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An emerging role for mitochondrial dynamics in schizophrenia

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ABSTRACT

Abnormal brain development has long been thought to contribute to the pathophysiology of schizophrenia. Impaired dendritic arborization, synaptogenesis, and long term potentiation and memory have been demonstrated in animal models of schizophrenia. In addition to aberrant nervous system development, altered brain metabolism and mitochondrial function has long been observed in schizophrenic patients. Single nucleotide polymorphisms in the mitochondrial genome as well as impaired mitochondrial function have both been associated with increased risk for developing schizophrenia. Mitochondrial function in neurons is highly dependent on fission, fusion, and transport of the organelle, collectively referred to as mitochondrial dynamics. Indeed, there is mounting evidence that mitochondrial dynamics strongly influences neuron development and synaptic transmission. While there are a few studies describing altered mitochondrial shape in schizophrenic patients, as well as in animal and *in vitro* models of schizophrenia, the precise role of mitochondrial dynamics in the pathophysiology of schizophrenia is all but unexplored. Here we discuss the influence of mitochondrial dynamics and mitochondrial function on nervous system development, and highlight recent work suggesting a link between aberrant mitochondrial dynamics and schizophrenia.

1. Introduction

Despite schizophrenia affecting ~1% of the world population we lack any concrete understanding of its etiology (Saha et al., 2005). Consequently, safe and effective therapeutic options are limited. While antipsychotic pharmaceuticals serve as the first-line of therapy for schizophrenia, they are not effective in treating the negative symptoms of schizophrenia, and improve positive symptoms in only 50% of patients (van Os and Kapur, 2009). Moreover, many schizophrenic patients helped by anti-psychotic drugs experience extrapyramidal side effects decreasing rates of compliance (Tenback et al., 2010; Barry et al., 2012). The first symptoms of schizophrenia commonly do not manifest until late adolescence or early adulthood, suggesting preventative therapies may be possible as long as biomarkers are identified. Many lines of evidence suggest the pathology of schizophrenia is related to impaired brain development and connectivity (Rajasekaran et al., 2015). Additionally, several clinical studies have linked mitochondrial dysfunction with increased risk of developing schizophrenia (Park and Park, 2012; Rajasekaran et al., 2015). Recent work also suggests aberrant mitochondrial dynamics may contribute to abnormal connectivity in the brains of schizophrenic patients (Millar et al., 2005; Devine et al., 2016; Norkett et al., 2016). While mitochondrial dynamics regulate nervous system development and are associated with numerous human neurological disorders (Flippo and Strack, 2017), whether mitochondrial dynamics plays a role in the pathology of schizophrenia remains relatively unexplored. Here we review the influence of mitochondrial dynamics on nervous system development and suggest a potential role for mitochondrial dynamics in the pathology of schizophrenia based on recent studies implicating schizophrenia risk genes in mitochondrial dynamics.

2. Mitochondrial dynamics in nervous system development

2.1. Mitochondrial transport

In compartmentalized cells like neurons, mitochondrial localization plays a crucial role in determining local energy supply. Mitochondria are highly concentrated in energy demanding compartments of neurons such as the pre-synaptic terminals and the nodes of Ranvier in axons (Bogan and Cabot, 1991; Fabricius et al., 1993; Mutsaers and Carroll, 1998; Shepherd and Harris, 1998). Interestingly, ~60% of synaptic terminals in the CA1 region of the hippocampus lack mitochondria, which poses still relatively unexplored questions about the precise role of mitochondria at the synapse (Shepherd and Harris, 1998). Regardless, mitochondrial localization throughout the cell is mostly a result of mitochondrial transport as the majority of mitochondrial biogenesis occurs in the soma of the neuron, but evidence suggests limited biogenesis can occur in axons as well (Amiri and Hollenbeck, 2008; Saxton and Hollenbeck, 2012). Mitochondria can be transported bi-directionally throughout neuronal arbors and axons along microtubule tracks until they dock at a particular cellular location.

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The actin and microtubule cytoskeleton can serve as anchors for mitochondrial docking in neurons with mitochondria accumulating in regions that experience frequent calcium transients (Sheng and Cai, 2012). Mitochondrial transport arrest is mediated by the outer mitochondrial membrane (OMM) localized Ca^{2+} sensitive GTPase Miro and is believed to satisfy energy demands for Ca^{2+} extrusion (Cai and Sheng, 2009). Retrograde mitochondrial transport was thought to be required for degradation of damaged mitochondria, as the cell body contains most of the degradation machinery however, recent evidence indicates that while the neuronal cell body is the major site of mitochondrial autophagy (mitophagy), mitophagy does occur in axons (Maday, 2016).

Multi-subunit complexes of adaptor and motor proteins mediate mitochondrial transport (Saxton and Hollenbeck, 2012; Schwarz, 2013). Two large families of motor proteins interact with microtubules to move cargo in opposite directions, utilizing ATP as a power source. The kinesins mediate anterograde transport, while the dyneins are responsible for retrograde transport (Hirokawa et al., 2010). Mitochondria interact with motor proteins through various adaptor proteins that dictate the direction of mitochondrial transport and ultimately localization to specific sub-cellular locales. Milton, a well characterized adaptor protein in *D. melanogaster* interacts with the kinesin heavy chain KIF5, while associating with mitochondria through an additional interaction with Miro (Stowers et al., 2002; Glater et al., 2006). TRAK2, a mammalian orthologue of Milton also interacts with KIF5 and Miro to form a functional mitochondrial transport complex (Brickley et al., 2005; Fransson et al., 2006; Smith et al., 2006; MacAskill et al., 2009).

2.2. Mitochondrial transport proteins in nervous system development

Mammalian KIF5 is encoded by three genes (*KIF5A-C*), all of which are highly expressed in the nervous system (MacAskill and Kittler, 2010). Disruption of KIF5C mediated transport in rat primary hippocampal cultures impairs mitochondrial transport and promotes formation of small punctate mitochondria (Iworima et al., 2016). Furthermore, evidence suggests KIF5C is important for human nervous system development as a *de novo* mutation was reported in a patient presenting with intellectual disability, epilepsy, and CNS malformations (Willemsen et al., 2014). Additionally, a germline mosaic mutation in KIF5C was identified in a family in which all members carrying the mutation presented with impaired cortical development and microcephaly (Poirier et al., 2013). The neuron-specific kinesin heavy chain KIF5A is also critical, since missense mutations in this gene cause autosomal dominant spastic paraplegia type 10, a disorder that can present with a variety of both central and peripheral neurological problems, including cognitive decline, peripheral neuropathy, distal upper limb amyotrophy, as well as ALS-like symptoms (Goizet et al., 2009; Fink, 2013; Jerath et al., 2015; Lopez et al., 2015; Kaji et al., 2016). Additionally, a *de novo* mutation in KIF5A was described in a patient presenting with progressive neonatal degeneration of myelin and myoclonic seizures (Rydzanicz et al., 2016). KIF5-family proteins can both homo- and heterodimerize allowing for complex regulation of organelle transport (Kanai et al., 2000). Supporting a dominant-negative mechanism in which mutant KIF5A forms inactive complexes with wild-type KIF5 proteins, expression of mutant KIF5A in zebrafish was shown to interfere with axonal transport of mitochondria while promoting axonal degeneration and aberrant synaptic transmission (Campbell et al., 2014). Additionally, impaired ETC activity and developmental delay are observed in patients harboring mutations in KIF5A (Duis et al., 2016). While KIF5A is clearly important for nervous system development and function, the extent to which impaired mitochondrial transport contributes to the etiology of disease symptoms associated with mutations in KIF5A is uncertain given its role in transporting other cellular cargo.

