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Review: Genes Involved in Mitochondrial Physiology Within 22q11.2 Deleted Region and Their Relevance to Schizophrenia

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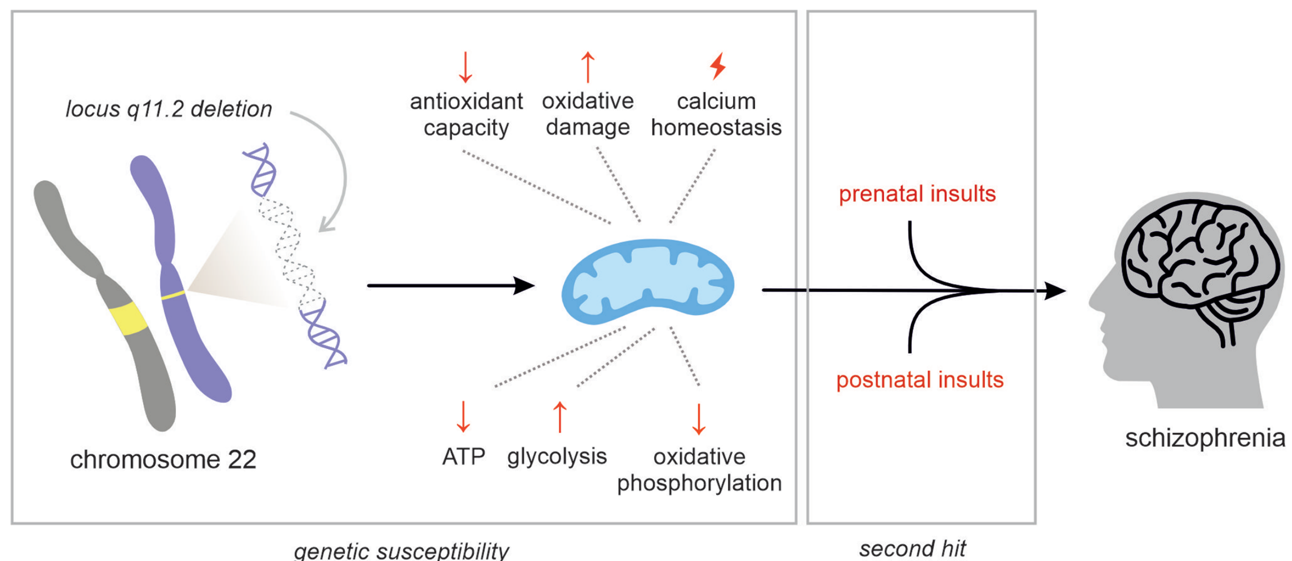
***Background and Hypothesis*: Schizophrenia is associated with altered energy metabolism, but the cause and potential impact of these metabolic changes remain unknown. 22q11.2 deletion syndrome (22q11.2DS) represents a genetic risk factor for schizophrenia, which is associated with the loss of several genes involved in mitochondrial physiology. Here we examine how the haploinsufficiency of these genes could contribute to the emergence of schizophrenia in 22q11.2DS. *Study Design*: We characterize changes in neuronal mitochondrial function caused by haploinsufficiency of mitochondria-associated genes within the 22q11.2 region (*PRODH, MRPL40, TANGO2, ZDHHC8, SLC25A1, TXNRD2, UFD1,* and *DGCR8*). For that purpose, we combine data from 22q11.2DS carriers and schizophrenia patients, in vivo (animal models) and in vitro (induced pluripotent stem cells, IPSCs) studies. We also review the current knowledge about seven non-coding microRNA molecules located in the 22q11.2 region that may be indirectly involved in energy metabolism by acting as regulatory factors. *Study Results*: We found that the haploinsufficiency of genes of interest is mainly associated with increased oxidative stress, altered energy metabolism, and calcium homeostasis in animal models. Studies on IPSCs from 22q11.2DS carriers corroborate findings of deficits in the brain energy metabolism, implying a causal role between impaired mitochondrial function and the development of schizophrenia in 22q11.2DS. *Conclusions*: The haploinsufficiency of genes within the 22q11.2 region leads to multifaceted mitochondrial dysfunction with consequences to neuronal function, viability, and wiring. Overlap between in vitro and in vivo studies implies a causal role between impaired mitochondrial function and the development of schizophrenia in 22q11.2DS.**

Graphical Abstract



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22q11.2 deletion syndrome leads to changes in energy metabolism: Lower ATP levels, enhanced glycolysis and decreased OXPHOS rates, decreased antioxidant capacity, and aberrant calcium homeostasis. Although 22q11.2DS is the strongest single genetic risk factor for schizophrenia development, prenatal or postnatal insults (as indicated by the second hit) are necessary for schizophrenia to develop

Key words: energy metabolism/22q11.2DS/schizophrenia /mitochondria

Introduction

Schizophrenia is a mental disorder that may include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms.[1] The specific symptom profile may differ between patients as only 2 of these 5 symptom categories are necessary for diagnosis.[1] And even after decades of research, the pathophysiology of schizophrenia remains elusive, although several plausible 'common pathways' (or rather common nodes) have been proposed.[2–5] Curiously, the fact that schizophrenia is defined on the cognitive-behavioral level may deem the search for clear and universal neurobiological causes futile—more than one pathophysiological route may lead to symptoms of schizophrenia, and schizophrenia itself does not constitute a singular disorder.[6–9]

Selecting a subgroup of individuals as homogeneous as our knowledge allows is, therefore, essential to investigate the pathophysiology of schizophrenia in detail. The 22q11.2 deletion syndrome (22q11.2DS) is associated with the development of schizophrenia in about 11% and 19% of cases in patients below and over the age of 18, respectively.[10] It is the most common genetic risk factor for schizophrenia, accounting for 0.4%–1% of schizophrenia cases in total.[11–14] Due to the known genetic background, the 22q11.2DS can be studied in vivo in gene-knockout animal models or in vitro in cellular models derived from induced pluripotent stem cells (IPSCs) isolated from 22q11.2DS human carriers. In this review, we focus on mitochondrial and metabolic abnormalities caused by 22q11.2 haploinsufficiency and relate them to the neurobiological changes observed in 22q11.2DS in animal and IPSCs-derived cellular models. We identified three main links between 22q11.2 haploinsufficiency and neurobiological changes in animal and human cellular models: Energy metabolism, calcium homeostasis, and oxidative stress.

