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Mitochondrial Etiology of Neuropsychiatric Disorders

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Abstract

The brain has the highest mitochondrial energy demand of any organ. Therefore, subtle changes in mitochondrial energy production will preferentially affect the brain. Considerable biochemical evidence has accumulated revealing mitochondrial defects associated with neuropsychiatric diseases. Moreover, the mitochondrial genome encompasses over a thousand nuclear DNA (nDNA) genes plus hundreds to thousands of copies of the maternally-inherited mitochondrial DNA (mtDNA). Therefore, partial defects in either the nDNA or mtDNA genes or combinations of the two can be sufficient to cause neuropsychiatric disorders. Inherited and acquired mtDNA mutations have recently been associated with autism spectrum disorders (ASD), which parallel previous evidence of mtDNA variation in other neurological diseases. Therefore, mitochondrial dysfunction may be central to the etiology of a wide spectrum of neurological diseases. The mitochondria and the nucleus communicate to coordinate energy production and utilization, providing the potential for therapeutics by manipulating nuclear regulation of mitochondrial gene expression.

Keywords

Mitochondria; OXPHOS; mtDNA; autism; Alzheimer's disease; nuclear receptors

Prodigious efforts have been invested in understanding the genetics and pathophysiology of pediatric and adult neurological diseases, yet a definitive understanding of their etiology and the anticipated rationally designed therapies have yet to be realized. One possible reason for this impasse maybe the assumptions on which these investigations have been based. In Western medicine it is assumed that clinical manifestations that primarily affect the brain are the product of brain-specific defects and that the important genes for neurological diseases are located on the nuclear DNA (nDNA). The alternative is that systemic mitochondrial bioenergetics defects are the cause of neuropsychiatric disorders since the brain is the most

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energetic tissue in the body and the most important mitochondrial bioenergetics genes are not in the nDNA, but located on the mitochondrial DNA (mtDNA).

A mitochondrial etiology of neuropsychiatric disorders is likely since the brain represents 2–3% of our body's mass yet consumes up to 20% of our oxygen and 25% of our glucose (1). Pyruvate generated from glucose via glycolysis is reacted with oxygen within our mitochondria to generate energy by oxidative phosphorylation (OXPHOS). Because of the brain's high reliance on mitochondrial energy, partial systemic mitochondrial defects can predispose to a wide range of neuropsychiatric disorders from autism to Alzheimer's disease.

Mitochondrial genetics and biology

The mitochondrial genome encompasses between one and two thousand nDNA-encoded genes required for mitochondrial function plus hundreds to thousands of copies per cell of the maternally inherited mtDNA. The mtDNA codes for the 13 most important polypeptides for mitochondrial OXPHOS plus the 12S and 16S rRNAs and the 22 tRNAs for mitochondrial protein synthesis. While classical Mendelian clinical disorders involve homozygous loss of function mutations, partial mitochondrial defects resulting from heterozygous nDNA gene mutations or heteroplasmic (mixed mutant and normal) mtDNA mutations can reduce mitochondrial function sufficiently to fall below the minimum bioenergetics levels for normal brain function, the brain's bioenergetics threshold (2–4).

The tissues with the highest energy demand are in rough rank order the brain, heart and muscle, kidney, and endocrine systems. Hence, the brain will be the first to be affected by the milder mitochondrial defects while more severe mitochondrial defects will begin to affect other organ systems as is commonly seen in neuropsychiatric disorders. Inefficient mitochondria will be less able to oxidize pyruvate and fatty acids resulting in the accumulation of glucose and triglycerides in the blood as seen in diabetes, obesity, and cardiovascular disease (2–4).

