NEUROSCIENCE

REVIEW

P. Petschner et al. / Neuroscience 370 (2018) 207–217

Genes Linking Mitochondrial Function, Cognitive Impairment and Depression are Associated with Endophenotypes Serving Precision Medicine

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Abstract—Mitochondria densely populate cells in central nervous system providing essential energy for neurons and influencing synaptic plasticity. Harm to these organelles can impair cognitive performance through damaged neurotransmission and altered Ca^{2+} homeostasis. Impaired cognition could be one underlying factor which can characterize major depressive disorder, a huge burden for society marked by depressed mood and anhedonia. A growing body of evidence binds mitochondrial dysfunctions with the disease. Cognitive disturbances with different severity are also observable in several patients, suggesting that damage or inherited alterations of mitochondria may have an important role in depression. Since several different biological and environmental factors can lead to depression, mitochondrial changes may represent a significant subgroup of depressive patients although cognitive correlates can remain undiscovered without a specific focus. Hypothesis driven studies instead of GWAS can pinpoint targets relevant only in a subset of depressed population. This review highlights results mainly from candidate gene studies on nuclear DNA of mitochondrion-related proteins, including *TOMM40*, *MTHFD1L*, *ATP6V1B2* and *MAO* genes, also implicated in Alzheimer's disease, and alterations in the mitochondrial genome to argue for endophenotypes where impaired mitochondrial function may be the leading cause for depressive symptomatology and parallel cognitive dysfunction.

Key words: mtDNA, ND5, precision medicine, oxidative phosphorylation, mutation load.

INTRODUCTION

Mitochondria were described in the mid-1800s by Kölliker, however, their function was better characterized a century later by delineating their role in energy production including β-oxidation, Krebs cycle, and oxidative phosphorylation (oxphos) (Liesa et al., 2009). Mitochondria contain their own genome (mitochondrial DNA, mtDNA) to encode for 13 necessary proteins of the

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Abbreviations: ADHD, attention-deficit hyperactive disorder; APP, amyloid precursor protein; *ATP6*, mitochondrially encoded ATP synthase 6 gene; *ATP6V1B2*, ATPase H+ transporting V1 subunit B2 gene; *ATP8*, mitochondrially encoded ATP synthase 8 gene; *CYTB*, mitochondrially encoded cytochrome b gene; D-loop, displacement loop; GWAS,, genome-wide association study; Hcy, homocysteine; MAO-A, monoamine oxidase A; *MAO-A*, monoamine oxidase A gene; MAO-B, monoamine oxidase B; *MAO-B*, monoamine oxidase B gene; MDD, major depressive disorder; mtDNA, mitochondrial DNA; MTHFD1L, monofunctional 10-formyltetrahydrofolate synthetase; *MTHFD1L*, monofunctional 10-formyltetrahydrofolate synthetase coding gene; *ND5*, NADH-ubiquinone oxidoreductase chain 5; oxphos, oxidative phosphorylation; SNP, single-nucleotide polymorphism; TIM23, translocase of the inner membrane 23; TOM, translocase of outer membrane complex; TOM40, subunit of the TOM complex; *TOMM40*, translocase of outer mitochondrial membrane 40 gene; VNTR, variable number tandem repeat.

https://doi.org/10.1016/j.neuroscience.2017.09.049
0306-4522/

electron transport chain and cover 92% of the body's energy demand through oxphos (Boekema and Braun, 2007; Wallace et al., 2010; Bansal and Kuhad, 2016). The brain is especially dependent on mitochondrial energy, since it only stores small amounts of glycogen and, thus, its energy reserves are highly limited. As a by-product of energy production, reactive oxygen species are formed, however, mitochondria also contribute to the defense against these free radicals producing protective factors (Adam-Vizi and Tretter, 2013; Sinha et al., 2013; Bansal and Kuhad, 2016). Another important feature of mitochondria is their involvement in programed cell death, apoptosis. Mitochondria can be involved in both extrinsic and intrinsic apoptotic pathways, the latter being more common in neurons (Kam and Ferch, 2000; Wyllie, 2010). It also became evident that, though sometimes truly round-shaped organelles, mitochondria can form connected tubules and their shape is regulated through fusion and fission and disturbances of this dynamism can lead to severe genetic diseases, e.g. Charcot–Mari e–Tooth disease type 2A (Bereiter-Hahn and Voth, 1994; Zuchner et al., 2004; Chan, 2006, 2012).

The above-discussed functions make mitochondria indispensable in network processes such as cognition. It has been demonstrated in mice that intact mitochondrial functions are required for proper synaptic plasticity (Weeber et al., 2002; Levy et al., 2003; Picard and McEwen, 2014). Mitochondria accumulate Ca^{2+} ions in their matrices and participate in intracellular signaling processes involving Ca^{2+}-dependent mechanisms. One of these processes is NMDA receptor-mediated long-term potentiation, serving as the cellular model for memory functions and higher order cognitive processes (Giacomello et al., 2007; Mattson et al., 2008; Herring and Nicoll, 2016). However, other mechanisms may also play a role. Apoptosis, while especially important during development (Roth and D'Sa, 2001), contributes to the normal physiology of the adult brain, too. For example, during learning in the Morris water maze, an animal model for spatial learning and memory, adult-born dentate granule cells may be removed through apoptosis, if they prove to be functionally unnecessary in networks (Deng et al., 2010). In addition, studies suggested impaired mitochondrial functions in different neurodegenerative disorders including Alzheimer's, Parkinson's, Huntington's disease and amyotrophic lateral sclerosis, where cognitive functions are fundamentally impaired contributing to one of the leading symptoms of these diseases [for a review see (Golpich et al., 2017)].

In addition to the already discussed cognitive dysfunctions, alterations in mitochondrion-mediated mechanisms seem to contribute to depression, considered a network-level disease too (Castren, 2005; Morava and Kozicz, 2013; Tobe, 2013; Bansal and Kuhad, 2016; Filipovic et al., 2017a, Shimamoto and Rappeneau, 2017). Major depressive disorder (MDD) is a high burden for society characterized by anhedonia and depressed mood and often also accompanied by cognitive disturbances. Previous studies found that depression was the initial symptom of mitochondrial diseases (Fattal et al., 2007), mutations of mitochondrial or mitochondrion-related nuclear genes associated with major depression (Onishi et al., 1997; Koene et al., 2009), and mitochondrial disorder showed co-morbidity with depression (Morava et al., 2010). Vice versa, mitochondrial mutations were also demonstrated in unipolar depression patients (Munakata et al., 2007; Ben-Shachar and Karry, 2008; Shao et al., 2008). From a cognitive angle, although mood symptoms were considered predominant in depression, and were the main focus of both diagnosis and treatment in these disorders, recently, cognitive symptoms and impairment in mood disorders attracted increased attention and were gaining wider recognition. It is important, however, that the role of most candidate genes in depression is thought to depend on stress exposure and/or traits and temperaments (Gonda et al., 2009; Bagdy et al., 2012; Juhasz et al., 2014; Sharma et al., 2016). Interestingly, the combination of genes associated with cognition and others associated with traits or temperaments also have emerged in gene–gene interactions (Lazary et al., 2009; Lazary et al., 2011). Cognitive dysfunction symptoms in major depression include attention, memory and executive function deficits contributing to decreased capacity for planning and decision (Hammar and Ardal, 2009). Besides significantly effecting function during acute depressive episodes, with treatment approaches focusing on mood symptoms, cognitive deficits often persist as residual symptoms after restoring mood and contribute to lack of complete functional recovery impairing social, academic and professional function in the long term, significantly decreased quality of life, and increased risk of relapse (Beats et al., 1996; Castaneda et al., 2008; Hammar and Ardal, 2009; Marazziti et al., 2010). Cognitive symptoms have been found to be present during 80–90% of depressive episode length and also 40–45% of the length of remission phases and executive function, verbal learning and memory deficits can also be identified during euthymic periods emphasizing their involvement in the pathophysiology of the disease and their importance in treatment (Biringer et al., 2005; Smith et al., 2006; Conradi et al., 2011).

While depression and accompanying cognitive impairment may not be exclusively of mitochondrial origin, substantial damage to mitochondrial functions can contribute to both of them. Thus, alterations in mitochondrial proteins (encoded either in nuclear genes or the mitochondrial genome) attenuating the functions and capabilities of these organelles can lead to a depressive phenotype which may be characterized by altered cognitive functions. The present review highlights some genes from mtDNA and from nuclear DNA involved in primary (TOMM40 and MTHFD1L) and secondary mitochondrial dysfunctions (ATP6V1B2 and MAO) linking mitochondria with diminished cognitive performance and major depression to argue for endophenotypes in the disease and provide testable biomarkers for further studies.