While no human mutations have been described in mitochondrial adaptor proteins for the transport machinery, animal and *in vitro* models provide evidence for a role of Miro and TRAK proteins in nervous system development. Global M*iro1* KO mice die from asphyxia shortly after birth, because of loss of motor neurons innervating the diaphragm (Nguyen et al., 2014). Neuron-specific deletion of *miro1* was shown to have a milder phenotype, impairing retrograde axonal mitochondrial transport, neuromuscular function, and leading to death around 40 days of age (Nguyen et al., 2014). The kinesin adaptors of the Milton family, TRAK1 and TRAK2 also play vital roles in mitochondrial transport as genetic inhibition of either impairs mitochondrial transport in primary hippocampal neuron cultures (van Spronsen et al., 2013; Loss and Stephenson, 2015). Predominant localization of TRAK1 to axons and TRAK2 to dendrites likely accounts for the finding that knockdown of TRAK1 selectively impairs axonal transport of mitochondria and axonal outgrowth, whereas TRAK2 knockdown inhibits dendritic mitochondrial transport and dendritic development (van Spronsen et al., 2013; Loss and Stephenson, 2015).

2.3. Mitochondrial fission and fusion

Mitochondria perform numerous essential functions including ATP synthesis, Ca^{2+} buffering, ROS production/sequestration, and apoptosis (Gautheron, 1984; Wang and Youle, 2009; Glancy and Balaban, 2012; Zorov et al., 2014). Regulation of these processes is partly accomplished through the opposing processes of mitochondrial fission and fusion (Kasahara and Scorrano, 2014). Nuclear encoded dynamin-related GTPases catalyze mitochondrial fission and fusion, with Mitofusins 1 and 2 (Mfn1/2) and optic atrophy 1 (Opa1) coordinating fusion of the OMM and inner mitochondrial membrane (IMM), respectively (Ishihara et al., 2013; Schrepfer and Scorrano, 2016). While precise mechanisms are unknown, Opa1 and Mfn1/2 form complexes both within and across membranes, tethering them closely akin to vesicle fusion proteins of the SNARE family. Oppositely, dynamin-related protein 1 (Drp1) is necessary for fission of the mitochondrial membranes (Otera et al., 2013). Drp1 is also important for peroxisomal fission and proliferation (Koch et al., 2003). However, this aspect of Drp1's function is far less well characterized and the effect of impaired peroxisomal fission on neuronal development is unclear. Primarily a cytosolic enzyme, Drp1 translocates to the OMM when activated (Chang and Blackstone, 2007; Cribbs and Strack, 2007; Cereghetti et al., 2008; Cribbs and Strack, 2009). Recruited by mitochondria-anchored adaptor proteins, Drp1 assembles into spirals around the mitochondrion, which constrict and ultimately divide the organelle in two (Fig. 1). Preceding Drp1 assembly, close apposition of tubular endoplasmic reticulum and localized actin polymerization are also necessary for mitochondrial fission (Friedman et al., 2011; Hatch et al., 2014; Prudent and McBride, 2016), while dynamin-2 was recently shown to catalyze the final membrane scission event (Lee et al., 2016).

2.4. Mitochondrial fusion enzymes in nervous system development and function

The importance of mitochondrial fission and fusion in nervous system development and function is evidenced by findings that mutations of the ubiquitously expressed mitochondrial fission and fusion enzymes have predominantly neurological phenotypes. Mutations in the OMM-fusion enzyme Mfn2 cause Charcot Marie Tooth Disease Type 2A (CMT2A), a severe and early onset motor and sensory peripheral neuropathy with autosomal dominant inheritance (Zuchner et al., 2004; Kijima et al., 2005). Mfn2 mutations are thought to be dominant-negative, inhibiting mitochondrial fusion by complexing with wild-type Mfn1 and Mfn2 (Cartoni and Martinou, 2009). Acting by a similar dominant-negative mechanism, hypomorphic mutations in the IMM-fusion enzyme Opa1 cause dominant optic atrophy (DOA, or Kyer's optic atrophy), the most common cause of hereditary blindness. DOA is characterized by early-onset loss of retinal ganglion cells and degeneration of the optic nerve (Lenaers et al., 2012). 20% of DOA patients present symptoms of multi-system neurological disorders, including deafness,

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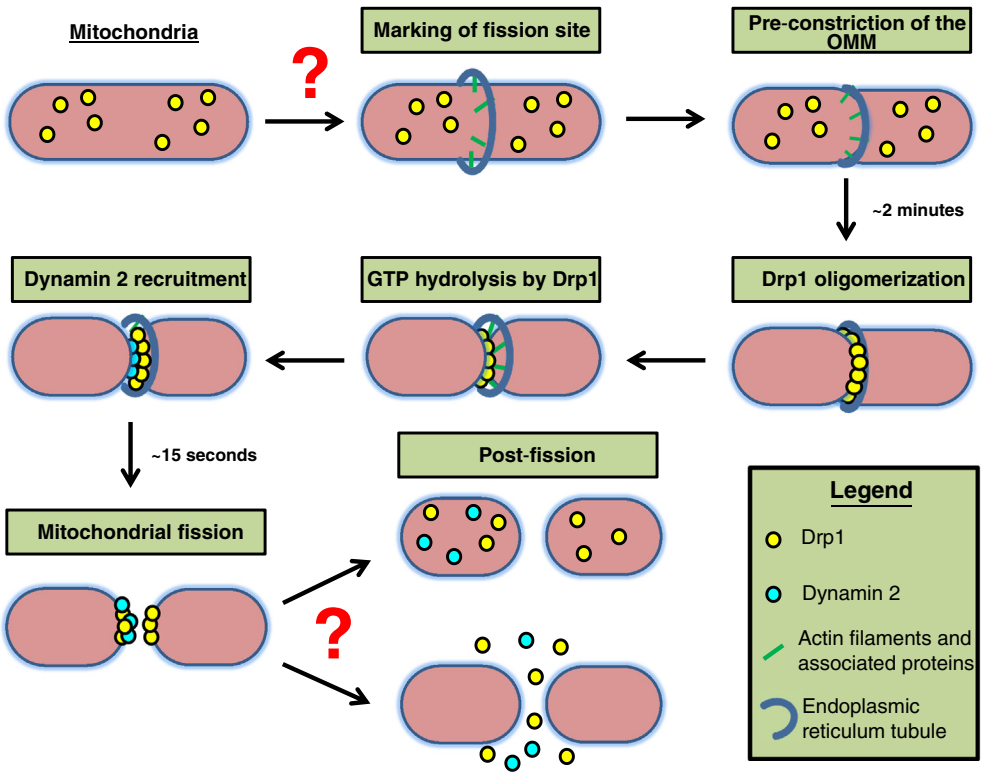

Fig. 1. Mechanism of mitochondrial fission. Drp1 translocates to the OMM and through interaction with various adaptor proteins (not shown). Through a selection process which is poorly understood actin filaments complex with ER tubules to mark fission sites and promote pre-constriction of the OMM. Pre-constriction allows for Drp1 oligomerization and GTP hydrolysis further constricting the mitochondrial membrane. Dynamin 2 is recruited to the fission site to promote complete fission of the mitochondrial membranes. Following fission, whether Drp1 or Dynamin 2 remain at the OMM and are recycled for future use, degraded, or just released from the mitochondria remains relatively unexplored. The timing of certain steps have been included if investigated.

ataxia, myopathy, and peripheral neuropathy, indicating an essential role for Opa1 in neurons in general (Yu-Wai-Man et al., 2010; Chao de la Barca et al., 2016).