mtDNA variation has a number of unique genetic features that may contribute to the unorthodox genetics of the psychiatric, metabolic, and cardiovascular diseases. The mtDNA codes for the core OXPHOS genes which include seven (ND 1–4, 4L, 5 & 6) of the ~45 polypeptides of OXPHOS complex I, one (cytochrome b) of the 11 polypeptides of OXPHOS complex III, three (COI–III) of the 13 polypeptides of complex IV, and two (ATP6&8) of the 18 polypeptides of OXPHOS complex V. The remaining ~80 OXPHOS polypeptides are coded in the nDNA. The inner mitochondrial membrane complexes I–IV constitute the electron transport chain (ETC) with complex I (NADH Dehydrogenase) oxidizing NADH to NAD⁺ and complex II (succinate dehydrogenase) oxidizing succinate to fumarate. Complexes I and II transfer the collected electrons to the inner membrane electron carrier, coenzyme Q (CoQ), which ferries the electrons to complex III. Complex III transfers the electrons to cytochrome c that further transfers the electrons to complex IV (cytochrome oxidase, COX) which uses four electrons to reduce 1 molecule of O₂ to 2 molecules of H₂O. As the electrons traverse complexes I, III, and IV the energy released is used to transport protons out across the mitochondrial inner membrane from the mitochondrial matrix to the

intermembrane space. The resulting proton electrochemical gradient across the mitochondrial inner membrane is utilized as a source of potential energy to drive complex V (ATP Synthase) to condense ADP + Pi to ATP within the mitochondrion. The mitochondrial ATP is then exchanged for the cytosolic ADP across the inner membrane by the various adenine nucleotide translocator isoforms (ANTs). Hence, the 13 mtDNA polypeptides are key electron and proton carriers of OXPHOS while nDNA encodes both mitochondrial OXPHOS and structural elements (2–4).

In addition to generating ATP the mitochondria produce reactive oxygen species (ROS), which act as signaling molecules at lower levels but can become toxic at high levels; regulate cellular redox status; control intracellular Ca²⁺ levels; initiate the intrinsic pathway of apoptosis through activation of the mitochondrial permeability transition pore (mtPTP); and regulate the levels of the essential intermediates that activate cellular signal transduction pathways and epigenome (ATP, acetylCoA, S-adenosylmethionine (SAM), α -ketoglutarate, succinate, glutamate, etc.). The mitochondrion needs to control nuclear-cytosolic signaling pathways since all cellular functions require energy (5, 6).

In addition to inter-mitochondrial and inter-nuclear signaling, a variety of transcription factors and epigenomic regulators previously assumed to function exclusively in the nucleus have now been found to also be located in the mitochondrion. Examples include Foxg1 (7), p53 (8, 9), DNMT1 (10), DNMT3 (11, 12), estrogen receptor beta (ER β) (13, 14) and numerous others. Hence, there is a complex and intimate interaction between the mtDNA and the nDNA (15, 16).

Clinically relevant mtDNA variants fall into three classes: ancient adaptive polymorphisms, recent deleterious mutations, and developmental-somatic mutations. Because the mtDNA is exclusively maternally inherited, male and female mtDNAs do not mix and thus cannot recombine. Therefore, the mtDNA sequence can only change by the sequential accumulation of mutations along radiating maternal lineages.

The sequence of a single mtDNA is called its haplotype and a cluster of related mtDNA haplotypes is designated a haplogroup. The human mtDNA tree has its origin in Africa, where it radiated for approximately 200,000 years giving rise to a plethora of African-specific mtDNA haplogroup lineages, designated African macro-haplogroup L. About 65,000 years ago, only two mtDNA lineages, which founded macro-haplogroups M and N, successfully left Africa and gave rise to all Eurasian and Native American mtDNA lineages. Macrohaplogroup N radiated into both Europe and Asia, while macrohaplogroup M was confined to Asia. In Europe macrohaplogroup N gave rise to the haplogroups H, I, J, K(Uk), T, U, V, W, and X while in Asia N gave rise to haplogroups which include A, B, F, and O. Macrohaplogroup M generated a plethora of Asian mtDNA lineages (M1–M80) which include haplogroups C, D, G, and Z. Only five mtDNA lineages left Eurasian to give rise to all Native Americans mtDNAs: A, B, and X from N and C and D from M (Figure 1) (3, 17).