Implications of Mitochondrial Pathophysiology in Schizophrenia

Mitochondria are membrane-bound organelles that perform a multitude of functions essential for the viability and functioning of neural cells. First, mitochondria play a pivotal role in cellular energy metabolism by providing the majority of Adenosine Triphosphate (ATP)[15] and participating in carbohydrate, amino acid, and lipid metabolism via citric acid cycle (CAC). Second, the mitochondrial antioxidant system partially eliminates reactive oxygen species (ROS) that form during oxidative phosphorylation (OXPHOS) in electron transport chain (ETC). Despite functioning as important second messenger molecules, ROS oxidatively damage proteins, DNA and RNA (reviewed in[16,17]), and their timely elimination by mitochondria is vital for cell viability. Third, mitochondria are involved in the regulation of cellular calcium homeostasis via mitochondria-associated membranes of the endoplasmic reticulum.[18] Fourth, cross-talk between mitochondria and the nucleus affects critical processes such as cell differentiation and stress adaptation.[19,20] Lastly, mitochondria are capable of fusion/fission processes that dynamically reflect current cellular needs.[21] On the other hand, extra- and intracellular stressors may induce mitochondrial fragmentation and lead to cell apoptosis.[22,23] All the processes mentioned above are intertwined; a change in one part of the system produces cascade effects in the others. For example, mitochondrial dysfunction may increase reliance on glycolysis and the production of ROS and reduce the cellular capacity to buffer calcium concentration.[24] Aberrations in these processes may affect the capacity of the cell to maintain membrane potentials and synaptic plasticity, restore ion gradients, and release or reuptake neurotransmitters[25] and ultimately lead to cellular death.[26,27]

Postmortem in vitro studies have shown that mitochondrial function is impaired in individuals with schizophrenia. Specifically, the brains of schizophrenia patients exhibit significant reductions in mitochondrial volume, density, and count.[28] The decrease in the mitochondria count or mitochondrial energy metabolism capacity was apparent in several brain regions implicated in schizophrenia pathology. Specifically, in the anterior cingulate cortex, mitochondria count was lowered by 40%;[29] in the hippocampus, mitochondrial oxidative energy metabolism was reduced,[30,31] and in the frontal and temporal cortices, cytochrome-c oxidase activity was diminished.[32] In line with these findings, the disruption of mitochondrial function (manifested by significantly reduced ATP levels), was also observed in the neurons derived from IPSCs of schizophrenia patients with 22q11.2DS.[33] IPSCs and cerebral organoids derived from non-syndromic schizophrenia patients showed a dysregulated expression of OXPHOS-related genes.[34,35] Moreover, cortical gray matter of non-syndromic schizophrenia patients displayed down-regulation of mitochondria-related genes, aligning with the reduced pyramidal neuron activity.[36] A possible interpretation may be that the relative down-regulation of mitochondrial metabolism genes in schizophrenia (with 22q11.2DS or non-syndromic) could be a secondary pattern to reduced cortical activity.

Mitochondria are closely linked to oxidative stress,[37,38] is a process likely involved in schizophrenia pathogenesis.[4] For example, it has been suggested that oxidative stress could be the main culprit of disrupted mitochondrial function in schizophrenia.[39] Increased oxidative stress and dysregulated redox homeostasis have been well-documented in schizophrenia patients.[40–42] Several candidate biomarkers for schizophrenia are involved in oxidative stress and energy metabolism.[43,44] Moreover, antioxidant treatment can reduce the severity of schizophrenia symptoms.[45–47]

Oxidative stress is directly linked to 2 key factors involved in the current understanding of schizophrenia pathophysiology: The hypofunction of N-methyl-D-aspartate (NMDA) receptors[4,48–51] and the altered function of parvalbumin-positive interneurons (PVIs).[46,52,53] NMDAR hypofunction can be induced by reducing endogenous antioxidant glutathione,[54,55] presumably by oxidation of the redox-sensitive extracellular sites of the NMDARs.[54] The reciprocal interaction between N-methyl-D-aspartate Receptor (NMDAR) hypofunction and oxidative stress has recently been reviewed.[4] Numerous studies documented both disturbances in gamma oscillations and their relation to cognitive deficits in schizophrenia.[56,57] The PVIs play a crucial role in pyramidal neuron synchronization and generation of network oscillations.[58,59] Due to their high firing rate, PVIs have high demands on both energy production and antioxidant systems. These high demands leave PVIs especially vulnerable to metabolic insufficiency and elevated ROS levels, resulting in negative consequences for network activity. Alternatively, oxidative stress may negatively affect PVIs function by impairing myelination[60,61] and disrupting the integrity of perineuronal nets.[41,62,63] Taken together, mitochondrial function and cell metabolism are likely disrupted in schizophrenia with downstream consequences for neuronal and network function.

22q11.2 Deletion Syndrome

Microdeletion of the 22q11.2 locus in chromosome 22 is a known risk factor for schizophrenia of relatively common occurrence (1:4000 live births).[64] The 22q11.2DS, also known as DiGeorge syndrome, is associated with morphological alterations and aberrant brain development. Approximately 11.5% of 22q11.2DS carriers develop schizophrenia later in life.[10] 22q11.2DS is also associated with disrupted energy metabolism: Based on plasma metabolomics, lymphocytic mitochondrial outcomes, and epigenetics, children with 22q11.2DS show an apparent shift from oxidative phosphorylation to glycolysis (higher lactate/pyruvate ratio) and increased concentration of 2-hydroxyglutaric acid,[65] indicating a possible link between vulnerability to mitochondrial dysfunction and emergence of schizophrenia. Interestingly, in 22q11.2DS, only patients with schizophrenia displayed mitochondrial hypofunction, whereas patients without schizophrenia showed regular ATP production[66] and (presumably a compensatory) mitochondrial biogenesis.[66]

Schizophrenia Risk Genes in 22q11.2 Region

Here we focus on gene products associated with schizophrenia risk, which are located in the 22q11.2 region and have been confirmed to be present in mitochondria (SLC25A1, TXNRD2, MRPL40, PRODH, and COMT). Next, we review gene products that have been shown to have an impact on mitochondrial function, albeit likely indirectly (TANGO2, ZDHHC8, UFD1L, and DGCR8).[67–69] For more information on these gene products, please refer to Table 1 and Table 2. In addition to gene products, we summarize current knowledge about the seven non-coding microRNAs (miRs) identified in the 22q11.2 region and miRs dysregulated by *DGCR8* haploinsufficiency. In each case, we summarize and evaluate the gene's link to schizophrenia. Due to the availability of targeted genetic manipulations, most evidence comes from genetically modified animal models.[70–72]