Mfn2 mutations associated with CMT2A in humans promote mitochondrial fragmentation in dorsal root ganglion neurons and impair axonal mitochondrial transport suggestive of a link between mitochondrial fission/fusion equilibrium and mitochondrial transport (Baloh et al., 2007). Indeed, a physical link to the microtubule-based transport machinery was proposed based on an interaction of Mfn2 with the Miro/Milton complex (Misko et al., 2010). Global, constitutive deletion of Mfn2 is embryonic lethal in mice (Chen et al., 2003). However, mice that lack Mfn2 in cerebellar Purkinje neurons only are viable and provide clues as to the role of mitochondrial fusion in nervous system development (Chen et al., 2007). Purkinje-neuron specific deletion of Mfn2 impairs not only fusion and dendritic localization of mitochondria, but also dendrite and dendritic spine development. Ultimate degeneration of Purkinje neurons is associated with excessive ROS production and results in impaired motor coordination (Chen et al., 2007). In contrast to mice, zebrafish lacking Mfn2 globally are viable, but have a reduced life span. They display progressive loss of motor function associated with abnormal muscle innervation. Similar to mice, Mfn2 loss-of-function in zebrafish reduces mitochondrial transport and depletes mitochondria from distal axons (Chapman et al., 2013).

Like Mfn2, mice lacking Opa1 in all tissues die during embryogenesis (Davies et al., 2007). While nervous system-specific knockouts of Opa1 have yet to be described, a 50% reduction in overall Opa1 levels in mice expressing only one functional Opa1 allele recapitulates DOA in patients, including early-onset degeneration of the optic nerve and vision loss (Davies et al., 2007). Opa1 depletion in zebrafish embryos using antisense morpholinos causes bioenergetic deficiencies and impairs development of multiple organs, including the eyes, and confirms an evolutionary conserved role for Opa1 in embryonic development (Rahn et al., 2013). *In vitro* experiments indicate that Opa1 has a critical role in dendritogenesis and synaptogenesis. Knock down of Opa1 in cultured rat cortical neurons promotes mitochondrial fragmentation, decreases expression of electron transport chain components, and reduces mitochondrial DNA (mtDNA) content (Bertholet et al., 2013). This apparent loss of mitochondria results in reduced dendritic outgrowth and synapse formation.

2.5. Drp1 in nervous system development and function

There is a wealth of evidence indicating that mitochondrial fission is as important as fusion in the development of the nervous system and Drp1 is the best characterized of the mitochondrial-shaping enzymes. In contrast to Mfn2 and Opa1, there are no known heritable disorders attributable to Drp1 mutations. The likely reason is that even modest Drp1 impairment is incompatible with survival past childhood. Indeed, *de novo* mutations in *Dnm1l*, the human gene encoding Drp1, have been reported in severe cases of birth defects. The first identified mutation was neonatal lethal and resulted in large-scale brain malformations (Waterham et al., 2007). More recently identified *de novo* mutations in *Dnm1l* presented later in childhood as encephalopathy, seizures, and impaired nociception (Fahrner et al., 2016; Nasca et al., 2016; Sheffer et al., 2016; Vanstone et al., 2016; Yoon et al., 2016). All mutations reported so far are dominant-negative, interfering with oligomerization, mitochondrial fission activity, and mitochondrial recruitment of Drp1, to an extent inversely related to age of symptom onset. Mouse models in which Drp1 has been deleted support a vital function of the fusion enzyme and allow for more detailed analysis of nervous system development.

Global, constitutive deletion of *Dnm1l* in mice is embryonic lethal (Ishihara et al., 2009; Wakabayashi et al., 2009). However, more recent mouse models with delayed conditional deletion of *Dnm1l* in specific

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neuronal populations are viable. Two groups independently reported on the phenotypes of mice with early postnatal Drp1 deletion in principal glutamatergic neurons of the forebrain (Shields et al., 2015; Oettinghaus et al., 2016). Both groups reported hippocampal atrophy, but no overt cell loss, indicating loss of synaptic connections. Correspondingly, mice exhibited impaired synaptic transmission and hippocampus-dependent learning and memory (Shields et al., 2015; Oettinghaus et al., 2016). Interestingly, even though mitochondria appeared swollen, no change in the number of presynaptic mitochondria were observed in Drp1 KO neurons, suggesting that Drp1 is not required for mitochondrial trafficking. However, deletion of Drp1 specifically in dopaminergic neurons impairs axonal mitochondrial transport suggesting neuron-specific effects of Drp1 deletion on mitochondrial transport (Berthet et al., 2014). Experiments in primary cultures revealed that hippocampal glutamatergic Drp1 KO neurons cannot maintain synaptic ATP levels when stimulated at high frequencies. Since ATP levels were similarly decreased in synaptic terminals with and without mitochondria, lack of Drp1 compromises the intrinsic bioenergetic capacity of axonal mitochondria rather than causing local energy gradients (Shields et al., 2015).

2.6. Mitochondrial function and dynamics in schizophrenia

As described above, there is now ample evidence that an appropriate balance of mitochondrial fission and fusion is necessary for normal brain development and function. Schizophrenia is widely considered a neurodevelopmental disorder with both environmental and genetic causes and risk factors. Indeed, recent longitudinal imaging studies in schizophrenic patients with early childhood diagnosis revealed altered trajectories of thickness growth of highly connected cortical regions, supporting Carl Wernicke's hypothesis from the late 19th century that schizophrenia is caused by altered connectivity between brain regions (Ordonez et al., 2016). Given their critical role in process outgrowth and synaptogenesis, mitochondria and mitochondrial dynamics are plausibly, if not likely involved in the pathogenesis of schizophrenia. In support, impaired mitochondrial function and characteristic single nucleotide polymorphisms (SNPs) in mtDNA have been observed in schizophrenic patients (Rajasekaran et al., 2015). Additionally, recent work described below suggests that altered mitochondrial dynamics may contribute to aberrant brain development in schizophrenia (Millar et al., 2005, Kvajo et al., 2008a, 2008b, Devine et al., 2016, Norkett et al., 2016) providing new targets for schizophrenia therapeutics.

2.7. Mitochondrial function in schizophrenia

Genetic studies have identified numerous candidate genes as risk factors for schizophrenia. In addition to genes encoded by nuclear DNA, mtDNA has also been suggested to play a role. In support of this hypothesis, a recent cross-sectional study found that risk for schizophrenia has a maternal inheritance bias (Verge et al., 2012). Additionally, several mtDNA SNPs are strongly associated with schizophrenia. Two SNPs in the gene encoding NADH dehydrogenase of ETC complex 1 are positively correlated with schizophrenia (Marchbanks et al., 2003; Rollins et al., 2009). Furthermore, several SNPs in the gene encoding ATP synthase subunit six, prevalent in a Japanese population, are associated with increased risk of developing schizophrenia (Ueno et al., 2009). In addition to mutations in protein coding genes in mtDNA, mutations in a gene encoding a tRNA (Leu(UUR)) is associated with schizophrenia as well (Munakata et al., 2005). While mtDNA SNPs are clearly associated with schizophrenia, how they impact mitochondria function and contribute to the pathogenesis of schizophrenia remains to be determined. However, decreased expression and activity of mitochondrially encoded ETC complexes has been observed post-mortem in various brain regions of schizophrenic patients (Maurer et al., 2001; Karry et al., 2004; Iwamoto et al., 2005; Ben-Shachar and Karry, 2007). As one might expect given impaired ETC activity, a shift toward glycolytic ATP production has been reported in post-mortem samples (Regenold et al., 2012). Additionally, lactate levels, a bi-product and marker of glycolysis, were increased in the cerebrospinal fluid from schizophrenic patients relative to control subjects (Regenold et al., 2009).

2.8. Mitochondrial dynamics in schizophrenia

In addition to impaired mitochondrial function, there is some evidence for aberrant mitochondrial dynamics in schizophrenia patients (Fig. 2). Decreased Opa1 expression and mitochondrial fragmentation are more frequently observed in the *post mortem* prefrontal cortex of schizophrenia patients (Rosenfeld et al., 2011). Additionally, two major schizophrenia candidate genes based on identified SNPs in schizophrenic patients have been suggested to promote mitochondrial fission. The first candidate gene, a nucleus-encoded mitochondrial protein known as G72 is specific to primates and has been proposed to function as an activator of D-amino acid oxidase, thereby decreasing synthesis of the NMDA receptor co-agonist D-serine (Chumakov et al., 2002; Sacchi et al., 2016). Another study reported mitochondrial localization of the longest G72 splice variant and found that overexpression of G72 increases mitochondrial fission and promotes dendrite branching in primary neurons (Kvajo et al., 2008a, 2008b). However, whether SNPs found in the gene encoding G72 in schizophrenia patients alters the activity of G72 is currently unknown.

