>155101</td>
<td>10</td>
<td>4</td>
<td>1.72</td>
<td>6.87</td>
</tr>
<tr>
<td>9</td>
<td>Malate dehydrogenase 1, NAD (soluble)</td>
<td>Malate shuttle (i), TCA cycle (i)</td>
<td>75375</td>
<td>10</td>
<td>4</td>
<td>1.71</td>
<td>6.85</td>
</tr>
<tr>
<td>10</td>
<td>Ubiquitin C-terminal esterase L1 (thiolesterase)</td>
<td>Ubiquitin (vii)</td>
<td>76118</td>
<td>10</td>
<td>4</td>
<td>1.71</td>
<td>6.82</td>
</tr>
</tbody>
</table>

Genes in bold were chosen for in situ hybridization analysis. Category notation provided in Figure 1. CoA, Coenzyme A; NAD, nicotinamide adenine dinucleotide.

One of the most important functions of the malate shuttle is to transfer hydrogen ions [in the form of reduced nicotinamide adenine dinucleotide (NADH)] from the cytoplasm into the mitochondria. Therefore, schizophrenia may be associated with increased [H]-reducing equivalents in the cytosol.

*Middleton et al, 2002, Neuropsychopharmacology*
Demographics: DLPFC was obtained from four groups of subjects. All subjects had rapid death and absence of prolonged hypoxia prior to death.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>pH</th>
<th>Age (yrs)</th>
<th>agonal stress rating</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ave</td>
<td>SD</td>
<td>Ave</td>
<td>SD</td>
<td>Ave</td>
</tr>
<tr>
<td>BPD</td>
<td>12</td>
<td>6.87</td>
<td>0.16</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>MDD</td>
<td>15</td>
<td>6.96&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.19</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>SZ</td>
<td>14</td>
<td>6.87</td>
<td>0.24</td>
<td>45&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
</tr>
<tr>
<td>C</td>
<td>37</td>
<td>6.81</td>
<td>0.19</td>
<td>53</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 compared to controls.

ASR = agonal stress rating; BPD = bipolar disorder; C = Control; DLPFC = dorsolateral prefrontal cortex; MDD = major depressive disorder; SD = standard deviation; SZ = schizophrenia.
The Mitochondria Common Deletion

• Is 4.9 kb in size.

• Accumulates in various brain regions during aging together with an OXPHOS decline (Corral-Debrinski et al., 1992, Nature Genetics)

• Plays a major role in classical mitochondrial disorders (Wallace, 1999, Science; Dimauro and DiDonato, 2005, Annals of Medicine)

• Is viewed as an indicator of long lasting mitochondrial oxidative stress.

Sabunciyanc et al., 2007, Journal of Neural Transmission
The mitochondrial common deletion is increased in aging and in psychiatric disorders.

The mitochondrial common deletion by PCR analysis was detected at significantly higher levels in BD compared to controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Fold change compared to controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>12</td>
<td>2.12</td>
<td>0.006</td>
</tr>
<tr>
<td>MDD</td>
<td>15</td>
<td>1.82</td>
<td>0.077</td>
</tr>
<tr>
<td>SZ</td>
<td>14</td>
<td>1.59</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Shao et al, 2008, Annals of Medicine
There was a strong effect of sex on mtDNA deletion, most pronounced in the three psychiatric groups.

For example, female BD group was significantly elevated in the common deletion compared to the female control group (2.9 fold change, $p = 0.01$), while the male BD group showed a trend for elevated common deletion compared to male controls (1.8, $p = 0.07$).
Affymetrix GeneChip Mitochondria Resequencing Array

• Genomic DNA was isolated from DLPFC for 77 subjects
• 300 ng DNA was used to amplify the mitochondrial genome in 3 long overlapping PCR fragments
• PCR reactions were quantified and equimolar amounts were pooled together to fragment using the GeneChip Fragmentation Reagent
• Using the GeneChip Resequencing Assay Kit, samples were labeled and hybridized to the arrays
• Arrays were washed and stained on the Affymetrix Fluidics 450 station and scanned on the Affymetrix 7G Scanner using GCOS software
• GSEQ software was used to create the output .CHP files
• The AffyMito Analysis Application created by Eric Wang, produced report files with call rates, rCRS concordance differences and haplogroup assignments in addition to intensity and base call files.

Rollins et al, 2009, PLoS ONE
Subjects with SZ showed a 22% increase in the number of synonymous substitutions relative to non synonymous mtDNA substitutions in DLPFC (p = 0.0017).