mtDNA haplogroup lineages are highly geographically delineated and correlate with indigenous populations. This is the result of the founder haplotypes having acquired functional mtDNA variants which changed mitochondrial energy metabolism. The resulting

altered energetic states permitted our ancestors to adapt to new environmental factors such as alternative food sources, activity demands, high altitude, warm versus cold regions, and diverse infectious agents. Regional selection of a founder functional variant resulted in the regional expansion of the mtDNAs bearing that variant leading to the haplogroups. As a result, each mtDNA haplogroup has distinctive mitochondrial physiological properties which strongly influence individual's physiologies (17–19).

The mtDNA has a much higher mutation rate than the nDNA. As a result, new deleterious mtDNA mutations are continuously arising along the human female germline resulting in maternally inherited diseases. Deleterious mtDNA mutations can range from mild to severe. Severe mtDNA mutations can affect individual phenotypes when heteroplasmic while milder mutations may only cause disease when purely mutant (homoplasmic). In either case, the effect of the mtDNA mutation can be highly variable, with heteroplasmic mtDNA mutations varying in percentage of heteroplasmy between siblings and among an individual's tissues resulting in variable energetic defects that may be slightly above or below the bioenergetic threshold. Similarly, mild homoplasmic mtDNA defects that are above the brain's bioenergetic threshold can by chance become associated with a mild nDNA genetic variant or exposed to a mitochondrial environmental toxin that impairs bioenergetics sufficiently to fall below bioenergetics thresholds and cause pathology (20).

mtDNA mutations not only arise in the female germline, but also during development and in tissues with age. These somatic mtDNA mutations are generally heteroplasmic and can augment the bioenergetic deficiencies of inherited mitochondrial defects. The accumulation of such somatic mtDNA mutations is thought to be an important factor in organ decline with aging and to also explain the delayed-onset and progressive course of common diseases. There is a strong correlation with age and increasing risk of neuropsychiatric disorders. This follows directly from a mitochondrial etiology of these diseases since the mtDNA accumulates mutations in tissues during development and aging. That these somatic mtDNA mutations relate to age-related phenotypic manifestations has been demonstrated by observing premature aging phenotypes in mice harboring error prone mtDNA DNA polymerase (21–23) and the introduction of a mitochondria-targeted catalase that reduces mtDNA deletion levels and extends lifespan (24).

Mitochondria and neuropsychiatric disorders

Extensive studies have demonstrated altered mitochondrial function in neuropsychiatric disorders of adults in Alzheimer's (AD), Parkinson's (PD), Huntington's Diseases (HD) and schizophrenia. Mitochondrial bioenergetics defects in AD, PD, and HD have been reported in patient tissues, blood cells, cell lines, and somatic cell cybrids (25–29). Alterations in neuronal mitochondrial trafficking have been reported in HD (30) and altered mitochondrial dynamics has been reported in HD (31) and AD and PD (32).

Extensive data has accrued implicating mtDNA mutations in AD, PD, and HD. An mtDNA polymorphism in the tRNA^{Gln} gene at nucleotide (nt) 4336 A>G was reported as early as 1993. This variant is present in 3.3% of late onset AD, 5.3% PD, and 6.8% AD-PD, but only

0.4% of the general population (33), and defines European haplogroup H5a. Additional mtDNA haplogroups have also been correlated with risk for both AD and PD (34–36).

Somatic mtDNA deletions have been reported in AD (37), PD (38, 39), and HD (40). Elevated mtDNA control region base substitution mutations have been extensively characterized in AD (41, 42) and PD (25) and mtDNA base substitutions have been found to be elevated systemically in AD (42). Mitochondrial morphological abnormalities have also been observed in bipolar disorder (BP) (43). BP pedigrees have been reported to show maternal transmission (44), and BP risk has been associated with mtDNA haplogroups (45). Finally, somatic mtDNA mutations are increased in schizophrenia brains (46, 47).