The second candidate gene, disrupted in schizophrenia 1 (DISC1), is perhaps the best characterized generalized risk factor for major psychiatric disorders. First identified in cytogenetic screens of a large Scottish family with high prevalence of schizophrenia and related psychoses, loss or truncation of DISC1 increases the risk to develop schizophrenia, depression, or bipolar disorder about 50-fold (Brandon et al., 2009). DISC1 associates with itself and with a large number of enzymes and transcription factors and is highly expressed in neural progenitor cells, where it is thought to regulate proliferation and differentiation. At least two of its splice variants have been localized to mitochondria (Millar et al., 2005; Park et al., 2010) and mutations in DISC1 have also been linked to altered mitochondrial dynamics. DISC1 interacts with Miro1/2 and TRAK1/2 of the mitochondrial transport machinery and promotes mitochondrial transport in both axons and dendrites of cultured primary neurons (Atkin et al., 2011; Ogawa et al., 2014; Norkett et al., 2016). A role for DISC1 in mitochondrial fission/fusion was suggested by its localization to contact sites with the endoplasmic reticulum, where mitochondrial fission occurs, and by its interaction with the mitochondrial fusion enzymes Mfn1 and Mfn2 (Norkett et al., 2016). Indeed, schizophrenia-associated DISC1 fusion and truncation mutant proteins inhibit both mitochondrial trafficking and fusion in an apparent dominant-negative manner, which in turn disrupts normal dendritic development of cultured neurons (Devine et al., 2016; Norkett et al., 2016).

There is also evidence that DISC1 disruption affects neurodevelopment *in vivo*. In a mouse model of schizophrenia expressing a truncated form of DISC1, the hippocampus displays several cytoarchitectural abnormalities, including displaced dentate granule neurons, altered axonal targeting, reduced dendrite growth and dendritic spine density. This is accompanied by defective short term plasticity at mossy fiber terminals and poor performance in a task that depends on working memory, which is commonly impaired in schizophrenia patients (Kvajo et al., 2008a, 2008b; Kvajo et al., 2011). Importantly, as it suggests a cell-autonomous effect, abnormal neuron development in DISC1-mutant mice was also observed *in vitro*, although it varied with the origin of the culture, with cortical neurons showing only subtle changes in spine development (Lepagnol-Bestel et al., 2013). Therefore, DISC1 may serve as a point of convergence for mitochondrial dynamics and nervous system development in schizophrenia. The critical questions of whether and how DISC1 regulates mitochondrial shape, distribution, and function *in vivo* remains to be addressed.

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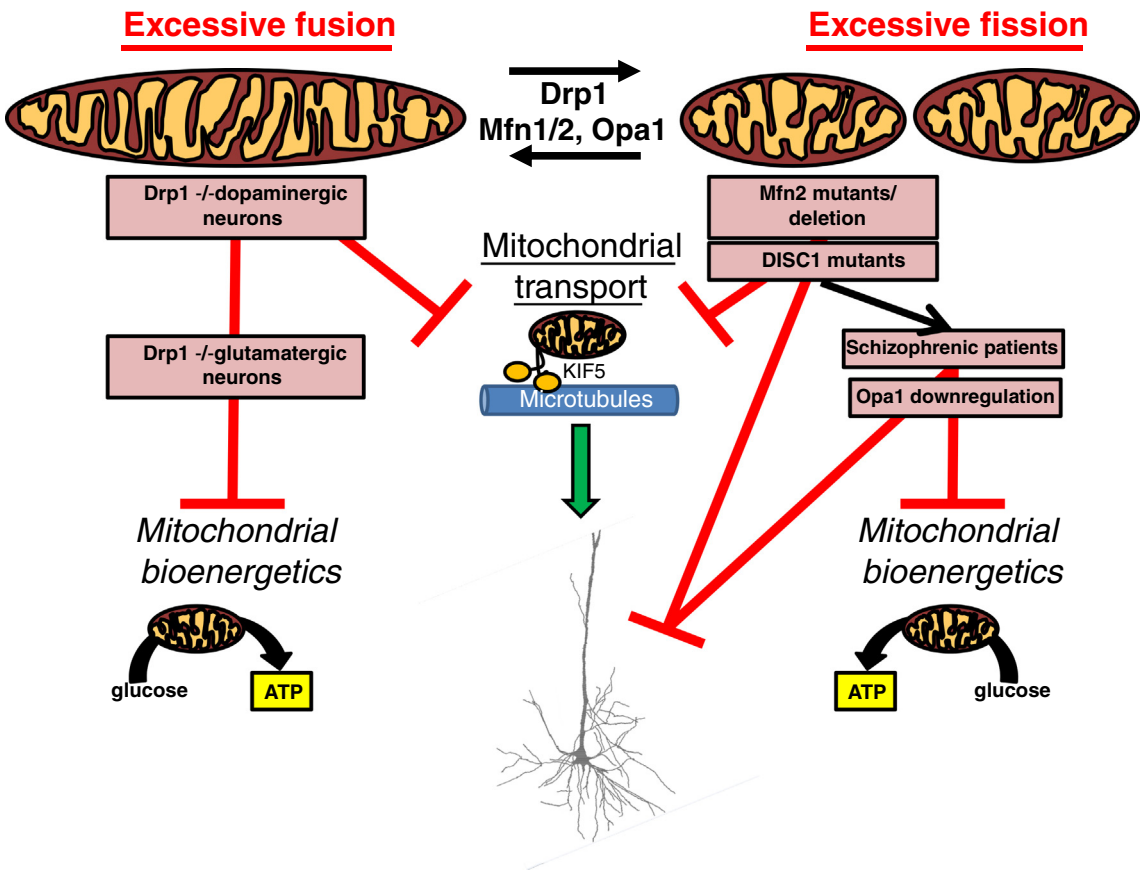

Fig. 2. The role of mitochondrial dynamics in neuron development. Deletion of Drp1 specifically in dopaminergic neurons impairs mitochondrial transport and function while deletion of Drp1 specifically in glutamatergic neurons does not impair mitochondrial transport, but does impair mitochondrial function. Interestingly, excessive fission through mutations in Mfn2 or DISC1 also impairs mitochondrial transport in addition to dendritogenesis and spine formation. Mutations in DISC1 are associated with increased risk for developing schizophrenia (black arrow) with schizophrenic patients also exhibiting mitochondrial fragmentation more frequently in post-mortem samples of the pre-frontal cortex. Additionally, Opa1 expression is decreased in the prefrontal cortex of schizophrenic patients. In addition to altered mitochondrial dynamics, schizophrenic patients exhibit evidence of impaired mitochondrial function and impaired dendritic spine formation and global connectivity. Knockdown of Opa1 in primary neuron cultures impairs mitochondrial function, dendritogenesis, and spine formation similar to what is observed in schizophrenic patients.

3. Conclusions

Schizophrenia is a quantitative trait disorder influenced by the cumulative actions of genetics, epigenetics, and the environment. Recent work demonstrating an association of schizophrenia with mtDNA SNPs and matrilineal inheritance suggest altered mitochondrial function as a risk factor. Neurons are unique in their structural organization with mitochondrial function influenced by mitochondrial shape and localization within different neuronal sub-compartments. Mitochondrial shape and localization are in turn determined by the dynamic processes of mitochondrial fission, fusion, and transport. Recent characterization of DISC1 mutations associated with schizophrenia reinforces the link between abnormal mitochondrial dynamics, nervous system development, and schizophrenia risk, as mutant DISC1 impairs mitochondrial fusion and mitochondrial transport. It remains to be seen if promoting mitochondrial fusion or transport in the context of DISC1 disruption would rescue normal brain development. Because mitochondrial fission/fusion enzymes are already evaluated as potential drug targets for the treatment of neurological disorders, further insights into the role of mitochondria in brain development may lead to new therapies of schizophrenia and other psychiatric disorders.

