frontiers in Psychiatry

ORIGINAL RESEARCH
published: 10 March 2021
doi: 10.3389/fpsyt.2020.556803

Tourette Syndrome Risk Genes Regulate Mitochondrial Dynamics, Structure, and Function

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Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder characterized by motor and vocal tics with an estimated prevalence of 1% in children and adolescents. GTS has high rates of inheritance with many rare mutations identified. Apart from the role of the neurexin trans-synaptic connexus (NTSC) little has been confirmed regarding the molecular basis of GTS. The NTSC pathway regulates neuronal circuitry development, synaptic connectivity and neurotransmission. In this study we integrate GTS mutations into mitochondrial pathways that also regulate neuronal circuitry development, synaptic connectivity and neurotransmission. Many deleterious mutations in GTS occur in genes with complementary and consecutive roles in mitochondrial dynamics, structure and function (MDSF) pathways. These genes include those involved in mitochondrial transport (*NDE1*, *DISC1, OPA1*), mitochondrial fusion (*OPA1*), fission (*ADCY2*, *DGKB, AMPK/PKA, RCAN1, PKC*), mitochondrial metabolic and bio-energetic optimization (*IMMP2L*, *MPV17, MRPL3, MRPL44*). This study is the first to develop and describe an integrated mitochondrial pathway in the pathogenesis of GTS. The evidence from this study and our earlier modeling of GTS molecular pathways provides compounding support for a GTS deficit in mitochondrial supply affecting neurotransmission.

Keywords: Tourette syndrome genes, Tourette syndrome cause, Tourette syndrome etiology, mitochondrial fission, mitochondrial supply

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Child and Adolescent Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *28 April 2020*
Accepted: *23 November 2020*
Published: *10 March 2021*

Citation:
Clarke RA, Furlong TM and Eapen V (2021) Tourette Syndrome Risk Genes Regulate Mitochondrial Dynamics, Structure, and Function. Front. Psychiatry 11:556803. doi: 10.3389/fpsyt.2020.556803

INTRODUCTION

Gilles de la Tourette Syndrome (GTS) is a neurodevelopmental disorder with an estimated prevalence of 1% in children and adolescents (1). Neuroanatomical evidence suggests that GTS pathology is related to abnormal brain development and the physiological involvement of the cortico–striato–thalamo– cortical (CSTC) circuitry connecting the cortex, basal ganglia and thalamus (1). Clinical evidence further suggests the involvement of neurotransmitters such as dopamine, glutamate and γ-aminobutyric acid (GABA) (1). Epidemiological, phenomenological and genetic evidence demonstrate broad overlap between GTS and autism spectrum disorder (ASD) (2, 3) with both exhibiting high incidence in first-degree relatives, high monozygotic to dizygotic concordance (4), and with both conditions beginning during childhood with a high male preponderance. Furthermore, GTS and ASD share associated clinical features of compulsive behaviors, obsessions, involuntary movements (tics in GTS and stereotypies in ASD), poor speech control and echolalia common in both conditions (5). Attention deficit hyperactivity disorder (ADHD) is also present in both ASD and GTS (5, 6). GTS is over represented in ASD, with 5% having GTS and up to 40% experiencing tics (5). Similarly, the rate of autism in GTS exceeds

that expected by chance, with reports of ASD in around 22.8% of children and 8.7% in adults (7), subclinical autistic symptoms occurring in a third of GTS populations, and a further two-thirds showing social deficits relating to the autism spectrum (8). Pharmaco-therapeutic agents such as the α2-adrenergic agonists Clonidine and Guanfacine and the antipsychotics such as Risperidone and Aripiprazole are usually the first-line of therapy for moderate to severe GTS. However, side effects are particularly problematic during childhood years when the symptoms are most predominant and often affect compliance and hence there is a critical need for targeted therapeutic development based on a better understanding of the genetic etiology of the disorder.

GTS is one of the most heritable neuropsychiatric disorders of non-Mendelian inheritance, however, with the exception of the neurexin trans-synaptic connexus (NTSC) little is known regarding the molecular basis of GTS (9). One of the strongest mutation associations to date has been with *neurexin 1* and the genes encoding the NTSC which regulate neuronal circuitry development, synaptic connectivity and neurotransmission (2, 3, 10, 11). Members of the NTSC family of synaptic proteins bind across the synapse in different combinations to facilitate trans-synaptic cell-adhesion that helps establish and maintain neural circuits and neurotransmission within the brain. All major gene families of the NTSC (**Figure 1**) have been repeatedly mutated or otherwise associated with GTS and ASD (2, 11). Moreover, the number of mutations identified in and associated with the NTSC has continued to grow to such an extent that the NTSC now represents a collective mutation hot spot for GTS and ASD (2, 11, 13–22). Moreover, the NTSC model for GTS (**Figure 1**) provides a reliable starting point for further mutation pathway analysis into the mitochondrial regulation of neuronal circuitry development, synaptic connectivity and neurotransmission as it relates to mutations in GTS.