22q11.2DS Risk Genes Localized Within Mitochondria

SLC25A1 encodes solute carrier family 25 member 1 (SLC25A1), a mitochondrial tricarboxylate transport protein that regulates the movement of citrate across the inner mitochondrial membrane in exchange for cytoplasmic malate (figure 1A). Two functions of SLC25A1 are especially relevant to fatty acid metabolism and metabolism of 2-hydroxyglutarate: First, mitochondrial efflux of citrate is a prerequisite for fatty acid and cholesterol synthesis.[73] Second, altered citrate efflux disrupts CAC activity and elevates 2-hydroxyglutarate levels, resulting in 2-hydroxyglutaric aciduria.[74] In the brain, altered 2-hydroxyglutarate levels can disrupt the astrocytic intermediary metabolism and neurotransmitter synthesis and even cause neuronal death.[75] Patients with *SLC25A1* mutations show neurological symptoms ranging from seizures and developmental delay to encephalopathy.[76,77] Children with *SLC25A1* haploinsufficiency (due to 22q11.2DS) show metabolic defects that involve a shift from OXPHOS to glycolysis, accompanied by increased reductive carboxylation of alpha-ketoglutarate.[65] Metabolic alterations observed in these children were accompanied by increased signaling by hypoxia-inducible factor 1 alpha (HIF-1α) and Myc.[65] HIF-1α is, besides the involvement in the shift to anaerobic metabolism (ie, glycolysis), implicated in neovascularization, angiogenesis, and cell survival (reviewed in[78]). In contrast, Myc is responsible for growth control, differentiation, and apoptosis.[79] Lastly, SLC25A1 haploinsufficiency was associated with disrupted calcium homeostasis in 22q11.2DS

Table 1. List of Gene Products Localized Within Mitochondria

Gene	HumanGeneID	MouseGeneID	Full Name	SLR	Function	Sub-compartment	Expression
SLC25A1	6576	13358	Solute carrier family 25 member 1	A-B	Metabolism > Carbohydrate metabolism > Gluconeogenesis Metabolism > Carbohydrate metabolism > CAC-associated Metabolism > lipid metabolism Small molecule transport > SLC25A1 family	MIM	cerebrum, cerebellum, brainstem, spinal cord
TXNRD2	10587	26462	Thioredoxin reductase 2	A-B	Metabolism > Detoxification > ROS and glutathione metabolism Metabolism > Detoxification > Selenoproteins	Matrix	Cerebrum, spinal cord
MRPL40	64976	18100	Mitohondrial ribosomal protein L40	A-B	Mitochondrial central dogma > translation > mitochondrial ribosome	Matrix	cerebrum, cerebellum, brainstem, spinal cord
PRODH	5625	19125	Proline dehydrogenase	A-B	metabolism > AA metabolism > proline metabolism > electron carriers > Q-linked reactions	MIM	cerebrum, cerebellum, brainstem, spinal cord
COMT	1312	12846	Catechol-O-methyl-transferase	A-B	Metabolism > Amino acid metabolism > catechol metabolism	Membrane	identified in liver mito

Note: MIM, Mitochondrial Inner Membrane.

Table 2. List of Gene Products Localized Outside Mitochondria

Gene	HumanGeneID	MouseGeneID	Full name	SLR	Function	Compartment	Tissue:
TANGO2	128989	27883	Transport and Golgi Organization Homolog 2	A-B	secretory protein loading in the ER	Cytoplasm	brain, cortex, cerebellum, spinal cord
ZDHHC8	29801	27801	Zinc-finger DHHC-type Palmitoyltransferase 8	A-B	Protein import, sorting and homeostasis > palmitoylation glutamatergic transmission > ABCA1 Predicted function in dopamine DRD2 regulation	GA Membranes MT Membranes Cytoplasm	brain, cortex, cerebellum, spinal cord
UFD1L	7353	22230	Ubiquitin Recognition Factor in ER associated degradation 1	A-B	Protein import, sorting and homeostasis > degaradation of ubiquitinated proteins	Cytoplasm ER Nucleus	brain, cortex, cerebellum, spinal cord
DGCR8	54487	94224	Dgcr8 Microprocessor Complex Subunit	A-B	Cellular central dogma > miR biogenesis > pre-miR processing	Nucleus Cytoplasm	brain, cortex, cerebellum, spinal cord

Note: ER, Endoplasmic Reticulum; GA, Golgi Apparatus.