Conflict of interest

The authors declare no conflict of interest.

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References

Amiri, M., Hollenbeck, P.J., 2008. Mitochondrial biogenesis in the axons of vertebrate peripheral neurons. Dev. Neurobiol. 68 (11), 1348–1361.

Atkin, T.A., MacAskill, A.F., Brandon, N.J., Kittler, J.T., 2011. Disrupted in Schizophrenia-1 regulates intracellular trafficking of mitochondria in neurons. Mol. Psychiatry 16 (2), 122–124 (121).

Baloh, R.H., Schmidt, R.E., Pestronk, A., Milbrandt, J., 2007. Altered axonal mitochondrial transport in the pathogenesis of Charcot-Marie-Tooth disease from mitofusin 2 mutations. J. Neurosci. 27 (2), 422–430.

Barry, S.J., Gaughan, T.M., Hunter, R., 2012. Schizophrenia. BMJ Clin. Evid. 2012.

Ben-Shachar, D., Karry, R., 2007. Sp1 expression is disrupted in schizophrenia; a possible mechanism for the abnormal expression of mitochondrial complex I genes, NDUFV1 and NDUFV2. PLoS One 2 (9), e817.

Berthet, A., Margolis, E.B., Zhang, J., Hsieh, I., Zhang, J., Hnasko, T.S., Ahmad, J., Edwards, R.H., Sesaki, H., Huang, E.J., Nakamura, K., 2014. Loss of mitochondrial fission depletes axonal mitochondria in midbrain dopamine neurons. J. Neurosci. 34 (43), 14304–14317.

Bertholet, A.M., Millet, A.M., Guillermin, O., Daloyau, M., Davezac, N., Miquel, M.C., Belenguer, P., 2013. OPA1 loss of function affects in vitro neuronal maturation. Brain 136 (Pt 5), 1518–1533.

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Bogan, N., Cabot, J.B., 1991. Light and electron microscopic analyses of intraspinal axon collaterals of sympathetic preganglionic neurons. Brain Res. 541 (2), 241–251.

Brandon, N.J., Millar, J.K., Korth, C., Sive, H., Singh, K.K., Sawa, A., 2009. Understanding the role of DISC1 in psychiatric disease and during normal development. J. Neurosci. 29 (41), 12768–12775.

Brickley, K., Smith, M.J., Beck, M., Stephenson, F.A., 2005. GRIF-1 and OIP106, members of a novel gene family of coiled-coil domain proteins: association in vivo and in vitro with kinesin. J. Biol. Chem. 280 (15), 14723–14732.

Cai, Q., Sheng, Z.H., 2009. Moving or stopping mitochondria: Miro as a traffic cop by sensing calcium. Neuron 61 (4), 493–496.

Campbell, P.D., Shen, K., Sapio, M.R., Glenn, T.D., Talbot, W.S., Marlow, F.L., 2014. Unique function of Kinesin Kif5A in localization of mitochondria in axons. J. Neurosci. 34 (44), 14717–14732.

Cartoni, R., Martinou, J.C., 2009. Role of mitofusin 2 mutations in the physiopathology of Charcot-Marie-Tooth disease type 2A. Exp. Neurol. 218 (2), 268–273.

Cereghetti, G.M., Stangherlin, A., Martins de Brito, O., Chang, C.R., Blackstone, C., Bernardi, P., Scorrano, L., 2008. Dephosphorylation by calcineurin regulates translocation of Drp1 to mitochondria. Proc. Natl. Acad. Sci. U. S. A. 105 (41), 15803–15808.

Chang, C.R., Blackstone, C., 2007. Cyclic AMP-dependent protein kinase phosphorylation of Drp1 regulates its GTPase activity and mitochondrial morphology. J. Biol. Chem. 282 (30), 21583–21587.

Chao de la Barca, J.M., Prunier-Mirebeau, D., Amati-Bonneau, P., Ferre, M., Sarzi, E., Bris, C., Leruez, S., Chevrollier, A., Desquiret-Dumas, V., Gueguen, N., Verny, C., Hamel, C., Milea, D., Procaccio, V., Bonneau, D., Lenaers, G., Reynier, P., 2016. OPA1-related disorders: diversity of clinical expression, modes of inheritance and pathophysiology. Neurobiol. Dis. 90, 20–26.

Chapman, A.L., Bennett, E.J., Ramesh, T.M., De Vos, K.J., Grierson, A.J., 2013. Axonal transport defects in a mitofusin 2 loss of function model of Charcot-Marie-tooth disease in zebrafish. PLoS One 8 (6), e67276.

Chen, H., Detmer, S.A., Ewald, A.J., Griffin, E.E., Fraser, S.E., Chan, D.C., 2003. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. J. Cell Biol. 160 (2), 189–200.

Chen, H., McCaffery, J.M., Chan, D.C., 2007. Mitochondrial fusion protects against neurodegeneration in the cerebellum. Cell 130 (3), 548–562.

Chumakov, I., Blumenfeld, M., Guerassimenko, O., Cavarec, L., Palicio, M., Abderrahim, H., Bougueleret, L., Barry, C., Tanaka, H., La Rosa, P., Puech, A., Tahri, N., Cohen-Akenine, A., Delabrosse, S., Lissarrague, S., Picard, F.P., Maurice, K., Essioux, L., Millasseau, P., Grel, P., Debailleul, V., Simon, A.M., Caterina, D., Dufaure, I., Malekzadeh, K., Belova, M., Luan, J.J., Bouillot, M., Sambucy, J.L., Primas, G., Saumier, M., Boubkiri, N., Martin-Saumier, S., Nasroune, M., Peixoto, H., Delaye, A., Pinchot, V., Bastucci, M., Guillou, S., Chevillon, M., Sainz-Fuertes, R., Meguenni, S., Aurich-Costa, J., Cherif, D., Gimalac, A., Van Duijn, C., Gauvreau, D., Ouellette, G., Fortier, I., Raelson, J., Sherbatich, T., Riazanskaia, N., Rogaev, E., Raeymaekers, P., Aerssens, J., Konings, F., Luyten, W., Macciardi, F., Sham, P.C., Straub, R.E., Weinberger, D.R., Cohen, N., Cohen, D., 2002. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 99 (21), 13675–13680.

Cribbs, J.T., Strack, S., 2007. Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death. EMBO Rep. 8 (10), 939–944.

Cribbs, J.T., Strack, S., 2009. Functional characterization of phosphorylation sites in dynamin-related protein 1. Methods Enzymol. 457, 231–253.

Davies, V.J., Hollins, A.J., Piechota, M.J., Yip, W., Davies, J.R., White, K.E., Nicols, P.P., Boulton, M.E., Votruba, M., 2007. Opa1 deficiency in a mouse model of autosomal dominant optic atrophy impairs mitochondrial morphology, optic nerve structure and visual function. Hum. Mol. Genet. 16 (11), 1307–1318.

Devine, M.J., Norkett, R., Kittler, J.T., 2016. DISC1 is a coordinator of intracellular trafficking to shape neuronal development and connectivity. J. Physiol. 594 (19), 5459–5469.

Duis, J., Dean, S., Applegate, C., Harper, A., Xiao, R., He, W., Dollar, J.D., Sun, L.R., Waberski, M.B., Crawford, T.O., Hamosh, A., Stafstrom, C.E., 2016. KIF5A mutations cause an infantile onset phenotype including severe myoclonus with evidence of mitochondrial dysfunction. Ann. Neurol. 80 (4), 633–637.