MITOCHONDRIAL DNA

The human mtDNA encodes 2 ribosomal RNAs, 22 transfer RNAs and 13 proteins of the electron transport

chain, organized in nucleoids with only a few noncoding bases between the genes (Anderson et al., 1981; Morava and Kozicz, 2013). MtDNA is always maternally inherited and no recombination occurs (Byrne et al., 2009). Consequently, mutations in mtDNA are in linkage disequilibrium with all other variants. Thus, characterized by a given set of variants nine major haplogroups evolved and are present currently in the European population (Byrne et al., 2009). MtDNA is prone to mutations, one individual of every 200 is a pathogenic mutation carrier, but usually without symptoms (Cree et al., 2009). In normal tissues all mtDNA in a given cell is identical, referred to as homoplasmy. If mutations are present, a smaller or larger subset of the mitochondria will contain them, thus, cells will have both wild-type and mutant mitochondria, called heteroplasmy (DiMauro and Schon, 2008). Usually a certain ‘‘mutation load”, a certain degree of heteroplasmy of the cells is required to produce phenotypic symptoms and threshold for disease manifestation is high, around 80–90%. The reason for such a high threshold may be that mitochondria can counteract deleterious mutations. Different pathogenic mtDNA mutation-carrying cells, after hybridization were able to restore respiratory activity suggesting that fusion of mitochondria with polymorphisms at different sites could compensate for the original defects (Ono et al., 2001; Chan, 2006).

An impact of mitochondrial genetic variations on cognitive functions in mice was demonstrated by Sharpley et al. (Sharpley et al., 2012). Interestingly, animals with heteroplasmy from two ‘‘normal” mitochondrial genomes differing by 91 nucleotides performed worse in the Barnes cognitive maze test than any of the homoplasmy group (Sharpley et al., 2012). In contrast, in elderly adults’ rate of heteroplasmy at certain candidate mutation sites in the complex I of the respiratory chain showed associations with decreased cognitive performance in the Modified Mini-Mental State Examination (Tranah et al., 2015). Common variants in mtDNA were also tested in a mitochondrial genome-wide association study (GWAS) for cognitive performance. Altogether 1385 individuals (di- and monozygotic twins and non-twin siblings) were included in the study, which found no genome-wide significant associations between mtDNA and cognitive performance. However, variants (most of them in the NADH-ubiquinone oxidoreductase chain 5 (*ND5*) gene) were nominally associated with several cognitive test parameters (Byrne et al., 2009). In another study, protective mitochondrial haplogroups for Alzheimer’s disease were found (Ridge et al., 2012). It was also demonstrated in a case-series that mutations in the mtDNA are associated with cognitive disturbances, namely, affected individuals with symptoms of mitochondrial disease showed worse performance on several cognitive tests, among them the Wechsler Adult Intelligence Scale subtests, parts of Rey Auditory Verbal Learning Test, the Trail Making Test and Stroop Color-Word Test (Inczedy-Farkas et al., 2014). The results above suggest that variations in mtDNA can influence cognitive functions, although common haplogroups and rare mutations seem to be distinct phenomena with different effects.

MtDNA mutations in depression were also demonstrated. A deletion in mtDNA in a child was associated with mitochondrial disease symptoms and also with mild-moderate unipolar depression (Koene et al., 2009). Using post-mortem brain samples from human subjects none of the mitochondrial haplogroups was associated with schizophrenia, bipolar disorder or major depression (Sequeira et al., 2015). Major depression cases, however, showed rare homoplasmic mutations with possible functional consequences in the ATP synthase 8 (*ATP8*), ATP synthase 6 (*ATP6*), *ND5* and cytochrome b (*CYTB*) genes, while another subject with depression demonstrated subthreshold heteroplasmy rate at a variant in the displacement loop (D-loop) part of mtDNA (Sequeira et al., 2015).

In summary, mutations in mtDNA may influence cognitive performance and depression. However, common mutations or rare ones below a certain threshold were usually unable to show compelling evidence for association with the phenotypes (though small sample sizes may also play a role). In contrast, these mutations were deleterious and caused severe diseases above a certain threshold, with significantly attenuated cognitive performance and mood disorders, but also fatigue and other mitochondrion-associated symptoms. This all-or-nothing type of response can be a result of the compensatory capacities of these organelles. But mitochondria also rely on nuclear genes to maintain their normal capacities, like respiratory chain functions, translation, transcription and protein maintenance (DiMauro and Schon, 2008; Morava and Kozicz, 2013). Polymorphisms within these nuclear genes, (which are usually of small effect size, at least, in depression) may have smaller, but less compensable effects and can be responsible for different phenotypes, like mild cognitive impairments (Mastroeni et al., 2016).

TOMM40

The translocase of outer membrane (TOM) complex imports most of the pre-proteins into mitochondria (Larsen et al., 2017). TOM40, one of the seven subunits of the TOM complex, is the central pore of the mitochondrial protein import apparatus (Gottschalk et al., 2014). It has an essential role in the life of most eukaryotic organisms, and studies suggest that reducing TOM40 levels causes mitochondrial dysfunction (Gottschalk et al., 2014).

The translocase of outer mitochondrial membrane 40 (*TOMM40*) gene is located on chromosome 19 in the tight gene cluster *TOMM40-APOE-APOC1-APOC4-APOC2* with strong linkage disequilibrium (Gottschalk et al., 2014). Apolipoprotein E (*APOE*) gene’s ε4 allele is a well-known genetic risk factor for the development of Alzheimer’s disease (Corder et al., 1993; Farrer et al., 1997; Gibson et al., 2000); and is also associated with the onset (Butters et al., 2003) and severity of late-life depression (Yen et al., 2007). *TOMM40* is located only 15 kb upstream to APOE (Zeh, 2013), and GWASs also suggested association between *TOMM40* and Alzheimer’s disease (Grupe et al., 2007; Harold et al., 2009; Naj et al., 2010; Seshadri et al., 2010), but studies about

its independent role in Alzheimer's disease and depression are scarce (McFarquhar et al., 2014).

Some studies showed a connection between *TOMM40* and risk of late-onset Alzheimer's disease, cognitive performance and hippocampal atrophy independently of *APOE* (Gottschalk et al., 2014); while others couldn't detect an *APOE*-independent effect of *TOMM40* on Alzheimer's disease risk (Zeh, 2013; Gottschalk et al., 2014). The mixed results could be partly explained by technical and methodological differences between approaches of different researcher groups and the data collectively suggest the contribution of *TOMM40* to Alzheimer's disease and related phenotypes (Gottschalk et al., 2014).

A study (McFarquhar et al., 2014) identified an association between *TOMM40* rs2075650 and history of major depression. Risk allele carriers with lifetime or current depression showed decreased level of extraversion; and the risk allele was also associated with cognitive deficits (mild executive dysfunction, decrease in positive memory intrusions) during current depression, and with altered neuronal processing of sad faces in the cingulate cortex (independently of depression). The researchers suggested that *TOMM40* risk allele carriers have altered cingulate cortex functions, which could interact with depression.

In a study of knock-down mice (Zeh, 2013) it was found that the *TOMM40*$^{+/-}$ mice had decreased numbers of dopaminergic neurons at the age of two compared to their normal littermates. This result might relate to the association between *TOMM40* and depression through the well-known dopaminergic dysfunction in the disease (Dunlop and Nemeroff, 2007).

An interesting novel theory could add some important information to this topic. The *Alu* neurodegeneration hypothesis (Larsen et al., 2017) postulates an age-related genetic mechanism contributing to mitochondrial dysfunction, eventually leading to neuronal death. *Alu* elements are primate-specific retrotransposons within *TOMM40* with supposed fundamental role in primate evolution, and possibly underlying the origin of higher brain functions. The authors highlight that enhanced somatic retrotransposon activity in neurologic networks correlates with tissue-specific mitochondrial dysfunction which increases with time and/or epigenetic changes, and thus, contributes to neurodegenerative diseases. Through this mechanism, depression may be the first symptom of later life cognitive decline, with the first mild signs possibly measurable by neurocognitive tasks.

Further investigations are needed to better understand the relationship between *TOMM40*, cognitive deficits and depression, but it seems plausible that alterations of *TOMM40* may play a role in the disorders and mitochondrial functions.

MTHFD1L

As a member of the folate-mediated one-carbon metabolism, human mitochondrial monofunctional 10-formyl-tetrahydrofolate synthetase (C_1-THF synthase or MTHFD1L) enzyme is tightly associated with the matrix side of mitochondrial inner membrane (Prasannan and Appling, 2009), catalyzing the conversion of 10-formyl-tetrahydrofolate into formate, both in embryonic (Pike et al., 2010) and adult (Prasannan and Appling, 2009) mammalian mitochondria. Formate then fluxes out to get incorporated into the cytoplasmic branch of the folate-dependent one-carbon metabolism, being thus indispensable in cytoplasmic processes such as purine biosynthesis, thymidylate biosynthesis, and the methyl cycle (Pike et al., 2010).