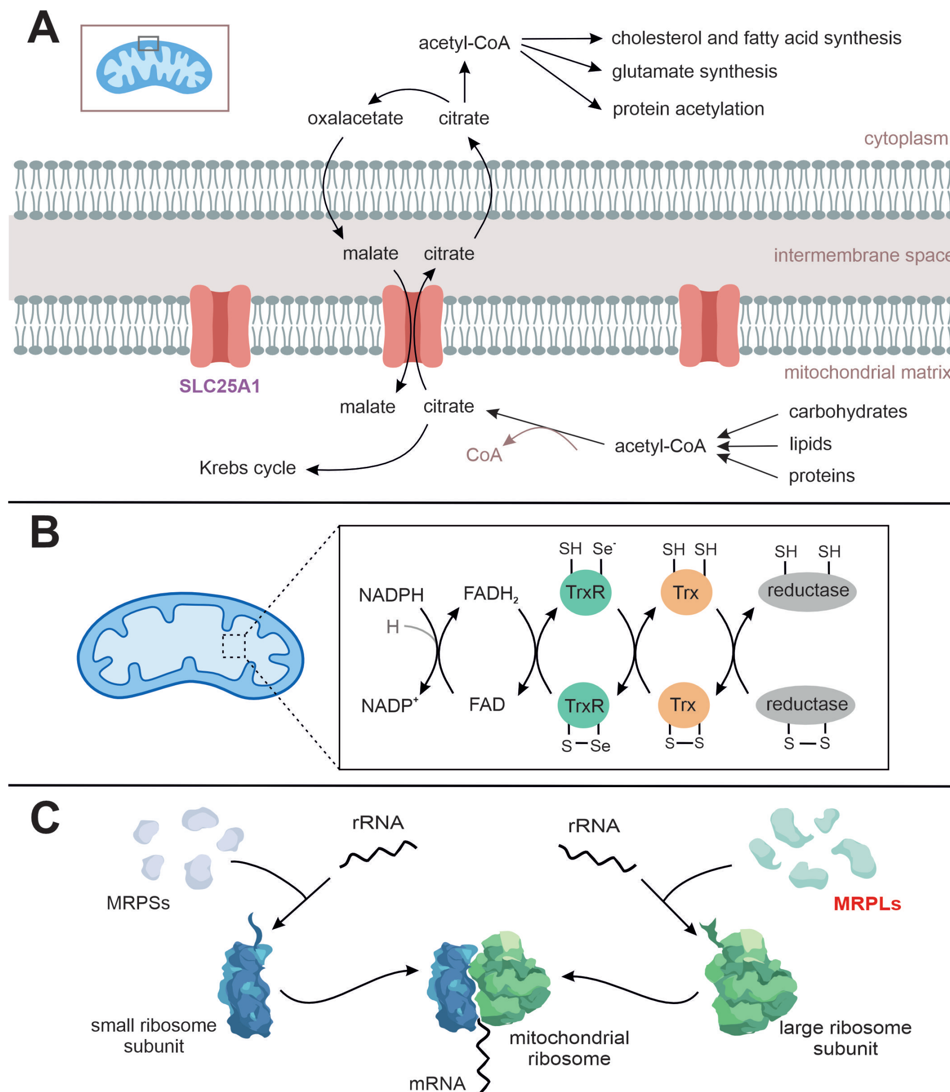

Fig. 1. Illustrative function of haploinsufficient gene products of 22q11.2DS in brain mitochondria. (A) SLC25A1 is a citrate/malate exchanger situated in the inner mitochondrial membrane. It functions in cytoplasm-mitochondria metabolic pathways encompassing all primary macronutrients. (B) TXNRD2 is one of the major components of the mitochondrial antioxidant pool, utilizing thioredoxin molecules for reactive oxygen species elimination. Thioredoxin becomes oxidized during the reduction of peroxiredoxins, ribonucleotide translocase, methionine sulfoxide reductase, and protein disulphides.[82] (C) MRPLs are essential building elements of the large subunit mitoribosome that regulate the translation of mitochondrial DNA-encoded genes. Mitochondrial ribosome synthesizes hydrophobic membrane proteins encoded by mtDNA, several of which (eg, COX1-3) are subunits of ETC.

and mouse models, presumably caused by impaired function of SLC25A1-SLC25A4 mitochondrial transporter interactome.[80] Components of SLC25A1-SLC25A4 interactome were also altered in idiopathic schizophrenia patients, indicating a common mechanism in schizophrenia etiology.[80] Moreover, dopaminergic neurons induced from isolated 22q11.2DS fibroblasts showed a significant reduction of mitochondria-associated membrane sites, which facilitate lipid molecules and calcium transport between mitochondria and endoplasmic reticulum,[81] which indicates fatty acid degradation by mitochondria may be disrupted in these neurons. In summary, SLC25A1 is a major energetic regulator affecting multiple levels of cellular homeostasis, from fatty acid and cholesterol metabolism, CAC turnover, and calcium homeostasis to ATP synthesis.

TXNRD2 encodes thioredoxin reductase 2, which participates in ROS detoxification by maintaining a steady level of reduced thioredoxin (figure 1B).[83] TXNRD2 then utilizes electrons from nicotinamide adenine dinucleotide phosphate to reduce the oxidized thioredoxin to its reduced form.[82] The human TXNRD2 is located within mitochondria, where it controls ROS levels and regulates mitochondrial matrix homeostasis. The haploinsufficiency of *TXNRD2* results in increased oxidative damage in the expressing neurons, which leads to the impaired formation of long-range axonal projections.[84] Furthermore, *TXNRD2* haploinsufficiency leads to the

abnormal shape of the mitochondria, suggesting possible functional damage to these organelles.[84] Both oxidative damage and abnormal mitochondrial shape are specific to Txnrd2-expressing cortical pyramidal neurons in layer 2/3.[84] Layer 2/3 pyramidal neurons emit long-range projections to other cortical areas and therefore have higher energy demands.[84] As a result, *Txnrd2*-haploinsufficient mice show decreased cortico-cortical connectivity.[84] Antioxidant treatment with N-acetylcysteine restores deficits in both connectivity and mitochondrial morphology in LgDel 22q11.2DS mouse model.[84] Of note, *TXNRD1,* a cytoplasmic analog, was associated with schizophrenia in 2-stage genome-wide association study concentrated on genes expressed in Central Nervous System (CNS) neurons.[85] *In* summary, *TXNRD2* encodes a protein essential for antioxidant defense; the insufficient function of this gene leads to oxidative damage with downstream consequences for neuronal activity and connectivity relevant to schizophrenia.

MRPL40 encodes mitochondrial ribosomal protein L40 (Mrpl40), a member of the polypeptide tunnel-exit of the large subunit of the mitochondrial ribosome (figure 1C). As illustrated by IPSCs studies, *MRPL40* hemizygosity hinders mitochondrial protein synthesis in principal neurons and, as a result, indirectly lowers complex I and IV activity and ATP levels.[33] MRPL40 also affects synaptic plasticity by disrupting intracellular calcium homeostasis in mice.[86] Additionally, the Mrpl40 haploinsufficiency impairs the mitochondrial permeability transition pore, resulting in enhanced calcium transients in the mitochondrial matrix and cytoplasm during high-frequency activity, eventually leading to enhanced synaptic vesicle release in presynaptic terminals.[86] Calcium interacts with the cytoskeleton and thus regulates the development of axons and dendrites and synaptic plasticity.[87,88] The altered synapse development and function observed in Mrpl40 haploinsufficiency well fit the disconnection hypothesis, which proposes that aberrant functional connectivity is the proximal cause of psychiatric symptoms.[89,90] In summary, Mrpl40 affects mitochondrial function by regulating the synthesis of proteins that affect OXPHOS and proteins that affect calcium transfer across the mitochondrial membrane.

PRODH encodes mitochondrial proline dehydrogenase which catalyzes the first rate-limiting step in proline degradation (figure 2A). Two aspects of proline degradation are relevant to neuronal metabolism: energy production and Gamma-aminobutyric acid (GABA) and glutamate synthesis. First, the proline degradation yields two electrons that can be utilized in the ETC to produce ATP but may be alternatively expended in ROS production. Second, the intermediate product of proline degradation, pyrroline-5-carboxylate, can be converted by the pyrroline-5-carboxylate dehydrogenase into glutamate (figure 2A). The metabolic link between proline and glutamate metabolism reportedly plays a prominent role in normal brain function.[91,92] Therefore, *PRODH*