Fabricius, C., Berthold, C.H., Rydmark, M., 1993. Axoplasmic organelles at nodes of Ranvier. II. Occurrence and distribution in large myelinated spinal cord axons of the adult cat. J. Neurocytol. 22 (11), 941–954.

Fahrner, J.A., Liu, R., Perry, M.S., Klein, J., Chan, D.C., 2016. A novel de novo dominant negative mutation in DNM1L impairs mitochondrial fission and presents as childhood epileptic encephalopathy. Am. J. Med. Genet. A.

Fink, J.K., 2013. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol. 126 (3), 307–328.

Flippo, K.H., Strack, S., 2017. Mitochondrial dynamics in neuronal injury, development and plasticity. J. Cell Sci. 130 (4), 671–681.

Fransson, S., Ruusala, A., Aspenstrom, P., 2006. The atypical Rho GTPases Miro-1 and Miro-2 have essential roles in mitochondrial trafficking. Biochem. Biophys. Res. Commun. 344 (2), 500–510.

Friedman, J.R., Lackner, L.L., West, M., DiBenedetto, J.R., Nunnari, J., Voeltz, G.K., 2011. ER tubules mark sites of mitochondrial division. Science 334 (6054), 358–362.

Gautheron, D.C., 1984. Mitochondrial oxidative phosphorylation and respiratory chain: review. J. Inherit. Metab. Dis. 7 (Suppl. 1), 57–61.

Glancy, B., Balaban, R.S., 2012. Role of mitochondrial Ca2 + in the regulation of cellular energetics. Biochemistry 51 (14), 2959–2973.

Glater, E.E., Megeath, L.J., Stowers, R.S., Schwarz, T.L., 2006. Axonal transport of mitochondria requires milton to recruit kinesin heavy chain and is light chain independent. J. Cell Biol. 173 (4), 545–557.

Goizet, C., Boukhris, A., Mundwiller, E., Tallaksen, C., Forlani, S., Toutain, A., Carriere, N., Paquis, V., Depienne, C., Durr, A., Stevanin, G., Brice, A., 2009. Complicated forms of autosomal dominant hereditary spastic paraplegia are frequent in SPG10. Hum. Mutat. 30 (2), E376–E385.

Hatch, A.L., Gurel, P.S., Higgs, H.N., 2014. Novel roles for actin in mitochondrial fission. J. Cell Sci. 127 (Pt 21), 4549–4560.

Hirokawa, N., Niwa, S., Tanaka, Y., 2010. Molecular motors in neurons: transport mechanisms and roles in brain function, development, and disease. Neuron 68 (4), 610–638.

Ishihara, N., Nomura, M., Jofuku, A., Kato, H., Suzuki, S.O., Masuda, K., Otera, H., Nakanishi, Y., Nonaka, I., Goto, Y., Taguchi, N., Morinaga, H., Maeda, M., Takayanagi, R., Yokota, S., Mihara, K., 2009. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. Nat. Cell Biol. 11 (8), 958–966.

Ishihara, N., Otera, H., Oka, T., Mihara, K., 2013. Regulation and physiologic functions of GTPases in mitochondrial fusion and fission in mammals. Antioxid. Redox Signal. 19 (4), 389–399.

Iwamoto, K., Bundo, M., Kato, T., 2005. Altered expression of mitochondria-related genes in postmortem brains of patients with bipolar disorder or schizophrenia, as revealed by large-scale DNA microarray analysis. Hum. Mol. Genet. 14 (2), 241–253.

Iworima, D.G., Pasqualotto, B.A., Rintoul, G.L., 2016. Kif5 regulates mitochondrial movement, morphology, function and neuronal survival. Mol. Cell. Neurosci. 72, 22–33.

Jerath, N.U., Grider, T., Shy, M.E., 2015. Progressive lower extremity weakness and axonal sensorimotor polyneuropathy from a mutation in KIF5A (c.611G>A;p.Arg204Gln). Case Rep. Genet. 2015, 496053.

Kaji, S., Kawarai, T., Miyamoto, R., Nodera, H., Pedace, L., Orlacchio, A., Izumi, Y., Takahashi, R., Kaji, R., 2016. Late-onset spastic paraplegia type 10 (SPG10) family presenting with bulbar symptoms and fasciculations mimicking amyotrophic lateral sclerosis. J. Neurol. Sci. 364, 45–49.

Kanai, Y., Okada, Y., Tanaka, Y., Harada, A., Terada, S., Hirokawa, N., 2000. KIF5C, a novel neuronal kinesin enriched in motor neurons. J. Neurosci. 20 (17), 6374–6384.

Karry, R., Klein, E., Ben Shachar, D., 2004. Mitochondrial complex I subunits expression is altered in schizophrenia: a postmortem study. Biol. Psychiatry 55 (7), 676–684.

Kasahara, A., Scorrano, L., 2014. Mitochondria: from cell death executioners to regulators of cell differentiation. Trends Cell Biol. 24 (12), 761–770.

Kijima, K., Numakura, C., Izumino, H., Umetsu, K., Nezu, A., Shiiki, T., Ogawa, M., Ishizaki, Y., Kitamura, T., Shozawa, Y., Hayasaka, K., 2005. Mitochondrial GTPase mitofusin 2 mutation in Charcot-Marie-Tooth neuropathy type 2A. Hum. Genet. 116 (1–2), 23–27.

Koch, A., Thiemann, M., Grabenbauer, M., Yoon, Y., McNiven, M.A., Schrader, M., 2003. Dynamin-like protein 1 is involved in peroxisomal fission. J. Biol. Chem. 278 (10), 8597–8605.

Kvajo, M., McKellar, H., Arguello, P.A., Drew, L.J., Moore, H., MacDermott, A.B., Karayiorgou, M., Gogos, J.A., 2008a. A mutation in mouse Disc1 that models a schizophrenia risk allele leads to specific alterations in neuronal architecture and cognition. Proc. Natl. Acad. Sci. U. S. A. 105 (19), 7076–7081.

Kvajo, M., Dhilla, A., Swor, D.E., Karayiorgou, M., Gogos, J.A., 2008b. Evidence implicating the candidate schizophrenia/bipolar disorder susceptibility gene G72 in mitochondrial function. Mol. Psychiatry 13 (7), 685–696.

Kvajo, M., McKellar, H., Drew, L.J., Lepagnol-Bestel, A.M., Xiao, L., Levy, R.J., Blazeski, R., Arguello, P.A., Lacefield, C.O., Mason, C.A., Simonneau, M., O'Donnell, J.M., MacDermott, A.B., Karayiorgou, M., Gogos, J.A., 2011. Altered axonal targeting and short-term plasticity in the hippocampus of Disc1 mutant mice. Proc. Natl. Acad. Sci. U. S. A. 108 (49), E1349–E1358.

Lee, J.E., Westrate, L.M., Wu, H., Page, C., Voeltz, G.K., 2016. Multiple dynamin family members collaborate to drive mitochondrial division. Nature 540, 139–143.

Lenaers, G., Hamel, C., Delettre, C., Amati-Bonneau, P., Procaccio, V., Bonneau, D., Reynier, P., Milea, D., 2012. Dominant optic atrophy. Orphanet J. Rare Dis. 7, 46.

Lepagnol-Bestel, A.M., Kvajo, M., Karayiorgou, M., Simonneau, M., Gogos, J.A., 2013. A Disc1 mutation differentially affects neurites and spines in hippocampal and cortical neurons. Mol. Cell. Neurosci. 54, 84–92.

Lopez, E., Casasnovas, C., Gimenez, J., Santamaria, R., Terrazas, J.M., Volpini, V., 2015. Identification of two novel KIF5A mutations in hereditary spastic paraplegia associated with mild peripheral neuropathy. J. Neurol. Sci. 358 (1–2), 422–427.