In addition, MTHFD1L enzyme has been proven to be important in maintaining proper mitochondrial function, since its knockdown reduces both basal oxygen consumption and electron transport chain capacity (Lee et al., 2017).

The *MTHFD1L* gene encoding the MTHFD1L enzyme has a single-nucleotide polymorphism (SNP), rs11754661, the A allele of which has been identified in a GWAS as a risk for Alzheimer's disease, and its significance survived the correction for genome-wide multiple testing (Naj et al., 2010). This association between rs11754661 A allele and Alzheimer's disease was replicated in two further studies (Ren et al., 2011; Ma et al., 2012), but not in another (Ramirez-Lorca et al., 2011).

The A allele of *MTHFD1L* rs11754661 has also been associated with depressive rumination (Eszlari et al., 2016). Rumination denotes a cognitive response style to stress: a process of thinking repetitively and passively about the person's own distress, depressed mood and its possible causes and consequences, remaining fixated on his or her feelings and concerns without any active problem solving (Nolen-Hoeksema et al., 2008). Thus, rumination is a cognitive risk factor for depression (Nolen-Hoeksema et al., 2008). The A allele of the *MTHFD1L* rs11754661 polymorphism is associated with higher levels of both rumination and current depressive symptoms, and a higher lifetime risk for depression; however, an asymmetry can be detected when taking into account the mediative effect of one on the other. Namely, the association of rs11754661 and depression is entirely mediated by rumination (Eszlari et al., 2016). Consequently, it can be assumed that this polymorphism of the *MTHFD1L* gene by increasing rumination may be relevant in the development of other disorders related to rumination (Nolen-Hoeksema et al., 2008).

Furthermore, the A allele of rs11754661 has been associated with high homocysteine (Hcy) levels (Wernimont et al., 2011). Hcy is a non-protein amino acid with manifold harmful effects. Its high level is associated with major depression, reduced hippocampal volume, and in healthy subjects impaired cognitive functions (Moustafa et al., 2014). Hcy exerts its harmful effects via multiple mechanisms, one of which is toxicity to mitochondria (Moustafa et al., 2014; Du et al., 2016). Furthermore, Hcy is part of the cytoplasmic branch of the folate-dependent one-carbon metabolism (Pike et al., 2010). In the cytoplasm, catabolism of Hcy is dependent on folate (Pike et al., 2010) and folic acid supplementation can effectively reduce Hcy levels (Moustafa et al., 2014; Du et al., 2016).

Future testing is required to determine whether the psychological and neuropsychiatric effects of this

MTHFD1L polymorphism are truly mediated by current Hcy levels. Nevertheless, *MTHFD1L* gene and the encoded mitochondrial protein MTHFD1L seems to be a promising target in the background of cognitive domains of depression.

ATP6V1B2

Another possible candidate linking mitochondria, cognition and depression is the ATPase H+ transporting V1 subunit B2 (*ATP6V1B2*) nuclear gene. The A allele of rs1106634, an intronic SNP in the *ATP6V1B2* gene, which encodes the B subunit of the vacuolar ATP-ase, has been implicated with a suggestive significance in a meta-analysis of 3 genome-wide association studies (GWASs) in major depression (Shyn et al., 2011), while its T allele was implicated in a genome-wide meta-analysis in bipolar disorder and schizophrenia (Wang et al., 2010).

Although specific effects of ATP6V1B2 rs1106634 in depression or cognition were not described before, knowledge is accumulating on the role of this protein with its possible involvement in neurotransmission. The B subunit in the ATP-catalytic site of the vacuolar proton pump ATP-ase is located in the V1 cytosolic domain in a transmembrane complex and plays a role in creating a proton gradient across membranes of synaptic vesicles, mediating acidification of eukaryotic organelles including endosomes and lysosomes, thus, playing a role in receptor-mediated endocytosis, protein sorting, as well as synaptic vesicle proton-gradient generation (Shyn and Hamilton, 2010). It may play a role in neurotransmission, as the proton-motive force created by vacuolar ATP-ases is involved in vesicle transport, reuptake and storage, and vacuolar ATP-ases also play a role in retrieval and reemployment of synaptic vesicles and energization of regenerated vesicles (Nelson, 1991; van Hille et al., 1994). Thus, even a small disruption in the electrochemical proton gradient may alter neurotransmitter release (Egashira et al., 2015). Vacuolar ATP-ase, thought to be a redox sensor and its function regulated by cellular redox status, may also impact risk of depression through its involvement in oxidative stress (Wang and Floor, 1998). An association between a chromosome region containing *ATP6V1B2* genes and myeloperoxidase levels reflecting prooxidative stress in a GWAS may support these assumptions (Reiner et al., 2013). Vacuolar ATP-ase also plays a role in maintaining developing cortical neural stem cells in mouse models (Lange et al., 2011).

Recently, a study on a large general population sample found evidence of an association between rs1106634 A allele and lifetime depression risk and also between this allele and worse neurocognitive performance on the paired associated learning test but not on the Stockings of Cambridge test. These results suggest that this gene has an effect on hippocampal but not on frontal dysfunction (Gonda et al., 2016), and propose a novel molecular mechanism in the long-term risk for development of depression and possibly also its cognitive symptoms. To emphasize the role of this variant in cognitive dysfunction, previously a study reported increased *ATP6V1B2* expression at both mRNA and protein levels in fibroblasts carrying a presenilin1 mutation, which is one of the major causes hypothesized in familiar Alzheimer's disease (Coffey et al., 2014).

Mitochondria may be involved in the manifestation of the effects of *ATP6V1B2* in depression and in cognitive symptoms of depression in several ways. Increased reactive oxygen species formation and decreased ATP production impair mitochondria (Bansal and Kuhad, 2016). Furthermore, *ATP6V1B2* was found to be expressed also in mitochondria (Jeon et al., 2011). MtDNA depletion was associated with a wide range of human illnesses and dysfunctional cellular states, with cells remodeling mitochondrial functions and altering mitochondrial protein composition (Jeon et al., 2011). During such states *ATP6V1B2* was reported to be upregulated, leading to downregulation of ATP synthesis (Jeon et al., 2011). Impaired mitochondrial function disrupting energy homeostasis and causing reduced ATP availability may play a crucial role in depressive symptoms especially cognitive dysfunction, lack of energy and fatigue (Karabatsiakis et al., 2014). In a study investigating mitochondrial respiration, significantly impaired mitochondrial function was reported including lower efficiency of coupling of respiration related to ATP turnover, and significant negative correlation between mitochondrial respiration and severity of depression symptoms including concentration difficulties, energy loss and fatigue suggesting a role for mitochondrial dysfunction in the pathophysiology of depression (Karabatsiakis et al., 2014).

Furthermore, mitochondria are the chief reactive oxygen species producer and disturbance of oxidative homeostasis and oxidative stress is known to play a role in depression and neurocognitive dysfunction as well (Karabatsiakis et al., 2014). Reactive oxygen species also have an adverse effect on mitochondrial DNA leading to accumulating lesions and, thus, impairing ATP production or respiratory chain function (Maes, 2011). Mitochondrial dysfunctions including increased mtDNA defects, decreased ATP production and enzyme activities show a significant association with depression (Gardner et al., 2003). Given the role of vacuolar ATP-ases as redox sensors and their function being influenced by cellular redox status, this may be a further pathway where the function of ATP6V1B2 and mitochondria converges.

MAO GENES

Monoamine oxidase genes encode the mitochondrial isoenzymes monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) and intracellularly both are located in the outer mitochondrial membrane (Squires, 1997). These isoenzymes vary in location and selectivity in the human body. MAO-A is more likely distributed in fibroblast cells and placenta while MAO-B can be found in platelets and lymphocytes. They are also located in the brain (Bond and Cundall, 1977; Donnelly and Murphy, 1977; Naoi et al., 2017). From the mitochondrial perspective, oxidative stress, through the production of hydrogen peroxide, which is partially the result of MAO

enzyme activity, can cause mitochondrial damage (Edmondson, 2014; Sorato et al., 2014). In addition, MAO enzymes have important roles in catabolizing monoamines serotonin, dopamine, noradrenaline, and adrenaline, as well as diverse trace amines, while they also play a role in degradation of different xenobiotics through oxidative deamination (Edmondson et al., 2009; Bortolato and Shih, 2011). MAO-A catalyzes degradation of monoamines, especially serotonin, playing a crucial role in mental disorders including unipolar depression and anxiety disorders (Bagdy et al., 1986; Heninger et al., 1996; Gingrich et al., 2003), underlining the importance of MAO-A enzymes in mental health and pathology. To assess MAO-B functions in the context of depression, cognitive dysfunction and the mitochondrion itself, it is important to say that both isoenzymes are working in a dichotomous way and prefer to degrade their specific monoamines. Nonetheless, MAO-A and MAO-B can compensate each other supporting the claim that there is nothing like an absolute specificity (Chen et al., 2004). While MAO-A shows more direct relationship toward depression (Kersting et al., 2007), MAO-B tends to affect emotional regulation, cognitive dysfunction, and disorders like Alzheimer's or Parkinson's disease, autism spectrum disorders (Dlugos et al., 2009; Chakraborti et al., 2016), attention-deficit hyperactive disorder (ADHD) (Li et al., 2008) and others. These results link both enzymes to depression and cognitive performance.