There is also interest in the hypothesis that mitochondrial gene variation may be an important factor in the etiology of autism spectrum disorder (ASD). Numerous metabolic and biochemical studies of ASD patients have noted mitochondrial dysfunction (48–53). While extensive nDNA genomic studies have identified a variety of heterozygous copy number variants (CNVs) (54, 55) and loss of function (LOF) mutations (56–58), each variant only accounts for a few cases (56, 57, 59–61) and the cumulative risk currently accounted for by CNV and LOF nDNA mutations is only about 20% (61), though inclusion of putative common variants may raise the cumulative nDNA risk to about ~50% (62). Hence, ASD is a polygenic disorder (63) in which nDNA CNVs, LOF, and common variants do not account for all of the genetic risk.

Multiple genes have been found to be inactivated in more than one psychiatric disorder with crossovers found between ASD, intellectual disability, attention deficit hyperactivity disorders (ADHD), and schizophrenia (61, 63, 64). LOF mutations in genes from ASD patients also overlap with metabolic and cardiac abnormalities (57). An in-depth study of a well characterized ASD cohort revealed that many of the CNVs delete bioenergetics genes (65) and a number of ASD LOF gene mutations have been found to affect mitochondrial-related functions such as the Wnt/ β -catenin signaling pathway, the CDH8 chromodomain DNA helicase genes (56, 66), and genes involved in calcium regulation, fatty acid oxidation (57), and mitochondrial branched chain amino acid metabolism (67). Thus, partial defects in mitochondrial function may be an important factor in the pathophysiology of ASD as well as other psychiatric disorders.

If mitochondrial dysfunction is central to the etiology of ASD, we would predict that a significant percentage of the ASD risk should be due to variation in the mtDNA OXPHOS genes. Both haplogroup-associated and heteroplasmic mtDNA mutations have recently been found to be associated with ASD. The role of ancient haplogroup variants in ASD risk was analyzed in the familial autism AGRE cohort from Autism Speaks. mtDNA single nucleotide polymorphisms (SNPs), previously interrogated during Illumina Genome Wide Association Studies (GWAS), were used to deduce the mtDNA haplogroups. The AGRE cohort is particularly appropriate for detecting inherited subclinical risk factors such as mtDNA variation since it has been found “that in the majority of AGRE multiplex families affected by ... known risk CNVs (21/30)[70%], a *de novo* or inherited (*nuclear*) event was not shared by all affected children” (55). By taking into account the family structure, the haplogroup studies revealed that relative to the most common European haplogroup (H-HV),

European haplogroups I, J, K, X, T, and U and Asian-Native American haplogroups A and M are at significantly increased risk of ASD with odds ratios (OR) ranging from 1.55 to 2.18. Since haplogroups I, J, K, X, T, and U represent about 55% of the European mtDNA lineages, mtDNA haplogroups would appear to make a major contribution to differential risk of ASD (68).

In another study, heteroplasmic mtDNA mutations were sought using off-target mtDNA sequence data from whole exome analysis of Simons Foundation Simplex mother-proband-sibling trios. This study revealed that ASD proband's were more likely to harbor deleterious heteroplasmic mtDNA mutations than their unaffected siblings. Putative deleterious mutations were found at heteroplasmic levels of 5–20% of the mtDNAs. Heteroplasmic mutations were found in both probands (21.2%) and non-autistic siblings (20.2%), but the probands harbored 52% more non-synonymous mutations, 53% higher non-polymorphic variants, and had 118% more predicted pathogenic heteroplasmic mutations. Thus, non-synonymous mutations were enriched ~1.5 fold and potentially pathogenic mutations were enriched ~2.2 fold in probands giving an OR of 2.55 for non-synonymous private heteroplasmic mutations (69). Presumably, these heteroplasmic mutations encompassed both maternal germline and developmental-somatic mutations.