Neuronal Mitochondria: Up to 20% of the total energy consumed by humans at rest is attributable to brain activity despite a brain-to-body mass ratio of only 2% (33, 34). This high energy consumption by the human brain is largely attributed to requirements for synaptic transmission (33, 34). Neurons require particularly large amounts of energy for synaptic vesicle release and to power the ion pumps that restore ion gradients in the synapse following the ion influx associated with neuronal firing (34). These high energy demands are largely met by neuronal mitochondria, which also power other important neurodevelopmental processes including neurite outgrowth (35–40) which ultimately provides for optimal synaptic connections and neurotransmission. Mitochondria have additional roles in the neuron including calcium buffering, which is of particular importance in mitochondrial dynamics and neurotransmission (40). Although mitochondria are essential in almost every cell type, the extended branching structure and specialized function of neurons comes with unique demands over extended distances that render neurons especially sensitive to deficits in mitochondrial dynamics, structure and function. The sensitivity of neuronal development and function to mitochondrial deficiencies is corroborated by the strong association between the mutation of mitochondrial component molecules and neurological disorders (41), and there is increasing evidence that mitochondrial dynamics and dysfunction contribute to neuropsychiatric disorders including Schizophrenia (SCZ) and Bipolar Disorder (42–44).

The higher brain functions affected in neurodevelopmental and psychiatric disorders are thought to require precise spatiotemporal regulation of neuronal circuitry development. In this developmental process the relationship between neuronal outgrowth, synaptogenesis and synaptic transmission is widely appreciated. However, the requirements that these neuro developmental processes have on mitochondria is still emerging. In our pathway analysis, we outline the importance of mitochondrial dynamics, structure and function to neuronal outgrowth and development, synaptogenesis and neurotransmission as the basis for understanding the genetic etiology of GTS.

METHODS

Data Mining and Mutation Pathway Analysis: In this study we integrated the findings from published and unpublished (database) sources including ASD brain gene expression profiling, GTS risk-gene mouse modeling of behavior, genome wide linkage studies, genome wide association studies, chromosomal translocations and copy number variations (CNVs), gene set analysis, haplotype sharing, cell modeling, whole exome sequencing (WES), and whole genome sequencing (WGS) of rare and common deleterious mutations in GTS and ASD (see sources in **Table 1**). In the case where a CNV spanned multiple genes only one gene was selected for inclusion in our pathway analysis (**Table 2**). In these cases, first priority was given to genes that directly regulate those pathways already implicated in GTS (9) including neuronal development (e.g., *SLIT2*), synaptic connectivity (e.g., NTSC pathway genes), synaptic function (e.g., *SAP97*) and neurotransmission (**Figure 1**) (9). Only then was the second priority exercised to assign a pathway to those genes that encode mitochondrial proteins. Following this selection process all mutations, deletions and duplications of mitochondrial protein genes in GTS were included within the mutation pathway analysis thereby eliminating any bias or cherry picking in our development of the first contiguous mitochondrial pathways to GTS (**Figures 2–4**).

RESULTS AND DISCUSSION

Mitochondrial Dynamics: Mitochondrial Transport

To optimize the development and function of neuronal circuitry, mitochondria need to be located at the right place at the right time in sufficient numbers and to be functioning at optimum efficiency. Given that neurons are often hyper-extended with a complex network of axonal and dendritic branches, such optimisation requires the active bidirectional transport of mitochondria to their required destinations along microtubule tracks (39, 86). This may involve long-distance transport of mitochondria from the soma, where the majority of