From a genetic angle, in the *MAO-A* gene four polymorphisms have shown associations with psychiatric diseases (Dorszewska et al., 2013): (1) *MAO-A* (*CA*)n, a dinucleotide repeat polymorphism in intron 2 (Black et al., 1991); (2) a 23 base pair variable-number tandem repeat (VNTR) polymorphism (Hinds et al., 1992); (3) Fnu4HI and EcoRV restriction fragment length polymorphisms (Lim et al., 1994); (4) *MAO-A*-uVNTR, a VNTR polymorphism upstream of *MAO-A* transcription initiation site (Sabol et al., 1998; Gutierrez et al., 2004). The first three were associated with psychiatric disorders (Bortolato and Shih, 2011), the last was reported to affect sleep quality and symptoms of depression (Brummett et al., 2007), although contradictory results were also published failing to demonstrate a relationship between *MAO-A*-uVNTR and major depression or bipolar disorder (Syagailo et al., 2001). *MAO-A*-uVNTR has been suggested to participate in cognitive disturbances in one study, although results did not survive correction for multiple testing (Yu et al., 2005). Additionally, the presence of CC genotype at the SNP, rs1137070, in the *MAO-A* gene predicted prolonged reaction time between infancy and childhood in girls. This attention deficit may be an effect of the altered availability of monoamine substances, including dopamine and serotonin that are also needed for brain development (Lundwall and Rasmussen, 2016). In addition, a *MAO-A* functional mutation was identified in a family with intellectual and behavioral disorders suggesting a role for this enzyme in cognitive functions (Piton et al., 2014). Furthermore, efficiency of the reversible MAO-A inhibitor moclobemide in elderly patients with dementia and depression also raise the idea that cognitive dysfunction and depression correlate with MAO-A functions (Amrein et al., 1999).

In case of *MAO-B,* polymorphisms rs10521432 and rs6651806 associated with negative emotional behavior, while rs10521432 and rs66518806 seemed to influence cognitive performance (Dlugos et al., 2009). Three other SNPs could be related to ADHD (Li et al., 2008), while the disease itself showed elevated co-occurrence in bipolar and unipolar depressive patients compared to healthy controls (Harmanci et al., 2016).

In summary, MAO overfunction appears to impair mitochondria through oxidative stress, while different polymorphisms may influence different facets of cognitive performance and mood disorders suggesting that *MAO-A* and *MAO-B* polymorphisms provide another link between mitochondria, mood and cognition.

CONCLUDING REMARKS

Our present review focusing on mutations linking mitochondria, cognitive performance and depression, suggests various ways in which genes affecting mitochondrial functions can contribute to depression and attenuated cognitive performance. In this regard there may be differences between mtDNA polymorphisms, which could remain compensated for a long time through mitochondrial fusion, and nuclear ones, which can have smaller, but constant effects. The different combination of such loads in an individual can result in specific depressive and cognitive symptoms, but can also lead to an underlying risk for the disease with impairments mild enough to remain unnoticed. Such minor defects can be provoked by environmental stress, as suggested by Morava et al. (2013), where the authors hypothesized that stress may evoke otherwise unnoticeable mitochondrial dysfunctions (probably caused by different genetic mutations) present in the individual, explaining for the distinct resilience and coping capacities characterizing each person (Morava and Kozicz, 2013). Indeed, we also argued previously that in addition to inherited or acquired genetic factors, environmental factors also contribute to depression, and their effects are mediated by genetic polymorphisms (Bagdy et al., 2012). Development of depression is typically and strongly connected to environmental factors like childhood adversity and/or recent negative live events. Genetic factors show weak direct effects (Mbarek et al., 2017; Xie et al., 2017) and in general they become apparent in the stress exposed groups or in gene-environment interactions (Juhasz et al., 2014, 2015; Kovacs et al., 2016a, 2016b, Bagdy et al., 2012). The risk genes described in this review belong to a set of genetic factors, where cognitive dysfunction is associated with the risk genes directly, but subsequent stress exposure may further sophisticate symptoms (Fig. 1). The presented evidences suggest that nuclear genes in combination with mitochondrial ones may shape together such endophenotypes (Fig. 1).

Mitochondrion-related nuclear polymorphisms associated with both depression and cognition, some even at a genome-wide level, support our assumptions, indicating that whatever the rate of contribution of mitochondrial mutations, if mitochondrial processes are

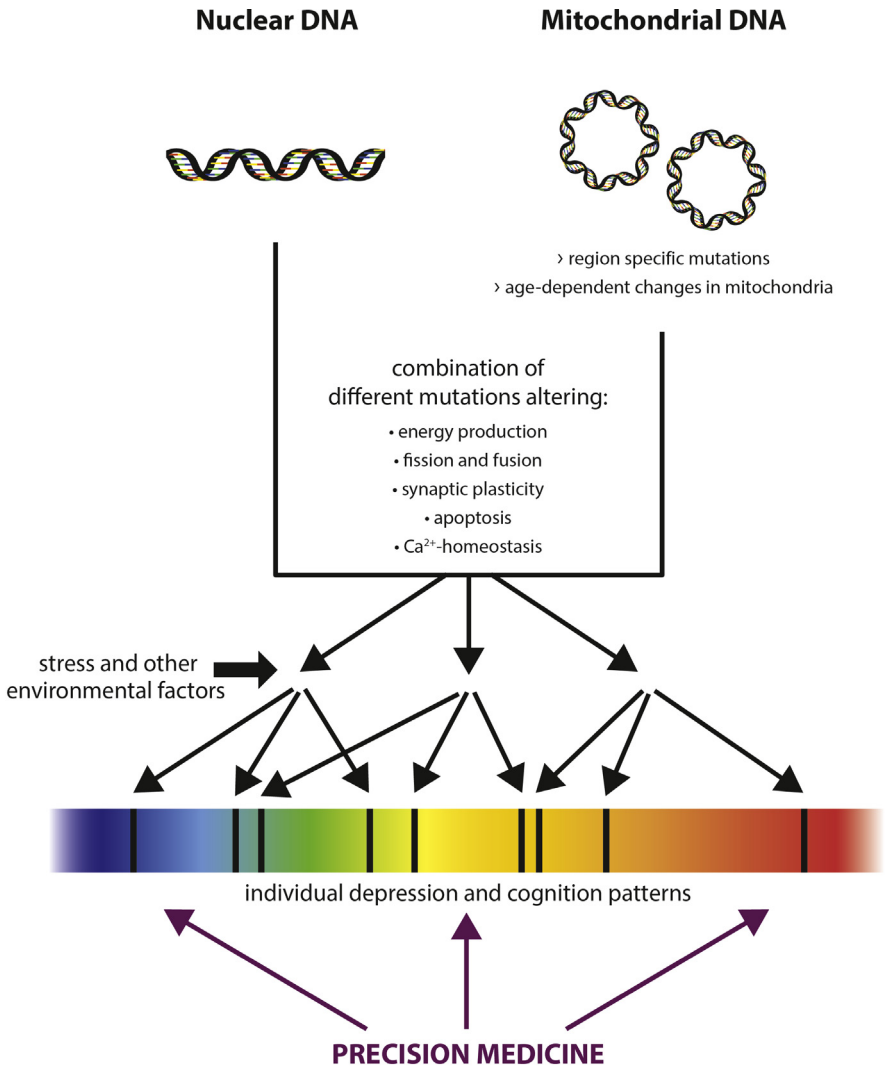

Fig. 1. Different endophenotypes based on nuclear and mitochondrial gene mutations.Genetic mutations in mitochondrial DNA or nuclear genes that are involved in mitochondrial functions may result in altered functions of mitochondria, involving cellular and network-level functions. These can manifest already in a disease phenotype but can also remain risk factors (first branch of arrows) elicited only through environmental stress (second branch of arrows). As a result, a wide scale of individual depressive and cognitive patterns with accompanying phenotypes (marked by black lines on the scale) may exist in the population Identification of these endophenotypes in individual patients and development of newer, selective therapeutics for them may help efforts of precision medicine (marked by purple arrows).

affected, cognitive symptoms are more prominent in depression. Still, these cognitive symptoms in mood disorders remain often overlooked, despite the fact that they impose a serious burden on patients significantly compromising quality of life and impairing daily function in all domains.