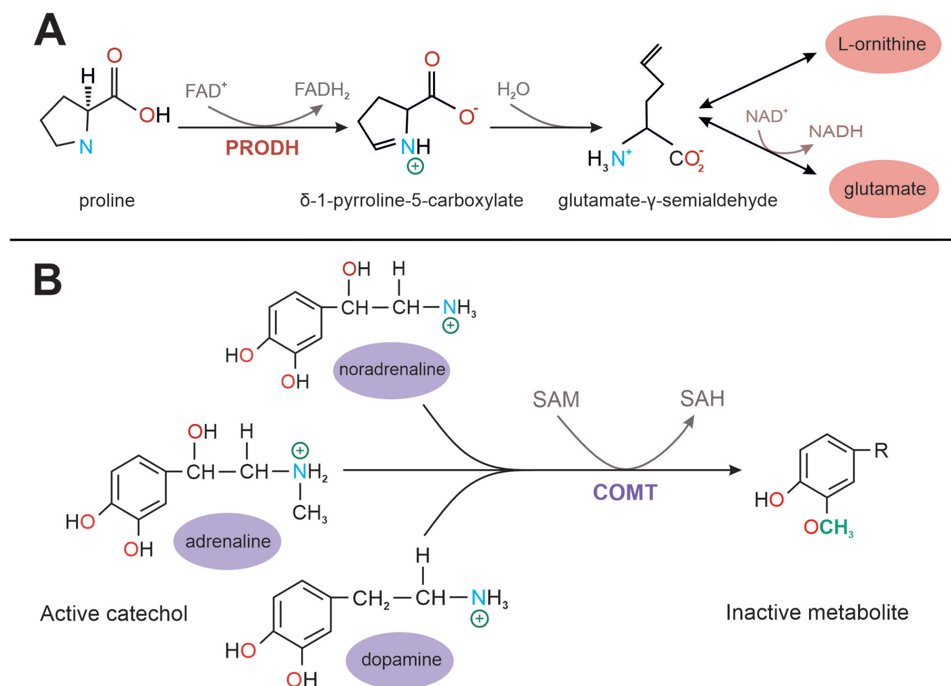

Fig. 2. Illustrative function of haploinsufficient gene products of 22q11.2DS in brain mitochondria. (A) PRODH haploinsufficiency in 22q11.2DS could lead to a d-1-pyrroline-5-carboxylate concentration switch, affecting L-glutamate synthesis and NADH/NAD+ and FADH2/FAD+ ratios. (B) COMT role in the inactivation of various catechols (SAH – S-Adenosyl-L-Homocysteine; SAM – S-Adenosylmethionine).

haploinsufficiency may lead to lower energy levels and reduced glutamate synthesis. Concurrently, insufficient proline degradation may lead to hyperprolinemia, which may negatively affect a wide range of cellular systems, including energy metabolism, protective mechanisms against excitotoxicity, and oxidative stress management.[93] Moreover, cytoplasmic proline elevation coheres with GABA synthesis inhibition through competitive inhibition of glutamate decarboxylase leading to synaptic dysfunction.[94] On the behavioral level, *Prodh*-deficient mice show sensorimotor-gating deficits,[95] one of the most common hallmarks of schizophrenia.[96] In humans, proline dehydrogenase insufficiency was identified as a risk factor for schizophrenia[97,98] and schizoaffective disorders,[99] and hyperprolinemia was associated with neurological symptoms and brain abnormalities.[100,101] In summary, PRODH haploinsufficiency may alter glutamate levels, affect energy metabolism via CAC intermediary metabolism alteration and lead to sensorimotor gating deficits.

COMT encodes a key enzyme for catecholamine and estrogen degradation (see figure 2B).[102,103] COMT-deficient mice display increased dopamine levels in the prefrontal cortex.[104] Furthermore, COMT activity can be affected by gene polymorphism; Val158Met substitution (rs4680) leads to 30% decrease in COMT activity and buildup of dopamine in the prefrontal cortex.[105] The effect of this polymorphism on the development of psychosis; however, remains controversial, with contradictory reports in the literature.[106–108] Haploinsufficiency of COMT in 22q11.2DS results in disrupted dopaminergic neurotransmission,[109–111] which may exacerbate the vulnerability for psychosis.[112] In terms of 22q11.2DS pathophysiology, it is important to mention epistatic interaction between COMT and PRODH. PRODH-deficient mice display upregulation of COMT, likely as a compensatory mechanism for PRODH deficiency.[113] Besides, the breakdown of catecholamines is also realized by mt-membrane bound monoamino oxidase (MAO-A, MAO-B), one of the resources of H_2O_2.[114,115]

22q11.2DS Risk Gene Products Localized Outside Mitochondria

TANGO2 encodes the Transport and Golgi Organization 2 Homolog protein (TANGO2) involved in Golgi complex organization and function[116] and mitochondrial physiology (figure 3A).[117] TANGO2 deficiency leads to disturbances in mitochondrial physiology and fatty and amino acid metabolism: It decreases mitochondrial carnitine/acylcarnitine carrier protein concentration,[118] reduces palmitate-[119] and oleate-induced β-oxidation and enhances superoxide production.[120] The symptoms of TANGO2-related disease, an autosomal-recessive disorder caused by *TANGO2* mutation, manifest in early childhood and include episodic metabolic crises with encephalo-cardiomyopathies, severe neurodevelopmental delay, and metabolic derangements.[119,121] The metabolic crises in TANGO2-related disease are associated with reduced mitochondrial ETC complex II activity.[121] In adults, a deficiency of TANGO2 protein is associated with cognitive decline[118] but not with the development of schizophrenia. While *TANGO2* mutation is not directly associated with increased schizophrenia risk, it may exacerbate mitochondrial damage in 22q11DS as it likely increases oxidative stress.

ZDHHC8 encodes a transmembrane zinc finger DHHC-type palmitoyl transferase 8 (ZDHHC8; figure 3B). ZDHHC8 catalyzes S-palmitoylation, a posttranslational modification during which palmitic acid is reversibly attached to cysteine residues of the substrate, which affects the trafficking and function of the protein.[123] ZDHHC8 is, directly or indirectly, involved in cholesterol transport, synaptic function, nitric oxide synthesis, and OXPHOS. First, one of the substrate proteins of ZDHHC8 is ATP-binding cassette sub-family A member 1 (ABCA1), a key regulator of cellular cholesterol export.[124] The loss of ABCA1 function increases esterified-cholesterol uptake from plasma into the brain[125] Second, ZDHHC8 may directly influence synaptic function as multiple targets of zDHHC8 within the synapse have been identified, such as cdc42[126] and PICK1[127] (see[128]). Alternatively, ZDHHC8 may influence synaptic ultrastructure indirectly, as loss of ABCA1 function reduces the number of synapses and synaptic vesicles.[125] Third, ZDHHC8 incorporates palmitate molecules into endothelial nitric oxide synthase (eNOS), thus governing the NOS localization and function in human endothelial cells.[129] Besides neuronal NOS and inducible NOS, endothelial NOS has been implicated in neurotransmission, neurotoxicity, immune function, and regulation of blood vessel tone.[130,131] Additionally to impaired vessel regulation, 22q11.2DS mouse model displayed blood-brain barrier dysfunction and neuroimmune vascular activation.[132] Concurrently, NO levels in the cerebellum, the hypothalamus, the hippocampus, and the striatum are significantly altered in schizophrenia patients (reviewed in[133]). Fourth, ZDHHC8 interacts with one of the components of mitochondrial complex III, cytochrome b-c1 complex subunit 1,[122] possibly affecting the function of complex III in the process. *ZDHHC8* haploinsufficiency in mice produced brain changes relevant to schizophrenia: ZDHHC8 deficiency reduced short and long-range connectivity and caused working memory deficits.[134] In summary, the impaired function of ZDHHC8 may negatively affect synaptic function, cholesterol transport, and NO synthesis. ZDHHC8 may also play a role in energy synthesis, as it interacts with proteins involved in OXPHOS.