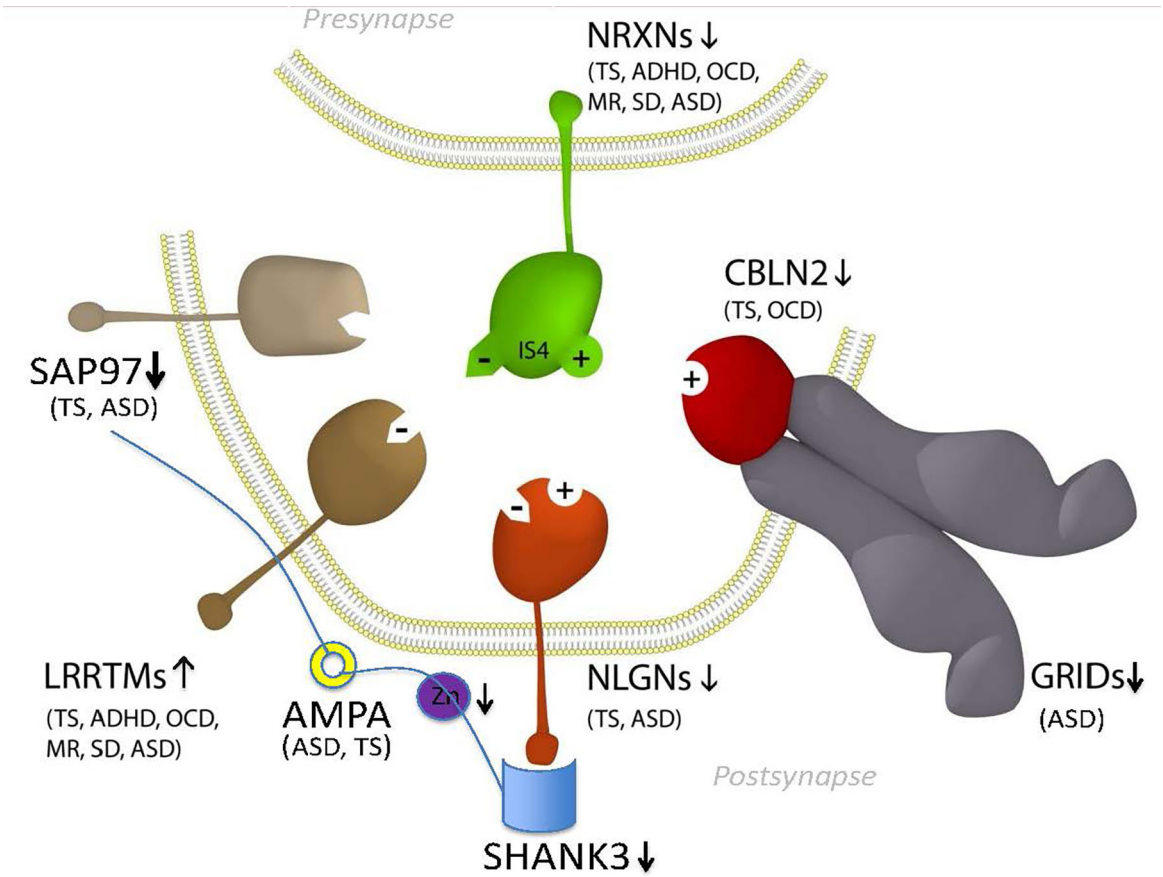

FIGURE 1 | Model NTSC pathway to GTS (2)—implicates the full complement of known neurexins (NRXNs) and their trans-synaptic cell-adhesion ligand gene families through multiple means of enquiry: neuroligins (NLGNs); leucine-rich repeat transmembrane proteins (LRRTMs); cerebellin precursors (CBLNs), Glutamate ionotropic receptor delta type subunit (GRIDS) and the synapse associated proteins (SAPs/DLGs) (2, 11, 12) in addition to the ProSAP proteins that interact in the NTSC postsynaptic signaling pathway (2, 11, 13–24). Presynaptic NRXNs 1-3 form competitive trans-synaptic complexes with postsynaptic ligands NLGNs, LRRTMs and CBLN-GRID complexes in the formation and/or maintenance of neuronal circuitry within the brain. Vertical arrows indicate putative pathogenic dose effects. NRXN1 isoforms with (+) and without (–) the 30 amino-acid insert at splice site 4 (IS4) indicate competitive binding of NRXN1 between its ligands. NRXN4/CNTNAP2 binds across the synapse with SAP97/DLG1 (12, 25). Comorbidities listed are those associated with the gene mutations and copy number variations (CNVs) in ASD and GTS (2, 11, 12, 26–32). Zinc represents one environmental factor important for mitochondrial protein import/processing and function that is also known to affect SHANK3 function (23, 24). Moreover the Zinc transporter ZnT7 has been recurrently linked with GTS in GWAS (2).

mitochondrial biogenesis occurs, to the pre- and post-synaptic termini where demands for mitochondrial homeostasis is highest (39, 86). Mitochondrial transport is also thought to optimize mitochondrial fission, fusion and function (39, 86).