From a therapeutic perspective, identification of mitochondrial risks would be essential. Some currently used antidepressants act as mitochondrial uncouplers releasing respiratory control, enhancing activity of ATPase and decreasing production of ATP. The selective serotonin reuptake inhibitor fluoxetine, for example, inhibited ATP production, and impacted ATPase activity in multiple studies (de Oliveira, 2016). In contrast, Filipovic et al. demonstrated elevated expression of 63 mitochondrion-related proteins following a chronic, 3-week-long fluoxetine treatment by proteomic analysis (Filipovic et al., 2017b). Both papers suggested effects of fluoxetine on mitochondrial functions. At the same time, equally long venlafaxine treatment caused no significant alteration in any mitochondrion-related genes in rat hippocampal samples in our transcriptomic study (unpublished data). In addition, imipramine, a member of the older tricyclic antidepressant class induced an increase in cytochrome b levels in mouse cortical regions after chronic administration (Huang et al., 1997), but again, venlafaxine could not influence cytochrome b levels in frontal cortical regions of rats (Tamasi et al., 2014). These differences between different classes of antidepressants may result from the distinct methodologies used, but they may just as likely represent consequences of different mechanisms of actions. If such differences indeed exist among therapeutics then better characterization of mitochondrial involvement in depression and its cognitive correlates and the parallel selection of antidepressants based on molecular evidences showing effects at the individual molecular patterns responsible could improve the disappointing 50–60% response rates to current interventions. For this, a more detailed analysis of therapeutics and causal genes in the disease, like those presented here, are both needed, with such an approach representing the next step toward precision medicine in depression and accompanying cognitive symptoms.

Acknowledgments—This study was supported by the National Hungarian Development Agency (Grant No. KTIA-NAP-13-1-2013-0001), the Hungarian Brain Research Program (Grant No. KTIA 13 NAP-A-II/14), the MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis University (Grant No. KTIA_NAP_13-2-2015-0001) and the New National Excellence Program of The Ministry of Human Capacities (ÚNKP-16-3, ÚNKP-17-3-III-SE-2, ÚNKP-17-4-I-SE-8). Xenia Gonda is recipient of the Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences. The sponsors had no further role in the writing of the paper; and in the decision to submit the paper for publication. We would like to thank to Anna Petschner for her contribution to the figure.

Individual contributions to the article—PP and XG contributed equally to the work and participated in manuscript drafting

(ATP6V1B2, mtDNA, Introduction and Concluding remarks), hypothesis formulation and figure design, NE participated in the manuscript drafting (MTHFD1L), DB drafted TOMM40 part of the manuscript and MT the MAO chapter. GJ and GB contributed to hypothesis formulation and manuscript drafting. All authors have read and approved the final version of the manuscript.

Declaration of interest—The authors declare that they have no competing interests.

REFERENCES

Adam-Vizi V, Tretter L (2013) The role of mitochondrial dehydrogenases in the generation of oxidative stress. Neurochem Int 62:757–763.

Amrein R, Martin JR, Cameron AM (1999) Moclobemide in patients with dementia and depression. Adv Neurol 80:509–519.

Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJ, Staden R, Young IG (1981) Sequence and organization of the human mitochondrial genome. Nature 290:457–465.

Bagdy G, Juhasz G, Gonda X (2012) A new clinical evidence-based gene-environment interaction model of depression. Neuropsychopharmacol Hung 14:213–220.

Bagdy G, Rihmer Z, Frecska E, Szadoczky E, Arato M (1986) Platelet MAO activity and the dexamethasone suppression test in bipolar depression. Psychoneuroendocrinology 11:117–120.

Bansal Y, Kuhad A (2016) Mitochondrial dysfunction in depression. Curr Neuropharmacol 14:610–618.

Beats BC, Sahakian BJ, Levy R (1996) Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol Med 26:591–603.

Ben-Shachar D, Karry R (2008) Neuroanatomical pattern of mitochondrial complex I pathology varies between schizophrenia, bipolar disorder and major depression. PLoS ONE 3:e3676.

Bereiter-Hahn J, Voth M (1994) Dynamics of mitochondria in living cells: shape changes, dislocations, fusion, and fission of mitochondria. Microsc Res Tech 27:198–219.

Biringer E, Lundervold A, Stordal K, Mykletun A, Egeland J, Bottlender R, Lund A (2005) Executive function improvement upon remission of recurrent unipolar depression. Eur Arch Psychiatry Clin Neurosci 255:373–380.

Black GC, Chen ZY, Craig IW, Powell JF (1991) Dinucleotide repeat polymorphism at the MAOA locus. Nucleic Acids Res 19:689.

Boekema EJ, Braun HP (2007) Supramolecular structure of the mitochondrial oxidative phosphorylation system. J Biol Chem 282:1–4.

Bond PA, Cundall RL (1977) Properties of monoamine oxidase (MAO) in human blood platelets, plasma, lymphocytes and granulocytes. Clin Chim Acta 80:317–326.

Bortolato M, Shih JC (2011) Behavioral outcomes of monoamine oxidase deficiency: preclinical and clinical evidence. Int Rev Neurobiol 100:13–42.

Brummett BH, Krystal AD, Siegler IC, Kuhn C, Surwit RS, Zuchner S, Ashley-Koch A, Barefoot JC, Williams RB (2007) Associations of a regulatory polymorphism of monoamine oxidase-A gene promoter (MAOA-uVNTR) with symptoms of depression and sleep quality. Psychosom Med 69:396–401.

Butters MA, Sweet RA, Mulsant BH, Ilyas Kamboh M, Pollock BG, Begley AE, Reynolds 3rd CF, DeKosky ST (2003) APOE is associated with age-of-onset, but not cognitive functioning, in late-life depression. Int J Geriatr Psychiatry 18:1075–1081.

Byrne EM, McRae AF, Duffy DL, Zhao ZZ, Martin NG, Wright MJ, Montgomery GW, Visscher PM (2009) Association study of common mitochondrial variants and cognitive ability. Behav Genet 39:504–512.

Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lonnqvist J (2008) A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord 106:1–27.

Castren E (2005) Is mood chemistry? Nat Rev Neurosci 6:241–246.

Chakraborti B, Verma D, Karmakar A, Jaiswal P, Sanyal A, Paul D, Sinha S, Singh AS, Guhathakurta S, Roychowdhury A, Panda CK, Ghosh S, Mohanakumar KP, Mukhophadhyay K, Rajamma U (2016) Genetic variants of MAOB affect serotonin level and specific behavioral attributes to increase autism spectrum disorder (ASD) susceptibility in males. Prog Neuropsychopharmacol Biol Psychiatry 71:123–136.

Chan DC (2006) Mitochondrial fusion and fission in mammals. Annu Rev Cell Dev Biol 22:79–99.

Chan DC (2012) Fusion and fission: interlinked processes critical for mitochondrial health. Annu Rev Genet 46:265–287.

Chen K, Holschneider DP, Wu W, Rebrin I, Shih JC (2004) A spontaneous point mutation produces monoamine oxidase A/B knock-out mice with greatly elevated monoamines and anxiety-like behavior. J Biol Chem 279:39645–39652.

Coffey EE, Beckel JM, Laties AM, Mitchell CH (2014) Lysosomal alkalization and dysfunction in human fibroblasts with the Alzheimer's disease-linked presenilin 1 A246e mutation can be reversed with camp. Neuroscience 263:111–124.

Conradi HJ, Ormel J, de Jonge P (2011) Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol Med 41:1165–1174.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261:921–923.

Cree LM, Samuels DC, Chinnery PF (2009) The inheritance of pathogenic mitochondrial DNA mutations. Biochim Biophys Acta 1792:1097–1102.

de Oliveira MR (2016) Fluoxetine and the mitochondria: a review of the toxicological aspects. Toxicol Lett 258:185–191.

Deng W, Aimone JB, Gage FH (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11:339–350.

DiMauro S, Schon EA (2008) Mitochondrial disorders in the nervous system. Annu Rev Neurosci 31:91–123.

Dlugos AM, Palmer AA, de Wit H (2009) Negative emotionality: monoamine oxidase B gene variants modulate personality traits in healthy humans. J Neural Transm (Vienna) 116:1323–1334.