UFD1L encodes the ubiquitin recognition factor in ER-associated degradation (UFD1) protein that forms a complex with nuclear protein localization-4 and valosin-containing protein (DOA1-CDC48-UFD1-NPL4

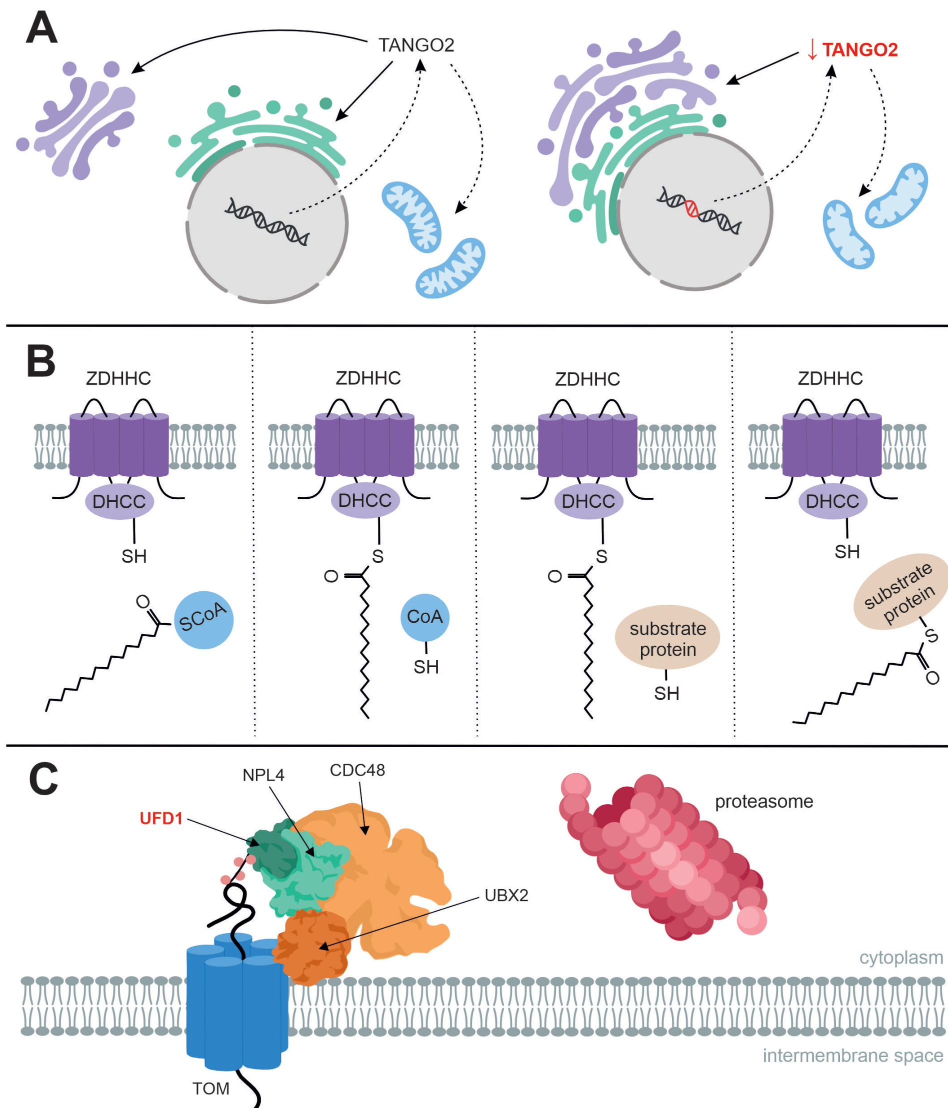

Fig. 3. Illustrative function of haploinsufficient gene products of 22q11.2DS outside brain mitochondria. (A) TANGO2 haploinsufficiency was reported to cause linked cisternae of the ER with Golgi complex together with altered mitochondrial cristae membrane dynamics. (B) ZDHHC8 is a transmembrane enzyme catalyzing S-palmitoylation of proteins such as ABCA1, eNOS, and a component of mitochondrial electron transport chain complex III.[122] (C) UFD1 serves in mitochondria-associated degradation of misfolded and damaged mitochondrial proteins that could negatively affect mitochondrial function.

complex) (figure 2A). As part of the ubiquitin-proteasome system, this complex is involved in the mitochondria-associated degradation of ubiquitinated proteins in cell mitosis.[135] Besides that, the ubiquitin-proteasome system regulates mitochondrial function and efficiency: For example, it safeguards substrate entry into the mitochondria, mediates the fusion control mechanism, and controls mitophagy.[136] Notably, UFD1 is also a component of the UFD1-containing complex located at ER-mitochondria contact sites; this complex is crucial for the canonical PINK1/PARKIN pathway, which protects the cells from mitochondrial-stress-induced dysfunction.[137] In summary, UFD1L haploinsufficiency may lead to the inefficiency of the proteasome system and mitophagy, accumulation of misfolded or damaged proteins and weakened protection from mitochondrial-stress-induced dysfunction.

DGCR8 encodes the microprocessor complex subunit, which mediates the biogenesis of miRs from the primary miRs transcript (Summarized in figure 4). The microprocessor complex subunit is a double-stranded RNA binding protein that functions as a non-catalytic subunit of the microprocessor complex, which is required for binding the double-stranded RNA substrate and facilitates cleavage of the RNA by Drosha, the ribonuclease III protein.[138] The compromised capability of miR processing and expression affects other cellular functions. One of the genes whose expression is altered