These observations suggest that certain mtDNA haplogroups impart reduced mitochondrial bioenergetics levels, but which are still above the brain's bioenergetics threshold. However, when these mtDNAs are combined with additional heterozygous nDNA or heteroplasmic mtDNA genetic mutations or exposed to environmental mitochondrial toxins then mitochondrial function falls below the brain's minimum needs and ASD ensues.

A striking genetic feature of ASD is the ~3–4:1♂:♀ male bias in ASD manifestations. This same male bias is characteristic of the sudden onset of blindness disease, Leber's Hereditary Optic Neuropathy (LHON), which is caused by mild homoplasmic mtDNA mutations (70, 71). The protection of females from blindness has been attributed to the presence of the estrogen receptor in the mitochondrion. Estradiol activates the mitochondrial estrogen receptor which increases mitochondrion antioxidant defenses (13, 14).

The potential role of partial mitochondrial dysfunction in generating neural-behavioral phenotype has been demonstrated for mouse models harboring partial defects in OXPHOS. Mice heteroplasmic for two normal but different mtDNAs manifest reduced activity, hyperexcitability, and a severe defect in long term memory (72). Mice harboring mutations in the ANT1 isoform experience mild brain mitochondrial OXPHOS inhibition. This perturbs the migration of the GABAergic inhibitory interneurons during neuronal development without perturbing the migration of the excitatory glutamatergic neurons. This should cause reduced neuronal inhibition creating hyperexcitation that could account for the hyperexcitability and perseverative behaviors associated with ASD (73).

The variability in symptoms in ASD pedigrees implies that relatively subtle changes in mitochondrial function must be sufficient to differentiate between being affected or not. This is the result of the mitochondrial influence on the nuclear-cytosol signal transduction pathways and the epigenome. ASD has been associated with low heteroplasmy levels of the

mtDNA tRNA^{Leu(UUR)} 3243A>G mutation (74). At ~20–30% heteroplasmy this mutation is associated with Type II diabetes (75) and autism (74), at ~50–90% the mutation is associated with varying severity neuromuscular disease including the MELAS syndrome (Mitochondria Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes) (76), while at close to 90% the mutant can cause pediatric lethality. To determine how subtle changes in the percentage heteroplasmy of a single mtDNA mutation could result in such dramatic differences in clinical phenotypes, cell lines were prepared with the same nucleus but differing percentages of the pathological mtDNA 3243A>G mutation. These cell lines were characterized physiologically and their gene expression profiles were determined by RNA sequencing. Consistent the expected defect in mitochondrial protein synthesis, as the percentage of mutant mtDNAs increased, the expression of the mtDNA coded COII protein declined proportionately. By contrast, respiration levels remained relatively high up to about 60% heteroplasmy, but with higher heteroplasmy respiration dropped precipitously to near zero, an example of a mitochondrial defect crossing an expression threshold. RNA sequencing analysis revealed a limited number of striking phase-like transitions in nuclear gene expression profile as the percentage of the 3243G heteroplasmic mutation increased, with the heteroplasmy levels correlating with the transcriptional phase transitions consistent with those of the different clinical phenotypes. This suggests that mitochondrial disease phenotypes are determined to a significant extent by changes in the nuclear gene expression state with the nucleus only being able to respond to differences in mitochondrial bioenergetics in a finite number of ways (15). Since subtle changes in mtDNA heteroplasmy can cause abrupt phase transitions in gene expression, it explains how individuals within the same maternal lineage can differ so markedly in the nature and severity of their neurological phenotypes.

Finally, individuals with subclinical mitochondrial defects are very sensitive to stress induced neurological symptoms (77). Mild mitochondrial variation has a profound effect on individual responses to stress. Exposing five mouse strains with mtDNA and nDNA variants in mitochondrial energy metabolic and antioxidant defense genes produced striking differential responses in plasma corticosterone, glucose, and catecholamine levels and in inflammation makers and hippocampal transcription factor levels (77). Hence, stressful experiences could trigger neuropsychiatric disorders in individuals with lower mitochondrial function, and subtle human bioenergetics differences may have a profound effect on individual personalities.