Donnelly CH, Murphy DL (1977) Substrate- and inhibitor-related characteristics of human platelet monoamine oxidase. Biochem Pharmacol 26:853–858.

Dorszewska J, Prendecki M, Oczkowska A, Rozycka A, Lianeri M, Kozubski W (2013) Polymorphism of the COMT, MAO, DAT, NET and 5-HTT genes, and biogenic amines in Parkinson's disease. Curr Genomics 14:518–533.

Du J, Zhu M, Bao H, Li B, Dong Y, Xiao C, Zhang GY, Henter I, Rudorfer M, Vitiello B (2016) The role of nutrients in protecting mitochondrial function and neurotransmitter signaling: implications for the treatment of depression, PTSD, and suicidal behaviors. Crit Rev Food Sci Nutr 56:2560–2578.

Dunlop BW, Nemeroff CB (2007) The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 64:327–337.

Edmondson DE (2014) Hydrogen peroxide produced by mitochondrial monoamine oxidase catalysis: biological implications. Curr Pharm Des 20:155–160.

Edmondson DE, Binda C, Wang J, Upadhyay AK, Mattevi A (2009) Molecular and mechanistic properties of the membrane-bound mitochondrial monoamine oxidases. Biochemistry 48:4220–4230.

Egashira Y, Takase M, Takamori S (2015) Monitoring of vacuolar-type H+ ATPase-mediated proton influx into synaptic vesicles. J Neurosci 35:3701–3710.

Eszlari N, Kovacs D, Petschner P, Pap D, Gonda X, Elliott R, Anderson IM, Deakin JF, Bagdy G, Juhasz G (2016) Distinct effects of folate pathway genes MTHFR and MTHFD1L on

ruminative response style: a potential risk mechanism for depression. Transl Psychiatry 6:e745.
Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium. JAMA 278:1349–1356.
Fattal O, Link J, Quinn K, Cohen BH, Franco K (2007) Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr 12:429–438.
Filipovic D, Todorovic N, Bernardi RE, Gass P (2017a) Oxidative and nitrosative stress pathways in the brain of socially isolated adult male rats demonstrating depressive- and anxiety-like symptoms. Brain Struct Funct 222:1–20.
Filipovic D, Costina V, Peric I, Stanisavljevic A, Findeisen P (2017b) Chronic fluoxetine treatment directs energy metabolism towards the citric acid cycle and oxidative phosphorylation in rat hippocampal nonsynaptic mitochondria. Brain Res 1659:41–54.
Gardner A, Johansson A, Wibom R, Nennesmo I, von Dobeln U, Hagenfeldt L, Hallstrom T (2003) Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients. J Affect Disord 76:55–68.
Giacomello M, Drago I, Pizzo P, Pozzan T (2007) Mitochondrial Ca2 + as a key regulator of cell life and death. Cell Death Differ 14:1267–1274.
Gibson GE, Haroutunian V, Zhang H, Park LC, Shi Q, Lesser M, Mohs RC, Sheu RK, Blass JP (2000) Mitochondrial damage in Alzheimer's disease varies with apolipoprotein E genotype. Ann Neurol 48:297–303.
Gingrich JA, Ansorge MS, Merker R, Weisstaub N, Zhou M (2003) New lessons from knockout mice: the role of serotonin during development and its possible contribution to the origins of neuropsychiatric disorders. CNS Spectr 8:572–577.
Golpich M, Amini E, Mohamed Z, Azman Ali R, Mohamed Ibrahim N, Ahmadiani A (2017) Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: pathogenesis and treatment. CNS Neurosci Ther 23:5–22.
Gonda X, Eszlari N, Anderson IM, Deakin JF, Bagdy G, Juhasz G (2016) Association of ATP6V1B2 rs1106634 with lifetime risk of depression and hippocampal neurocognitive deficits: possible novel mechanisms in the etiopathology of depression. Transl Psychiatry 6:e945.
Gonda X, Fountoulakis KN, Juhasz G, Rihmer Z, Lazary J, Laszik A, Akiskal HS, Bagdy G (2009) Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. Eur Arch Psychiatry Clin Neurosci 259:106–113.
Gottschalk WK, Lutz MW, He YT, Saunders AM, Burns DK, Roses AD, Chiba-Falek O (2014) The broad impact of TOM40 on neurodegenerative diseases in aging. J Parkinsons Dis Alzheimers Dis 1:12.
Grupe A, Abraham R, Li Y, Rowland C, Hollingworth P, Morgan A, Jehu L, Segurado R, Stone D, Schadt E, Karnoub M, Nowotny P, Tacey K, Catanese J, Sninsky J, Brayne C, Rubinsztein D, Gill M, Lawlor B, Lovestone S, Holmans P, O'Donovan M, Morris JC, Thal L, Goate A, Owen MJ, Williams J (2007) Evidence for novel susceptibility genes for late-onset Alzheimer's disease from a genome-wide association study of putative functional variants. Hum Mol Genet 16:865–873.
Gutierrez B, Arias B, Gasto C, Catalan R, Papiol S, Pintor L, Fananas L (2004) Association analysis between a functional polymorphism in the monoamine oxidase A gene promoter and severe mood disorders. Psychiatr Genet 14:203–208.
Hammar A, Ardal G (2009) Cognitive functioning in major depression - a summary. Front Hum Neurosci 3:26.
Harmanci H, Cam Celikel F, Etikan I (2016) Comorbidity of adult attention deficit and hyperactivity disorder in bipolar and unipolar patients. Noro psikiyatri arsivi 53:257–262.
Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schurmann B, Heun R, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Hull M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 41:1088–1093.
Heninger GR, Delgado PL, Charney DS (1996) The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry 29:2–11.
Herring BE, Nicoll RA (2016) Long-term potentiation: from CaMKII to AMPA receptor trafficking. Annu Rev Physiol 78:351–365.
Hinds HL, Hendriks RW, Craig IW, Chen ZY (1992) Characterization of a highly polymorphic region near the first exon of the human MAOA gene containing a GT dinucleotide and a novel VNTR motif. Genomics 13:896–897.
Huang NY, Strakhova M, Layer RT, Skolnick P (1997) Chronic antidepressant treatments increase cytochrome b mRNA levels in mouse cerebral cortex. J Mol Neurosci: MN 9:167–176.
Inczedy-Farkas G, Trampush JW, Perczel Forintos D, Beech D, Andrejkovics M, Varga Z, Remenyi V, Bereznai B, Gal A, Molnar MJ (2014) Mitochondrial DNA mutations and cognition: a case-series report. Arch Clin Neuropsychol 29:315–321.
Jeon J, Jeong JH, Baek JH, Koo HJ, Park WH, Yang JS, Yu MH, Kim S, Pak YK (2011) Network clustering revealed the systemic alterations of mitochondrial protein expression. Plos Comput Biol 7.
Juhasz G, Hullam G, Eszlari N, Gonda X, Antal P, Anderson IM, Hokfelt TG, Deakin JF, Bagdy G (2014) Brain galanin system genes interact with life stresses in depression-related phenotypes. Proc Natl Acad Sci U S A 111:E1666–1673.
Juhasz G, Gonda X, Hullam G, Eszlari N, Kovacs D, Lazary J, Pap D, Petschner P, Elliot R, Deakin JF, Anderson IM, Antal P, Lesch KP, Bagdy G (2015) Variability in the effect of 5-HTTLPR on depression in a large European population: the role of age, symptom profile, type and intensity of life stressors. PLoS ONE 10:e0116316.
Kam PC, Ferch NI (2000) Apoptosis: mechanisms and clinical implications. Anaesthesia 55:1081–1093.
Karabatsiakis A, Bock C, Salinas-Manrique J, Kolassa S, Calzia E, Dietrich DE, Kolassa IT (2014) Mitochondrial respiration in peripheral blood mononuclear cells correlates with depressive subsymptoms and severity of major depression. Transl Psychiatry 4:e397.
Kersting A, Kroker K, Horstmann J, Baune BT, Hohoff C, Mortensen LS, Neumann LC, Arolt V, Domschke K (2007) Association of MAO-A variant with complicated grief in major depression. Neuropsychobiology 56:191–196.
Koene S, Kozicz TL, Rodenburg RJ, Verhaak CM, de Vries MC, Wortmann S, van de Heuvel L, Smeitink JA, Morava E (2009) Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. J Affect Disord 114:327–332.
Kovacs D, Eszlari N, Petschner P, Pap D, Vas S, Kovacs P, Gonda X, Juhasz G, Bagdy G (2016a) Effects of IL1B single nucleotide polymorphisms on depressive and anxiety symptoms are determined by severity and type of life stress. Brain Behav Immun 56:96–104.
Kovacs D, Eszlari N, Petschner P, Pap D, Vas S, Kovacs P, Gonda X, Bagdy G, Juhasz G (2016b) Interleukin-6 promoter polymorphism interacts with pain and life stress influencing depression phenotypes. J Neurol Transm 123:541–548.