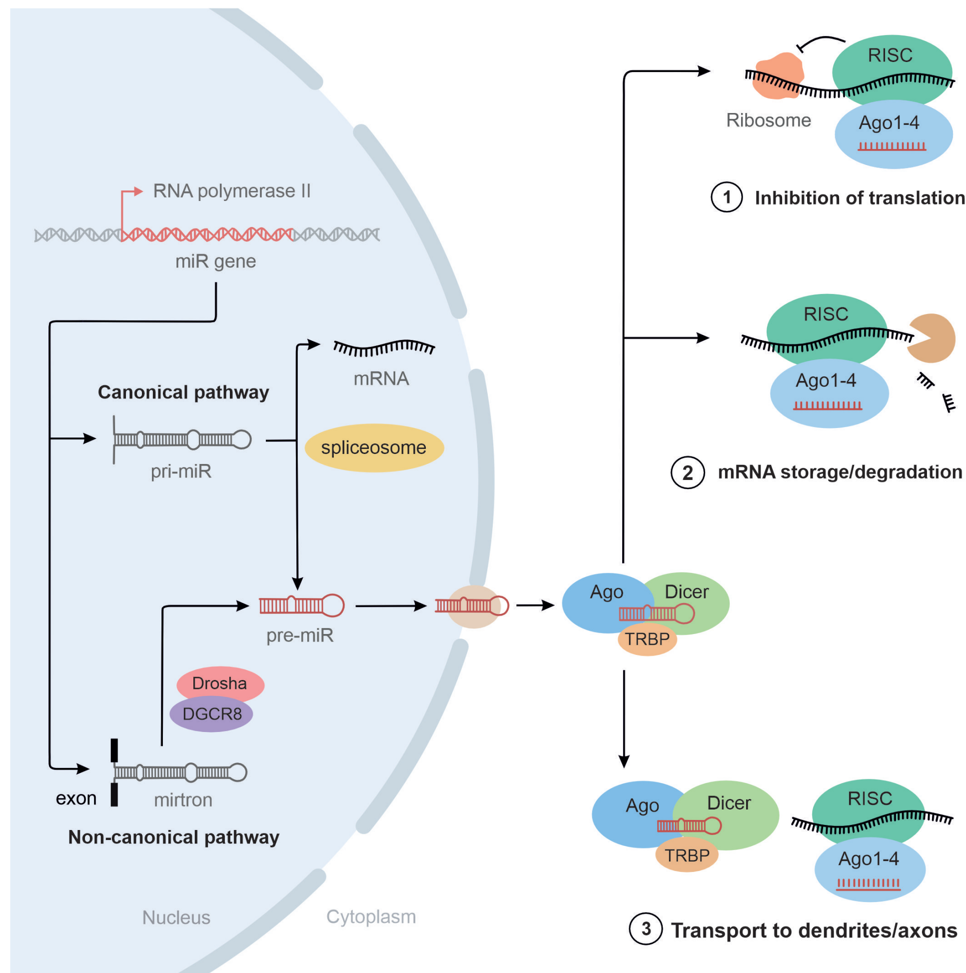

Fig. 4. *DGCR8 function and miR biogenesis.* MiRs control the expression of their target genes by binding to target sites in mRNAs. Each miR usually regulates up to several hundred mRNAs. However, one mRNA can be regulated via multiple miRs in a synergic fashion. The biogenesis of miR molecules is initiated in the nucleus. First, the primary transcript is processed via the Drosha-DGCR8 complex (the canonical pathway) or spliceosome (non-canonical pathway) into pre-miRNA. Next, pre-miR molecules are transported to the cytoplasm via Exportin 5 situated in the nuclear envelope. In the cytoplasm, pre-miR conversion to miR duplex is mediated by Dicer-TRBP or Ago2. While one duplex strand is degraded, the other becomes a mature miR. The mature miR represses translation (1), induces mRNA degradation (2) or is transported to dendrites and axons (3).

following DGCR8 dysfunction is SERCA2. Specifically, the reduced capability of the microprocessor complex subunit depletes downstream miR185 and miR25[139] responsible for SERCA2 translation downregulation inducing changes in cytoplasmic calcium. Concurrently, the abnormal increase of SERCA2 was observed in the hippocampus of non-22q11.2DS schizophrenic patients.[139] However, although SERCA2 level was identified as a possible risk factor for schizophrenia, it was suggested that the elevated risk of schizophrenia is associated with decreased SERCA2 levels.[140] The impact of SERCA2 on schizophrenia phenotype, therefore, has yet to be elucidated. Changes in the function of other miRs bound by microprocessor complex subunit were not yet reported. The impairment of the microprocessor complex subunit appears relevant to 22q11.2DS-associated and idiopathic schizophrenia. Reduced expression of *Dgcr8* was observed in the *post-* brain tissue of non-22q11.2DS schizophrenia patients.[141] The dosage decrease in *Dgcr8* gene output was suggested to explain the Two-hit model of schizophrenia in 22q11.2DS.[142] In *Dgcr8* haploinsufficient mice (*Dgcr8*$^{+/-}$), the dopamine D2 receptor is downregulated in the brain regions implicated in schizophrenia.[143,144] *Dgcr8*$^{+/-}$ mice also show increased expression of the D1 receptor in motile cilia on ependymal cells lining the lateral and the third ventricle of the brain, leading to ventricle enlargement,[145] a feature commonly reported in schizophrenia patients.[146]

Regarding morphological and functional changes, *Dgcr8*$^{+/-}$ mice show synaptic deficits and altered synaptic plasticity, decreased number of neurons in cortical layers 2–4, and impaired function and connectivity in the prefrontal cortex.[147,148] In the 22q11.2DS mouse model, the microprocessor complex subunit was shown

to regulate the chemokine receptor 4/chemokine ligand 12 pathway indispensable for the migration of interneurons.[149] More recently, *Dgcr8* was suggested to be a driver gene for frontal, parietal, temporal, and occipital lobe development during the late fetal period.[150] Decreased *DGCR8* expression causes reduced expression of pre-mir-9-2, which was, despite being located outside the 22q11.2 region, previously associated with an elevated risk of schizophrenia.[151,152] In summary, DGCR8 haploinsufficiency may dysregulate miR biosynthesis inside and outside the 22q11.2 locus. As miRs are essential modulators of gene expression, their dysregulation may affect mitochondrial function, energy metabolism, and calcium retention capacity in tissue- and time-specific manner.

MicroRNA Genes Situated Within the 22q11.2 Region

The importance of miRs in brain maturation, development, and function is being increasingly understood. MiRs are expressed in a tissue-specific manner during distinct phases of development and are thought to act as vital regulatory factors. The system of miRs and genes is complexly intertwined: Each miR has the potential to manipulate the expression of hundreds of target genes, while simultaneously, each miR´s expression may be regulated by numerous other genes. As a result, the miR stability and translation are much more difficult to trace than that of the typical transcription factors and signal transducing molecules.[153,154] MiRs are generally transcribed in the nucleus and transported to the cytoplasm; however, evidence suggests that miRs are present in or associated with other organelles, such as the endoplasmic reticulum, processing bodies, exosomes, and mitochondria (reviewed in[138,155]). Similarly, both miR-processing proteins, Argonaute and Dicer, have been identified in mitochondria.[156,157] The relationship between miR activity and mitochondria function seems to be reciprocal[157] as mitochondrial tethering of the endoplasmic reticulum regulates AGO2 trafficking, which acts as a rate-limiting step in miR biogenesis in mammalian cells.[158]

Seven miR coding genes have been identified in homo sapiens 22q11.2 locus so far: miR4761, miR185, miR3618, miR1306, miR6816, miR1286, and miR649.[159,160] These miRs may directly influence metabolism and mitochondrial function on various levels; the currently known list of miRs encoded in the human 22q11.2 region is summarized in supplementary table 1, together with their mouse orthologs (if available) and predicted gene targets (predictability ≥ 90%; based on mirdb.org;[161]). The major changes in energy metabolism induced by haploinsufficiency of miRs in 22q11.2DS are extracted in table 3.