Loss, O., Stephenson, F.A., 2015. Localization of the kinesin adaptor proteins trafficking kinesin proteins 1 and 2 in primary cultures of hippocampal pyramidal and cortical neurons. J. Neurosci. Res. 93 (7), 1056–1066.

MacAskill, A.F., Kittler, J.T., 2010. Control of mitochondrial transport and localization in neurons. Trends Cell Biol. 20 (2), 102–112.

MacAskill, A.F., Brickley, K., Stephenson, F.A., Kittler, J.T., 2009. GTPase dependent recruitment of Grif-1 by Miro1 regulates mitochondrial trafficking in hippocampal neurons. Mol. Cell. Neurosci. 40 (3), 301–312.

Maday, S., 2016. Mechanisms of neuronal homeostasis: autophagy in the axon. Brain Res. 1649 (Pt B), 143–150.

Marchbanks, R.M., Ryan, M., Day, I.N., Owen, M., McGuffin, P., Whatley, S.A., 2003. A mitochondrial DNA sequence variant associated with schizophrenia and oxidative stress. Schizophr. Res. 65 (1), 33–38.

Maurer, I., Zierz, S., Moller, H., 2001. Evidence for a mitochondrial oxidative phosphorylation defect in brains from patients with schizophrenia. Schizophr. Res. 48 (1), 125–136.

Millar, J.K., James, R., Christie, S., Porteous, D.J., 2005. Disrupted in schizophrenia 1 (DISC1): subcellular targeting and induction of ring mitochondria. Mol. Cell. Neurosci. 30 (4), 477–484.

Misko, A., Jiang, S., Wegorzewska, I., Milbrandt, J., Baloh, R.H., 2010. Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex. J. Neurosci. 30 (12), 4232–4240.

Munakata, K., Iwamoto, K., Bundo, M., Kato, T., 2005. Mitochondrial DNA 3243A>G mutation and increased expression of LARS2 gene in the brains of patients with bipolar disorder and schizophrenia. Biol. Psychiatry 57 (5), 525–532.

Mutsaers, S.E., Carroll, W.M., 1998. Focal accumulation of intra-axonal mitochondria in demyelination of the cat optic nerve. Acta Neuropathol. 96 (2), 139–143.

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Nasca, A., Legati, A., Baruffini, E., Nolli, C., Moroni, I., Ardissone, A., Goffrini, P., Ghezzi, D., 2016. Biallelic mutations in DNM1L are associated with a slowly progressive infantile encephalopathy. Hum. Mutat. 37 (9), 898–903.

Nguyen, T.T., Oh, S.S., Weaver, D., Lewandowska, A., Maxfield, D., Schuler, M.H., Smith, N.K., Macfarlane, J., Saunders, G., Palmer, C.A., Debattisti, V., Koshiba, T., Pulst, S., Feldman, E.L., Hajnoczky, G., Shaw, J.M., 2014. Loss of Miro1-directed mitochondrial movement results in a novel murine model for neuron disease. Proc. Natl. Acad. Sci. U. S. A. 111 (35), E3631–E3640.

Norkett, R., Modi, S., Birsa, N., Atkin, T.A., Ivankovic, D., Pathania, M., Trossbach, S.V., Korth, C., Hirst, W.D., Kittler, J.T., 2016. DISC1-dependent regulation of mitochondrial dynamics controls the morphogenesis of complex neuronal dendrites. J. Biol. Chem. 291 (2), 613–629.

Oettinghaus, B., Schulz, J.M., Restelli, L.M., Licci, M., Savoia, C., Schmidt, A., Schmitt, K., Grimm, A., More, L., Hench, J., Tolnay, M., Eckert, A., D'Adamo, P., Franken, P., Ishihara, N., Mihara, K., Bischofberger, J., Scorrano, L., Frank, S., 2016. Synaptic dysfunction, memory deficits and hippocampal atrophy due to ablation of mitochondrial fission in adult forebrain neurons. Cell Death Differ. 23 (1), 18–28.

Ogawa, F., Malavasi, E.L., Crummie, D.K., Eykelenboom, J.E., Soares, D.C., Mackie, S., Porteous, D.J., Millar, J.K., 2014. DISC1 complexes with TRAK1 and Miro1 to modulate anterograde axonal mitochondrial trafficking. Hum. Mol. Genet. 23 (4), 906–919.

Ordonez, A.E., Luscher, Z.I., Gogtay, N., 2016. Neuroimaging findings from childhood onset schizophrenia patients and their non-psychotic siblings. Schizophr. Res. 173 (3), 124–131.

van Os, J., Kapur, S., 2009. Schizophrenia. Lancet 374 (9690), 635–645.

Otera, H., Ishihara, N., Mihara, K., 2013. New insights into the function and regulation of mitochondrial fission. Biochim. Biophys. Acta 1833 (5), 1256–1268.

Park, C., Park, S.K., 2012. Molecular links between mitochondrial dysfunctions and schizophrenia. Mol. Cells 33 (2), 105–110.

Park, Y.U., Jeong, J., Lee, H., Mun, J.Y., Kim, J.H., Lee, J.S., Nguyen, M.D., Han, S.S., Suh, P.G., Park, S.K., 2010. Disrupted-in-schizophrenia 1 (DISC1) plays essential roles in mitochondria in collaboration with Mitofilin. Proc. Natl. Acad. Sci. U. S. A. 107 (41), 17785–17790.

Poirier, K., Lebrun, N., Broix, L., Tian, G., Saillour, Y., Boscheron, C., Parrini, E., Valence, S., Pierre, B.S., Oger, M., Lacombe, D., Genevieve, D., Fontana, E., Darra, F., Cances, C., Barth, M., Bonneau, D., Bernadina, B.D., N'Guyen, S., Gitiaux, C., Parent, P., des Portes, V., Pedespan, J.M., Legrez, V., Castelnau-Ptakine, L., Nitschke, P., Hieu, T., Masson, C., Zelenika, D., Andrieux, A., Francis, F., Guerrini, R., Cowan, N.J., Bahi-Buisson, N., Chelly, J., 2013. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. Nat. Genet. 45 (6), 639–647.

Prudent, J., McBride, H.M., 2016. Mitochondrial dynamics: ER actin tightens the Drp1 noose. Curr. Biol. 26 (5), R207–R209.

Rahn, J.J., Stackley, K.D., Chan, S.S., 2013. Opa1 is required for proper mitochondrial metabolism in early development. PLoS One 8 (3), e59218.

Rajasekaran, A., Venkatasubramanian, G., Berk, M., Debnath, M., 2015. Mitochondrial dysfunction in schizophrenia: pathways, mechanisms and implications. Neurosci. Biobehav. Rev. 48, 10–21.

Regenold, W.T., Phatak, P., Marano, C.M., Sassan, A., Conley, R.R., Kling, M.A., 2009. Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: implications for the mitochondrial dysfunction hypothesis. Biol. Psychiatry 65 (6), 489–494.

Regenold, W.T., Pratt, M., Nekkalapu, S., Shapiro, P.S., Kristian, T., Fiskum, G., 2012. Mitochondrial detachment of hexokinase 1 in mood and psychotic disorders: implications for brain energy metabolism and neurotrophic signaling. J. Psychiatr. Res. 46 (1), 95–104.

Rollins, B., Martin, M.V., Sequeira, P.A., Moon, E.A., Morgan, L.Z., Watson, S.J., Schatzberg, A., Akil, H., Myers, R.M., Jones, E.G., Wallace, D.C., Bunney, W.E., Vawter, M.P., 2009. Mitochondrial variants in schizophrenia, bipolar disorder, and major depressive disorder. PLoS One 4 (3), e4913.

Rosenfeld, M., Brenner-Lavie, H., Ari, S.G., Kavushansky, A., Ben-Shachar, D., 2011. Perturbation in mitochondrial network dynamics and in complex I dependent cellular respiration in schizophrenia. Biol. Psychiatry 69 (10), 980–988.