Lange C, Prenninger S, Knuckles P, Taylor V, Levin M, Calegari F (2011) The H(+) vacuolar ATPase maintains neural stem cells in the developing mouse cortex. Stem Cells Dev 20:843–850.
Larsen PA, Lutz MW, Hunnicutt KE, Mihovilovic M, Saunders AM, Yoder AD, Roses AD (2017) The Alu neurodegeneration hypothesis: a primate-specific mechanism for neuronal transcription noise, mitochondrial dysfunction, and manifestation of neurodegenerative disease. Alzheimers Dement. in press.
Lazary J, Juhasz G, Anderson IM, Jacob CP, Nguyen TT, Lesch KP, Reif A, Deakin JF, Bagdy G (2011) Epistatic interaction of CREB1 and KCNJ6 on rumination and negative emotionality. Eur Neuropsychopharmacol 21:63–70.
Lazary J, Lazary A, Gonda X, Benko A, Molnar E, Hunyady L, Juhasz G, Bagdy G (2009) Promoter variants of the cannabinoid receptor 1 gene (CNR1) in interaction with 5-HTTLPR affect the anxious phenotype. Am J Med Genet B Neuropsychiatr Genet 150B:1118–1127.
Lee D, Xu IMJ, Chiu DKC, Lai RKH, Tse APW, Li LL, Law CT, Tsang FHC, Wei LL, Chan CYK, Wong CM, Ng IOL, Wong CCL (2017) Folate cycle enzyme MTHFD1L confers metabolic advantages in hepatocellular carcinoma. J Clin Invest 127:1856–1872.
Levy M, Faas GC, Saggau P, Craigen WJ, Sweatt JD (2003) Mitochondrial regulation of synaptic plasticity in the hippocampus. J Biol Chem 278:17727–17734.
Li J, Wang Y, Hu S, Zhou R, Yu X, Wang B, Guan L, Yang L, Zhang F, Faraone SV (2008) The monoamine oxidase B gene exhibits significant association to ADHD. Am J Med Genet B Neuropsychiatr Genet 147:370–374.
Liesa M, Palacin M, Zorzano A (2009) Mitochondrial dynamics in mammalian health and disease. Physiol Rev 89:799–845.
Lim LC, Powell JF, Murray R, Gill M (1994) Monoamine oxidase A gene and bipolar affective disorder. Am J Hum Genet 54:1122–1124.
Lundwall RA, Rasmussen CG (2016) MAOA influences the trajectory of attentional development. Front Hum Neurosci 10:424.
Ma XY, Yu JT, Wu ZC, Zhang Q, Liu QY, Wang HF, Wang W, Tan L (2012) Replication of the MTHFD1L gene association with late-onset Alzheimer's disease in a Northern Han Chinese population. J Alzheimers Dis 29:521–525.
Maes M (2011) An intriguing and hitherto unexplained co-occurrence: depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. Prog Neuropsychopharmacol Biol Psychiatry 35:784–794.
Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L (2010) Cognitive impairment in major depression. Eur J Pharmacol 626:83–86.
Mastroeni D, Khdour OM, Delvaux E, Nolz J, Olsen G, Berchtold N, Cotman C, Hecht SM, Coleman PD (2016) Nuclear but not mitochondrial-encoded OXPHOS genes are altered in aging, mild cognitive impairment, and Alzheimer's disease. Alzheimers Dement. in press.
Mattson MP, Gleichmann M, Cheng A (2008) Mitochondria in neuroplasticity and neurological disorders. Neuron 60:748–766.
Mbarek H, Milaneschi Y, Hottenga JJ, Ligthart L, Geus EJC, Ehli EA, Willemsen G, Davies GE, Smit JH, Boomsma DI, Penninx BWJH (2017) Genome-wide significance for *PCLO* as a gene for major depressive disorder. Twin Res Hum Genet 25:1–4.
McFarquhar M, Elliott R, McKie S, Thomas E, Downey D, Mekli K, Toth ZG, Anderson IM, Deakin JF, Juhasz G (2014) TOMM40 rs2075650 may represent a new candidate gene for vulnerability to major depressive disorder. Neuropsychopharmacology 39:1743–1753.
Morava E, Gardeitchik T, Kozicz T, de Boer L, Koene S, de Vries MC, McFarland R, Roobol T, Rodenburg RJ, Verhaak CM (2010) Depressive behaviour in children diagnosed with a mitochondrial disorder. Mitochondrion 10:528–533.
Morava E, Kozicz T (2013) Mitochondria and the economy of stress (mal)adaptation. Neurosci Biobehav Rev 37:668–680.
Moustafa AA, Hewedi DH, Eissa AM, Frydecka D, Misiak B (2014) Homocysteine levels in schizophrenia and affective disorders-focus on cognition. Front Behav Neurosci 8:343.
Munakata K, Fujii K, Nanko S, Kunugi H, Kato T (2007) Sequence and functional analyses of mtDNA in a maternally inherited family with bipolar disorder and depression. Mutat Res 617:119–124.
Naj AC, Beecham GW, Martin ER, Gallins PJ, Powell EH, Konidari I, Whitehead PL, Cai G, Haroutunian V, Scott WK, Vance JM, Slifer MA, Gwirtsman HE, Gilbert JR, Haines JL, Buxbaum JD, Pericak-Vance MA (2010) Dementia revealed: novel chromosome 6 locus for late-onset Alzheimer disease provides genetic evidence for folate-pathway abnormalities. PLoS Genet 6:e1001130.
Naoi M, Maruyama W, Shamoto-Nagai M (2017) Type A monoamine oxidase and serotonin are coordinately involved in depressive disorders: from neurotransmitter imbalance to impaired neurogenesis. J Neural Transm. in press.
Nelson N (1991) Structure and pharmacology of the proton-atpases. Trends Pharmacol Sci 12:71–75.
Nolen-Hoeksema S, Wisco BE, Lyubomirsky S (2008) Rethinking rumination. Perspect Psychol Sci 3:400–424.
Onishi H, Kawanishi C, Iwasawa T, Osaka H, Hanihara T, Inoue K, Yamada Y, Kosaka K (1997) Depressive disorder due to mitochondrial transfer RNALeu(UUR) mutation. Biol Psychiatry 41:1137–1139.
Ono T, Isobe K, Nakada K, Hayashi JI (2001) Human cells are protected from mitochondrial dysfunction by complementation of DNA products in fused mitochondria. Nat Genet 28:272–275.
Picard M, McEwen BS (2014) Mitochondria impact brain function and cognition. Proc Natl Acad Sci U S A 111:7–8.
Pike ST, Rajendra R, Artzt K, Appling DR (2010) Mitochondrial C1-tetrahydrofolate synthase (MTHFD1L) supports the flow of mitochondrial one-carbon units into the methyl cycle in embryos. J Biol Chem 285:4612–4620.
Piton A, Poquet H, Redin C, Masurel A, Lauer J, Muller J, Thevenon J, Herenger Y, Chancenotte S, Bonnet M, Pinoit JM, Huet F, Thauvin-Robinet C, Jaeger AS, Le Gras S, Jost B, Gerard B, Peoc'h K, Launay JM, Faivre L, Mandel JL (2014) 20 ans apres: a second mutation in MAOA identified by targeted high-throughput sequencing in a family with altered behavior and cognition. Eur J Hum Genet 22:776–783.
Prasannan P, Appling DR (2009) Human mitochondrial C1-tetrahydrofolate synthase: submitochondrial localization of the full-length enzyme and characterization of a short isoform. Arch Biochem Biophys 481:86–93.
Ramirez-Lorca R, Boada M, Antunez C, Lopez-Arrieta J, Moreno-Rey C, Hernandez I, Marin J, Gayan J, Gonzalez-Perez A, Alegret M, Tarraga L, Real LM, Ruiz A (2011) The MTHFD1L gene rs11754661 marker is not associated with Alzheimer's disease in a sample of the Spanish population. J Alzheimers Dis 25:47–50.
Reiner AP, Hartiala J, Zeller T, Bis JC, Dupuis J, Fornage M, Baumert J, Kleber ME, Wild PS, Baldus S, Bielinski SJ, Fontes JD, Illig T, Keating BJ, Lange LA, Ojeda F, Muller-Nurasyid M, Munzel TF, Psaty BM, Rice K, Rotter JI, Schnabel RB, Tang WHW, Thorand B, Erdmann J, Jacobs DR, Wilson JG, Koenig W, Tracy RP, Blankenberg S, Marz W, Gross MD, Benjamin EJ, Hazen SL, Allayee H, Consortium C (2013) Genome-wide and gene-centric analyses of circulating myeloperoxidase levels in the charge and care consortia. Hum Mol Genet 22:3381-3393.
Ren RJ, Wang LL, Fang R, Liu LH, Wang Y, Tang HD, Deng YL, Xu W, Wang G, Chen SD (2011) The MTHFD1L gene rs11754661 marker is associated with susceptibility to Alzheimer's disease in the Chinese Han population. J Neurol Sci 308:32–34.
Ridge PG, Maxwell TJ, Corcoran CD, Norton MC, Tschanz JT, O'Brien E, Kerber RA, Cawthon RM, Munger RG, Kauwe JS (2012) Mitochondrial genomic analysis of late onset Alzheimer's disease reveals protective haplogroups H6A1A/H6A1B: the Cache County Study on Memory in Aging. PLoS ONE 7:e45134.
Roth KA, D'Sa C (2001) Apoptosis and brain development. Ment Retard Dev Disabil Res Rev 7:261–266.