The complexity of mitochondrial genetics makes illuminating the precise genetic and environmental factors that cause neuropsychiatric illness in any one patient difficult. However, that all of the complex genetic interactions may share a common pathophysiological effect, mitochondrial bioenergetics deficiency, it is conceivable that multiple neuropsychiatric diseases may be treatable by a finite number of bioenergetics interventions. Furthermore, neuropsychiatric therapies might be relatively mild since marked clinical improvement could be achieved through mild perturbations of mitochondrial bioenergetics that induced a phase shift in the nuclear gene expression profile. This might explain why activities such as diet, exercise, meditation, and psychotherapy are beneficial for some psychiatric patients (2–4).

Regulators of mitochondrial functions implicated in neuropsychiatric disorders

The power of altering mitochondrial bioenergetics by changing nDNA gene expression has been well established in complex diseases such as Type II diabetes. nDNA bioenergetics genes are coordinately regulated by ligand-activated nuclear receptor family of transcription factors, which bind to the promoters and enhancers of genes of mitochondrial function. Nuclear receptor activities can be further regulated by transcriptional coactivator and corepressor proteins. For example, the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ) upregulates mitochondrial biogenesis primarily in adipose tissue and is activated by binding polyunsaturated fatty acids such as arachidonic acid. PPAR γ is also the target molecule for the anti-diabetic drug rosiglitazone (78). Metformin is another important Type II diabetes drug. Current research indicates that metformin acts by partially inhibiting mitochondrial complex I, thus activating the energy deficiency sensing enzyme AMP Kinase (AMPK) (79). AMPK then phosphorylates and activates PPAR γ coactivator 1 alpha (PGC1 α) which in turn enhances the expression of mitochondrial biogenesis and bioenergetics genes (80).

While treatment of neurological disorders by modulation of mitochondrial function is still in its infancy, parallel approaches to those effective for diabetes have promise. This is demonstrated by serendipitous discovery that PPAR γ agonist, rosiglitazone treatment, is preventive of Alzheimer's disease (81–83). Alzheimer's disease has been associated with mitochondrial biochemical defects and mtDNA variants (25, 33, 34, 84, 85). Presumably, rosiglitazone activates neuronal PPAR γ increasing neuronal mitochondrial biogenesis and bioenergetics thus decreasing the probability that mitochondrial function will fall below cortical bioenergetic threshold, thus delaying the onset of Alzheimer's disease.

A primary regulator of mitochondrial function in the brain is the nuclear receptor estrogen-related receptor gamma (ERR γ) (86). Unlike heart which oxidizes fatty acids, the brain uses glucose as its primary substrate (87). During complex mental tasks such as learning and generation of memories, brain blood flow and glucose uptake are markedly increased (88, 89), a fact widely exploited in brain imaging (90, 91). These metabolic adaptations are mediated in part by transcriptional mechanisms that regulate expression of mitochondrial genes (92).

Expression of ERR γ is induced during neuronal differentiation and is correlated with increased mitochondrial biogenesis (86, 93, 94). ERR γ deficiency in cultured neurons significantly reduces maximal oxidative and glycolytic capacity indicating that ERR γ is essential during peak neuronal metabolic activity. Mice lacking ERR γ in cortical and hippocampal neurons have impaired spatial learning and memory. Defects of hippocampal long-term potentiation (LTP, a key neuronal mechanism underlying learning and memory (95, 96)) in these neuronal ERR γ KO mice can be completely ameliorated by feeding the mitochondrial substrate, pyruvate. In neurons, ERR γ binds to the promoters and enhancers and activates transcription of hundreds of mitochondrial OXPHOS, tricarboxylic acid cycle, and structural proteins genes. Hence, ERR γ -regulates neuronal metabolism is essential for optimal brain function (86).