Rydzanicz, M., Jagla, M., Kosinska, J., Tomasik, T., Sobczak, A., Pollak, A., Herman-Sucharska, I., Walczak, A., Kwinta, P., Ploski, R., 2016. KIF5A de novo mutation associated with myoclonic seizures and neonatal onset progressive leukoencephalopathy. Clin. Genet.

Sacchi, S., Binelli, G., Pollegioni, L., 2016. G72 primate-specific gene: a still enigmatic element in psychiatric disorders. Cell. Mol. Life Sci. 73 (10), 2029–2039.

Saha, S., Chant, D., Welham, J., McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. PLoS Med. 2 (5), e141.

Saxton, W.M., Hollenbeck, P.J., 2012. The axonal transport of mitochondria. J. Cell Sci. 125 (Pt 9), 2095–2104.

Schrepfer, E., Scorrano, L., 2016. Mitofusins, from mitochondria to metabolism. Mol. Cell 61 (5), 683–694.

Schwarz, T.L., 2013. Mitochondrial trafficking in neurons. Cold Spring Harb. Perspect. Biol. 5 (6).

Sheffer, R., Douiev, L., Edvardson, S., Shaag, A., Tamimi, K., Soiferman, D., Meiner, V., Saada, A., 2016. Postnatal microcephaly and pain insensitivity due to a de novo heterozygous DNM1L mutation causing impaired mitochondrial fission and function. Am. J. Med. Genet. A 170 (6), 1603–1607.

Sheng, Z.H., Cai, Q., 2012. Mitochondrial transport in neurons: impact on synaptic homeostasis and neurodegeneration. Nat. Rev. Neurosci. 13 (2), 77–93.

Shepherd, G.M., Harris, K.M., 1998. Three-dimensional structure and composition of CA3→CA1 axons in rat hippocampal slices: implications for presynaptic connectivity and compartmentalization. J. Neurosci. 18 (20), 8300–8310.

Shields, L.Y., Kim, H., Zhu, L., Haddad, D., Berthet, A., Pathak, D., Lam, M., Ponnusamy, R., Diaz-Ramirez, L.G., Gill, T.M., Sesaki, H., Mucke, L., Nakamura, K., 2015. Dynamin-related protein 1 is required for normal mitochondrial bioenergetic and synaptic function in CA1 hippocampal neurons. Cell Death Dis. 6, e1725.

Smith, M.J., Pozo, K., Brickley, K., Stephenson, F.A., 2006. Mapping the GRIF-1 binding domain of the kinesin, KIF5C, substantiates a role for GRIF-1 as an adaptor protein in the anterograde trafficking of cargoes. J. Biol. Chem. 281 (37), 27216–27228.

van Spronsen, M., Mikhaylova, M., Lipka, J., Schlager, M.A., van den Heuvel, D.J., Kuijpers, M., Wulf, P.S., Keijzer, N., Demmers, J., Kapitein, L.C., Jaarsma, D., Gerritsen, H.C., Akhmanova, A., Hoogenraad, C.C., 2013. TRAK/Milton motor-adaptor proteins steer mitochondrial trafficking to axons and dendrites. Neuron 77 (3), 485–502.

Stowers, R.S., Megeath, L.J., Gorska-Andrzejak, J., Meinertzhagen, I.A., Schwarz, T.L., 2002. Axonal transport of mitochondria to synapses depends on milton, a novel Drosophila protein. Neuron 36 (6), 1063–1077.

Tenback, D.E., van Harten, P.N., Slooff, C.J., van Os, J., 2010. Incidence and persistence of tardive dyskinesia and extrapyramidal symptoms in schizophrenia. J. Psychopharmacol. 24 (7), 1031–1035.

Ueno, H., Nishigaki, Y., Kong, Q.P., Fuku, N., Kojima, S., Iwata, N., Ozaki, N., Tanaka, M., 2009. Analysis of mitochondrial DNA variants in Japanese patients with schizophrenia. Mitochondrion 9 (6), 385–393.

Vanstone, J.R., Smith, A.M., McBride, S., Naas, T., Holcik, M., Antoun, G., Harper, M.E., Michaud, J., Sell, E., Chakraborty, P., Tetreault, M., Care4Rare, C., Majewski, J., Baird, S., Boycott, K.M., Dyment, D.A., MacKenzie, A., Lines, M.A., 2016. DNM1L-related mitochondrial fission defect presenting as refractory epilepsy. Eur. J. Hum. Genet. 24 (7), 1084–1088.

Verge, B., Alonso, Y., Miralles, C., Valero, J., Vilella, E., Boles, R.G., Martorell, L., 2012. New evidence for the involvement of mitochondrial inheritance in schizophrenia: results from a cross-sectional study evaluating the risk of illness in relatives of schizophrenia patients. J. Clin. Psychiatry 73 (5), 684–690.

Wakabayashi, J., Zhang, Z., Wakabayashi, N., Tamura, Y., Fukaya, M., Kensler, T.W., Iijima, M., Sesaki, H., 2009. The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice. J. Cell Biol. 186 (6), 805–816.

Wang, C., Youle, R.J., 2009. The role of mitochondria in apoptosis*. Annu. Rev. Genet. 43, 95–118.

Waterham, H.R., Koster, J., van Roermund, C.W., Mooyer, P.A., Wanders, R.J., Leonard, J.V., 2007. A lethal defect of mitochondrial and peroxisomal fission. N. Engl. J. Med. 356 (17), 1736–1741.

Willemsen, M.H., Ba, W., Wissink-Lindhout, W.M., de Brouwer, A.P., Haas, S.A., Bienek, M., Hu, H., Vissers, L.E., van Bokhoven, H., Kalscheuer, V., Nadif Kasri, N., Kleefstra, T., 2014. Involvement of the kinesin family members KIF4A and KIF5C in intellectual disability and synaptic function. J. Med. Genet. 51 (7), 487–494.

Yoon, G., Malam, Z., Paton, T., Marshall, C.R., Hyatt, E., Ivakine, Z., Scherer, S.W., Lee, K.S., Hawkins, C., Cohn, R.D., C. Finding of Rare Disease Genes in Canada Consortium Steering, 2016. Lethal disorder of mitochondrial fission caused by mutations in DNM1L. J. Pediatr. 171 (313–316), e311–e312.

Yu-Wai-Man, P., Griffiths, P.G., Gorman, G.S., Lourenco, C.M., Wright, A.F., Auer-Grumbach, M., Toscano, A., Musumeci, O., Valentino, M.L., Caporali, L., Lamperti, C., Tallaksen, C.M., Duffey, P., Miller, J., Whittaker, R.G., Baker, M.R., Jackson, M.J., Clarke, M.P., Dhillon, B., Czermin, B., Stewart, J.D., Hudson, G., Reynier, P., Bonneau, D., Marques Jr., W., Lenaers, G., McFarland, R., Taylor, R.W., Turnbull, D.M., Votruba, M., Zeviani, M., Carelli, V., Bindoff, L.A., Horvath, R., Amati-Bonneau, P., Chinnery, P.F., 2010. Multi-system neurological disease is common in patients with OPA1 mutations. Brain 133 (Pt 3), 771–786.

Zorov, D.B., Juhaszova, M., Sollott, S.J., 2014. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol. Rev. 94 (3), 909–950.

Zuchner, S., Mersiyanova, I.V., Muglia, M., Bissar-Tadmouri, N., Rochelle, J., Dadali, E.L., Zappia, M., Nelis, E., Patitucci, A., Senderek, J., Parman, Y., Evgrafov, O., Jonghe, P.D., Takahashi, Y., Tsuji, S., Pericak-Vance, M.A., Quattrone, A., Battaloglu, E., Polyakov, A.V., Timmerman, V., Schroder, J.M., Vance, J.M., 2004. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat. Genet. 36 (5), 449–451.

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