Sabol SZ, Hu S, Hamer D (1998) A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet 103:273–279.
Sequeira A, Rollins B, Magnan C, van Oven M, Baldi P, Myers RM, Barchas JD, Schatzberg AF, Watson SJ, Akil H, Bunney WE, Vawter MP (2015) Mitochondrial mutations in subjects with psychiatric disorders. PLoS ONE 10:e0127280.
Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramirez-Lorca R, Debette S, Longstreth Jr WT, Janssens AC, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JI, Aulchenko YS, Harris TB, Petersen RC, Berr C, Owen MJ, Lopez-Arrieta J, Varadarajan BN, Becker JT, Rivadeneira F, Nalls MA, Graff-Radford NR, Campion D, Auerbach S, Rice K, Hofman A, Jonsson PV, Schmidt H, Lathrop M, Mosley TH, Au R, Psaty BM, Uitterlinden AG, Farrer LA, Lumley T, Ruiz A, Williams J, Amouyel P, Younkin SG, Wolf PA, Launer LJ, Lopez OL, van Duijn CM, Breteler MM (2010) Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 303:1832–1840.
Shao L, Martin MV, Watson SJ, Schatzberg A, Akil H, Myers RM, Jones EG, Bunney WE, Vawter MP (2008) Mitochondrial involvement in psychiatric disorders. Ann Med 40:281–295.
Sharma S, Powers A, Bradley B, Ressler KJ (2016) Gene x environment determinants of stress- and anxiety-related disorders. Annu Rev Psychol 67:239–261.
Sharpley MS, Marciniak C, Eckel-Mahan K, McManus M, Crimi M, Waymire K, Lin CS, Masubuchi S, Friend N, Koike M, Chalkia D, MacGregor G, Sassone-Corsi P, Wallace DC (2012) Heteroplasmy of mouse mtDNA is genetically unstable and results in altered behavior and cognition. Cell 151:333–343.
Shimamoto A, Rappeneau V (2017) Sex-dependent mental illnesses and mitochondria. Schizophr Res. in press.
Shyn SI, Hamilton SP (2010) The genetics of major depression: moving beyond the monoamine hypothesis. Psychiat Clin N Am 33:125–140.
Shyn SI, Shi J, Kraft JB, Potash JB, Knowles JA, Weissman MM, Garriock HA, Yokoyama JS, McGrath PJ, Peters EJ, Scheftner WA, Coryell W, Lawson WB, Jancic D, Gejman PV, Sanders AR, Holmans P, Slager SL, Levinson DF, Hamilton SP (2011) Novel loci for major depression identified by genome-wide association study of sequenced treatment alternatives to relieve depression and meta-analysis of three studies. Mol Psychiatry 16:202–215.
Sinha K, Das J, Pal PB, Sil PC (2013) Oxidative stress: the mitochondria-dependent and mitochondria-independent pathways of apoptosis. Arch Toxicol 87:1157–1180.
Smith DJ, Muir WJ, Blackwood DHR (2006) Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. Bipolar Disord 8:40–46.
Sorato E, Menazza S, Zulian A, Sabatelli P, Gualandi F, Merlini L, Bonaldo P, Canton M, Bernardi P, Di Lisa F (2014) Monoamine oxidase inhibition prevents mitochondrial dysfunction and apoptosis in myoblasts from patients with collagen VI myopathies. Free Radic Biol Med 75:40–47.
Squires RF (1997) Discovery of monoamine oxidase forms A and B. Vopr Med Khim 43:433–439.
Syagailo YV, Stober G, Grassle M, Reimer E, Knapp M, Jungkunz G, Okladnova O, Meyer J, Lesch KP (2001) Association analysis of the functional monoamine oxidase A gene promoter polymorphism in psychiatric disorders. Am J Med Genet 105:168–171.
Tamasi V, Petschner P, Adori C, Kirilly E, Ando RD, Tothfalusi L, Juhasz G, Bagdy G (2014) Transcriptional evidence for the role of chronic venlafaxine treatment in neurotrophic signaling and neuroplasticity including also Glutamatergic [corrected] - and insulin-mediated neuronal processes. PLoS ONE 9:e113662.
Tobe EH (2013) Mitochondrial dysfunction, oxidative stress, and major depressive disorder. Neuropsychiatr Dis Treat 9:567–573.
Tranah GJ, Yaffe K, Katzman SM, Lam ET, Pawlikowska L, Kwok PY, Schork NJ, Manini TM, Kritchevsky S, Thomas F, Newman AB, Harris TB, Coleman AL, Gorin MB, Helzner EP, Rowbotham MC, Browner WS, Cummings SR, Health A, Body Composition S (2015) Mitochondrial DNA heteroplasmy associations with neurosensory and mobility function in elderly adults. J Gerontol A Biol Sci Med Sci 70:1418–1424.
van Hille B, Richener H, Schmid P, Puettner I, Green JR, Bilbe G (1994) Heterogeneity of vacuolar H(+)-ATPase: differential expression of two human subunit B isoforms. Biochem J 303(Pt 1):191–198.
Wallace DC, Fan W, Procaccio V (2010) Mitochondrial energetics and therapeutics. Annu Rev Pathol 5:297–348.
Wang KS, Liu XF, Aragam N (2010) A genome-wide meta-analysis identifies novel loci associated with schizophrenia and bipolar disorder. Schizophr Res 124:192–199.
Wang YL, Floor E (1998) Hydrogen peroxide inhibits the vacuolar H+-ATPase in brain synaptic vesicles at micromolar concentrations. J Neurochem 70:646–652.
Weeber EJ, Levy M, Sampson MJ, Anflous K, Armstrong DL, Brown SE, Sweatt JD, Craigen WJ (2002) The role of mitochondrial porins and the permeability transition pore in learning and synaptic plasticity. J Biol Chem 277:18891–18897.
Wernimont SM, Clark AG, Stover PJ, Wells MT, Litonjua AA, Weiss ST, Gaziano JM, Tucker KL, Baccarelli A, Schwartz J, Bollati V, Cassano PA (2011) Folate network genetic variation, plasma homocysteine, and global genomic methylation content: a genetic association study. BMC Med Genet 12:150.
Wyllie AH (2010) "Where, O death, is thy sting?" A brief review of apoptosis biology. Mol Neurobiol 42:4–9.
Xie T, Stathopoulou MG, Andres F, Siest G, Murray H, Martin M, Cobaleda J, Delgado J, Lamont J, Penas-Lledo E, LLerena A, Visvikis-Siest S (2017) VEGF-related polymorphisms identified by GWAS and risk for major depression. Transl Psychiatry 7:e1055.
Yen YC, Rebok GW, Gallo JJ, Yang MJ, Lung FW, Shih CH (2007) ApoE4 allele is associated with late-life depression: a population-based study. Am J Geriatr Psychiatry 15:858–868.
Yu YW, Tsai SJ, Hong CJ, Chen MC, Yang CW, Chen TJ (2005) Association study of a functional MAOA-uVNTR gene polymorphism and cognitive function in healthy females. Neuropsychobiology 52:77–82.
Zeh RM (2013) Neurological and molecular biological characterisation of the mutant mouse line TOM40 PhD Thesis. Technical University of Munich, Department of Experimental Genetics.
Zuchner S, Mersiyanova IV, Muglia M, Bissar-Tadmouri N, Rochelle J, Dadali EL, Zappia M, Nelis E, Patitucci A, Senderek J, Parman Y, Evgrafov O, Jonghe PD, Takahashi Y, Tsuji S, Pericak-Vance MA, Quattrone A, Battaloglu E, Polyakov AV, Timmerman V, Schroder JM, Vance JM (2004) Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat Genet 36:449–451.

(Received 6 April 2017, Accepted 25 September 2017)
(Available online 5 October 2017)