Genetic Interactions Within Mitochondrial Genes in 22q11.2DS

22q11.2DS patients and models display changes directly or indirectly related to mitochondrial function. At present, altered calcium homeostasis, changes in energy metabolism, and increased oxidative stress were most often described in relation to mitochondria-related genes in the 22q11.2 region. Albeit it is unknown to what extent, some of the changes in mitochondrial physiology may be attributed to the genetic interactions of haploinsufficient genes.

Abnormalities in calcium signaling and homeostasis in 22q11.2DS may arise from several potential mechanisms. First, the elevation of SERCA 2 (via *DGCR8*) may limit cellular calcium distribution and storage capacities. Second, the impaired function of mitochondrial transition pores (via *MRPL40*) together with reduced SLC25A1-A4 interactome (via *SLC25A1*) could incapacitate mitochondrial calcium proficiency. Moreover, MRPL40 and SLC25A1 interaction is necessary for mitochondrial ribosomal integrity and proteostasis.[162] Third, altered energy metabolism (see below) may affect the efficacy of several ion pumps and, consequently, membrane potentials. All of these mechanisms may exacerbate mitochondrial calcium overload, potentially leading to mitochondrial fragmentation and cell death.

In 22q11.2DS, a shift in energy metabolism towards less efficient, mitochondria-independent glycolysis is associated with decreased OXPHOS rates, reduced CAC turnover, and lowered ATP levels. The basis of these changes likely lies in several factors. Firstly, the synthesis of mtDNA-encoded proteins (via *MRPL40*), many of

Table 3. MicroRNA Molecules Situated Within 22q11.2 Locus. Standardized Gene Abbreviations are Used. Locus 22q11.21 Contains Four Low Copy Repeats, Often Consecutively Termed LCR22A-D

microRNA	LCR22	Assumed Function of Target Genes (Target Gene)
miR4761	A-B	fatty acid metabolism (FAR2)
miR185	A-B	calcium homeostasis (calsequestrin, SERCA2); metabolic signaling (PKCA, HIF1AN)
miR3618	A-B	changes in ATP/ADP ratios (adenylate kinase)
miR1306	A-B	pyruvate metabolism (PDHA1); altered phosphatidylethanolamine/choline levels (PHOSPHO1)
miR6816	A-B	
miR1286	A-B	ATP transport across mitochondrial membrane (VDAC3); mitochondrial distribution within the cell (DRP1)
miR649	B-D / C-D	oxoglutarate/succinate ratios (P3H2); mitochondrial protein levels (Mrpl42)

which are directly involved in OXPHOS and ETC, is limited. Secondly, the decreased expression of *TANGO2* and *ZDHHC8*, whose products interact with cristae morphology and the components of ETC, respectively, may also contribute to lower OXPHOS rates. Thirdly, altered CAC metabolism (via *PRODH*) may hinder proline turnover, further limiting OXPHOS rates. Fourthly, dysregulated miR systems (via *DGCR8* and *miR1286*) and reduced ATP production capacities due to OXPHOS limits (exacerbated also by insufficient antioxidant capacity—see below) may limit mitochondrial-cytoplasm ATP turnover. Finally, enhanced MYC/HIF1α signaling (via *SLC25A1* and *miR1286*) may promote a metabolic shift toward less efficient ATP-yielding glycolysis to ensure sustenance of vital functions.

Mitochondria represent a crucial and tightly regulated cellular antioxidant pool, so the increased oxidative stress observed in 22q11.2DS patients and models may stem from several factors. For instance, the reduced mitochondrial antioxidant capacity (via *TXNRD2*) with eNOS malfunction (via *ZDHHC8*) could limit the ability of mitochondria to buffer radical species affecting long-range connectivity and synaptic function.[84,122] Next, increased generation of radicals by MAO (via *COMT* and *PRODH*) may exacerbate oxidative stress. Finally, the diminished ability of mitochondria efficiency to buffer radical species production coupled with enhanced radical production may affect individual OXPHOS complexes (vulnerable to radical damage) and contribute to altered CAC (dependent on OXPHOS rates), ATP levels and calcium buffering and homeostasis.

Conclusions

Mitochondria, in addition to their well-established role in energy metabolism, coordinate diverse vital cellular processes. Changes in mitochondrial physiology could directly lead to or aggravate the pathological changes in mitochondria (ie, shape, number, and fragmentation) of schizophrenia patients. Dysregulated fusion and fission processes may restrict mitochondrial capacity to maintain ion and metabolic homeostasis; for example, mitochondria may be unable to reach the physiological level of total daily metabolic rate that would affect both, cellular calcium buffer capacity and radical generation control. As a result, the viability of neurons may be negatively affected, further disrupting associated processes such as brain development or neuronal network function.

Because 22q11.2DS is a significant yet insufficient risk factor for schizophrenia, it is plausible that the observed mitochondrial dysfunction in 22q11.2DS reduces an individual's resilience to schizophrenia. When combined with other risk genes (ie, reaching a genetic burden threshold) or adverse environmental factors that increase schizophrenia risk (such as prenatal inflammation or drug abuse), 22q11.2DS may contribute directly to cellular and brain network pathologies observed in schizophrenia, as described above. Furthermore, the changes in mitochondrial function and morphology are likely not exclusive to gene deletion and may occur in other genetic or environmental contexts (ie, allelic variants, gene dosage, etc.), further underscoring the importance of understanding the role of mitochondria in schizophrenia pathogenesis. Polygenic risk factors outside 22q11.2 appear to play an important role in schizophrenia susceptibility, as it was shown that the same genes contribute to development of schizophrenia in both 22q11.2DS and in the general population.[163] Determining which genetic environment renders neuronal populations vulnerable to mitochondrial damage is crucial not only for understanding the 22q11.2DS but also for the interplay between genes and phenotypes of psychiatric disorders.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin.

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Authors Contribution

DKo – conceptualization of the first draft, supervision, data research, writing – original draft, writing – review and editing, the conceptualization of all visuals and graphics, corresponding author; BK - data research; writing – review and editing; LK – conceptualization of the first draft, writing – review, and editing of the final draft; DKu – visualization and graphics, writing – major review and editing the final form; KV – resources, supervision, editing of the final draft; HB – conceptualization of the first draft, resources, supervision, research, writing – original draft, writing – review, and editing.

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