In addition to OXPHOS genes, neuronal ERR γ also regulates glycolysis genes but few fatty acid oxidation genes (86). This is consistent with neurons using glucose as their sole energy substrate. ERR γ is also an important transcriptional regulator of mitochondrial functions in the heart (97–101), which is heavily dependent on fatty acid oxidation. Accordingly in the heart ERR γ binds to fatty acid oxidation gene promoters (97–99). Thus ERR γ regulates mitochondrial functions in a cell type-specific manner consistent with the cell's metabolic properties.

The ERR γ related nuclear receptors, ERR α and ERR β , are also expressed in brain, but with distinct time and spatial patterns (86, 102–104). ERR γ is abundant in the cerebral cortex, hippocampus, olfactory bulb, midbrain and brain stem. ERR β is primarily expressed in the developing brain. ERR α is more ubiquitously expressed in the adult brain. Hence, inactivation of the various ERRs in mice resulted in different phenotypes (98, 105, 106). Genetic alterations of human ERR genes may also be associated with neurological diseases. Mutations in ERR α are linked to eating disorders and inactivation of ERR α in the mouse results in reduced operant response to high fat diet, compulsivity/behavioral rigidity, and social deficits (107).

As in the case of PPAR γ , the ERRs can interact with PGC1 α (108). By binding to various transcription factors (PPARs, ERRs, NRF1, Gabpa, etc) PGC1 α can enhance the transcriptional activation of mitochondrial gene arrays (97, 109–112). Whole body and neuronal inactivation of PGC1 α in mice results in decreased expression of mitochondrial genes, and degeneration in many areas of the brain and particularly the striatum with associated behavioral anomalies (myoclonus, dystonia, claspings, etc.) (113–115). These effects are analogous to behavioral phenotypes of mouse models of Huntington's disease and Parkinson's disease which also are associated with impaired PGC-1 α function (116–121).

Thus, activation of either ERR γ or PGC1 α to up-regulate mitochondrial biogenesis and thus bioenergetics may hold promise for treating a variety of neuropsychiatric disorders. Conceivably, ERR γ could be activated by an exogenous ligand and PGC1 α could be activated by inducing post-translational modifications such as by activation of AMPK. Alternatively, the levels of either protein might be regionally up-regulated by viral mediated transduction. Activating ERR or PGC1 α may also enhance other cellular pathways such as ROS defense that often help prevent neuronal cell death. In any case, these new observations suggest that generalized mitochondrial interventions might provide therapeutic approaches for a broad array of neuropsychiatric diseases providing hope for young and the old alike.

Conclusion

mtDNA mutations are sufficient to cause neuropsychiatric disorders. Mitochondrial dysfunction contributes to a broad range of neurological diseases. Modulating mitochondrial function may represent an important therapeutic avenue in treating various neuropsychiatric disorders.

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Figure 1. Regional Radiation of Human mtDNAs from their Origin in Africa and Colonization of Eurasia and the Americas Implies that Environmental Selection Constrained Regional mtDNA Variation

All African mtDNAs are subsumed under macrohaplogroup L and coalesce to a single origin about 130,000–170,000 year before present (YBP). African haplogroup L0 is the most ancient mtDNA lineage found in the Koi-San peoples, L1 and L2 in Pygmy populations. The M and N mtDNA lineages emerged from Sub-Saharan African L3 in northeastern Africa, and only derivatives of M and N mtDNAs successfully left Africa, giving rise to macrohaplogroups M and N. N haplogroups radiated into European and Asian indigenous populations, while M haplogroups were confined to Asia. Haplogroups A, C, and D became enriched in northeastern Siberia and were positioned to migrate across the Bering Land Bridge 20,000 YBP to found Native Americans. Additional Eurasian migrations brought to the Americas haplogroups B and X. Finally, haplogroup B colonized the Pacific Islands. Figure reproduced from (MITOMAP, 2015).