<table>
<thead>
<tr>
<th>Group</th>
<th>[A]</th>
<th>[B]</th>
<th>[A] / [A + B]</th>
<th>[A] / [A + B] / Chi-Square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dS &gt; dN</td>
<td>193</td>
<td>239</td>
<td>0.44</td>
<td>(1.11)</td>
<td>2.42</td>
</tr>
<tr>
<td>dN = dS</td>
<td>202</td>
<td>296</td>
<td>0.40</td>
<td>(1.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>SZ</td>
<td>247</td>
<td>257</td>
<td>0.49</td>
<td>(1.22)</td>
<td>9.82</td>
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<tr>
<td>Control</td>
<td>297</td>
<td>445</td>
<td>0.40</td>
<td>(1.00)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Codon-based test of purifying selection for pair wise analysis between sequences. Values of p < 0.05 were considered significant and tabulated; column [A] shows the number of significant pair wise comparisons; column [B] is the number of SNPs by group for neutral selection. The column showing the ratio of [A] / [A + B] is to normalize the purifying SNPs by the total SNPs for the group.
An allelic association analysis was conducted across polymorphic sites in mtDNA sequence for 77 subjects. Permutation analysis (n = 50,000) for each polymorphism was run using PLINK to establish an empirical p-value for SZ v C, MDD v C, and BD v C comparisons.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Position mtDNA (rCRS)</th>
<th>Gene</th>
<th>Allele 1</th>
<th>Allele Frequency Affected</th>
<th>Allele Frequency Unaffected</th>
<th>Allele 2</th>
<th>p-value permutation</th>
<th>Base</th>
<th>A</th>
<th>G</th>
<th>C</th>
<th>T</th>
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<tbody>
<tr>
<td>BD</td>
<td>114</td>
<td>D-loop</td>
<td>T</td>
<td>0.250</td>
<td>0.030</td>
<td>C</td>
<td>0.032</td>
<td>C</td>
<td>1856</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>195</td>
<td>D-loop</td>
<td>C</td>
<td>0.571</td>
<td>0.125</td>
<td>T</td>
<td>0.007</td>
<td>T</td>
<td>11</td>
<td>280</td>
<td>1574</td>
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<td>ND4L</td>
<td>C</td>
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<td>0.086</td>
<td>T</td>
<td>0.037</td>
<td>T</td>
<td>2704</td>
<td></td>
<td></td>
<td></td>
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<td>G</td>
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<td>0.000</td>
<td>A</td>
<td>0.014</td>
<td>A</td>
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<td>750</td>
<td>12S rRNA</td>
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<td>0.000</td>
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<td>0.000</td>
<td>C</td>
<td>0.042</td>
<td>C</td>
<td>2432</td>
<td>272</td>
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<td>15043</td>
<td>Cytb</td>
<td>A</td>
<td>0.400</td>
<td>0.143</td>
<td>G</td>
<td>0.042</td>
<td>G</td>
<td>777</td>
<td>1927</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rollins et al, 2009, PLoS ONE
**Heteroplasmy detection on the Affymetrix Mitochondrial Resequencing Array**

<table>
<thead>
<tr>
<th>Subject</th>
<th>% Heteroplasmy</th>
<th>T10652C</th>
<th>T14783C</th>
<th>G15043A</th>
<th>T9540C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2267</td>
<td>80</td>
<td>C</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>2976</td>
<td>70</td>
<td>CT</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3071</td>
<td>69</td>
<td>CT</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>2169</td>
<td>69</td>
<td>CT</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3525</td>
<td>68</td>
<td>CT</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3100</td>
<td>67</td>
<td>CT</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3306</td>
<td>56</td>
<td>CT</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3633</td>
<td>24</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td>T</td>
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<tr>
<td>3731</td>
<td>15</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td>T</td>
</tr>
</tbody>
</table>

* % Heteroplasmy calculated using Coon et al 2006 method

Three mtSNPs M, N, or D haplogroups

- **Homoplasmic mutation**
  - Subject 2267: C allele at 10652
  - Subject 3633: T allele at 10652
  - Subject 2267: C allele at 10652

- **GSEQ Probe Intensities**
  - Subject 3633: T allele at 10652
  - Subject 3306: CT alleles at 10652
  - Subject 2267: C allele at 10652

*Rollins et al, 2009, PLoS ONE*
psych    non-psych

| cac | 14 | 4 |
| tgt | 27 | 31 |

Right : p-value = 0.018574
2-Tail : p-value = 0.029585
Brain pH showed an association with three mtDNA SNPs which define super haplogroup (U, K, UK). This super haplogroup had a significantly higher postmortem pH, i.e. a 1.54 fold decrease in H+ concentration compared to the remaining haplogroups; permuted p-value was 0.01 for 5,000 random group tests.
Mitochondria resequencing array is a useful tool for resequencing.

• Concordance of MitoChip Sequencing and ABI Sanger Sequencing
  • Affymetrix Genetic Sequence Analysis Analysis Software (GSEQ) assigned high quality base pair calls to **98.2%** of the mtDNA genome on all 77 chips analyzed.
  • Three individual mitochondrial genomes were previously sequenced on the ABI 3130 capillary electrophoresis (CE) sequencer.
  • All 103 calls that were different from the rCRS were **100% concordant between microarray and CE sequencing in these three individuals.**

• The microarray procedure detected the known heteroplasmonic mutation A5793G with 45% heteroplasmy (Coon et al., 2006, Mitochondrion).

• The microarray also detected two previously detected heteroplastic positions, G13590A and T16093C, found by Sanger sequencing (Hartmann et al., 2008, Human Mutation).

• The overall sensitivity for the analysis of heteroplasmy is being further analysed by other validation methods.

Rollins et al, 2009, PLoS ONE
Conclusions

• An increase in the common deletion and an overall decrease in mitochondrial transcript expression (data not shown) may be susceptibility factors in SZ, BP and MDD.
  ❏ Females showed a higher common mtDNA deletion rates than males in two studies.
  ❏ Aging increases the mtDNA common deletion in brain.

• Subjects with SZ have lower expression levels of almost the entire mtDNA genome in SZ.

• Subjects with SZ have increased mitochondrial DNA substitutions compared to control subjects.

• The UK macro haplogroup maintained a higher pH in response to terminal brain hypoxia.

• There is a post hoc haplogroup association with psychiatric disorders for a three SNP haplogroup T14783C, G15043A, and T9540C.
Conte NIMH Center Grant

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Site Directors: William Bunney, Ted Jones, Huda Akil, Stan Watson, Rick Myers

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