Dynein and Kinesin Motor Proteins

Transport of mitochondria is regulated by the dynein and kinesin motor proteins through their interaction with the microtubule cytoskeleton of the cell (**Figure 2**). The kinesins (KIFs) mediate anterograde mitochondrial transport away from the soma of the neuron while dynein complexes regulate retrograde transport (87). *DNAH6, the dynein axonemal heavy chain* 6 gene implicated in mitochondrial depletion syndrome is mutated in GTS as are *DNAH5* and a number of kinesin genes including *KIF6* and *KIF7* (**Figure 2**) (58). Moreover, *DYNC1H1* which encodes the dynein 1 heavy chain mitochondrial transporter is mutated in ASD and *KIF1A* which encodes the Kinesin 1A mitochondrial transporter is disrupted and duplicated in ASD (18, 20).

KIFs form homo and heteromeric complexes in the regulation of organelle transport including but not limited to mitochondria (88). The importance of the motor proteins, and the microtubule network they travel on, in nervous system development and function is evidenced from their strong association with neurological phenotypes. Mutations in KIF5-family members give rise to a range of dominant negative phenotypes including deficits in mitochondrial transport, structure and function and reduced activity of the electron transport chain (ETC) (89, 90), axonal degeneration and aberrant synaptic transmission (**Figure 2**) (58, 91). GTS mutations have also been identified in genes that regulate tubulin and microtubule dynamics including: duplication of the *TUBB2A* and *TUBB2B* tubulin genes and the mutation of *TUBB3* (58); mutation of the *TTLL1*, *TTLL2,* and *TTLL5* tubulin ligase genes (58); recurrent duplication of the

TABLE 1 | Data sources.

Data type	Author	References
Genome wide linkage studies	Curtis 2004	(45)
	Zhang 2002	(46)
	Verkerk 2006	(12)
	Simonic 1998	(47)
	IMGSAC 1998	(48)
	Barret 1999	(49)
	Shao 2002	(50)
	Shellenberg 2006	(51)
	Maestrini 2010	(52)
	TSAIC 2007	(53)
Genome wide association studies (GWAS)	Suarez-Rama 2015	(54)
	Lintas 2009	(55)
	Philippi 2005	(56)
	Eicher 2015	(57)
Copy number variations (CNVs)	Wang 2018	(58)
	Lintas 2017	(20)
	Malhotra 2012	(59)
	Johnstone 2015	(60)
	Fernandez 2012	(61)
	McGrath 2014	(62)
	Sundaram 2010	(63)
	Clarke 2018	(11)
	Bertelsen 2014	(64)
	Elia 2010	(65)
	Jang 2019	(66)
	Huang 2017	(31)
Whole exome sequencing (WES)	Wang 2018	(58)
	Sundaram 2011	(67)
	Gauthier 2011	(30)
Whole genome sequencing (WGS)	RK CY 2017	(18)
	Turner 2016	(21)
	Leblond 2019	(22)
Gene set analysis	Wittkowski 2014	(68)
	Clarke 2012	(2)
	Wang 2011	(69)
	De Leeuw 2015	(70)
Haplotype sharing	Casey 2012	(71)
Karyotype, LOH Analysis and PCR	Clarke 2018	(11)
	Boghosian-Sell 1996	(72)
	Petek 2001	(73)
	Zhang 2015	(74)
	Patel 2011	(75)
	Robertson 2006	(76)
	Clarke 2009	(25)
	Fang 2017	(11)
ASD brain gene expression profiling	Tang 2013	(77)
	Anitha 2013	(78)
	Anitha 2012	(79)
	Voineagu 2012	(80)
	Schwede 2018	(81)
	Ji L 2012	(82)
	Lintas 2009	(55)
GTS gene mouse modeling and behavior	Shen 2019	(83)
	Lu B 2008	(84)
	Kreilaus 2019	(85)
	Shoen 2019	(23)
Cell modeling	Lam 2019	(27)

microtubule polymerization gene *KANK1* implicated in spastic paraplegia (58, 92); and mutation of the *CAMSAP1* gene that regulates microtubule dynamics and neurite outgrowth (**Table 2** and **Figure 2**) (58, 93).

Mitochondrial Transport Adaptor and Accessory Proteins

Mitochondrial transport provides for the site-specific requirements and function of the neuron (39, 86, 94–97) and it has been demonstrated that mitochondria directly regulate synaptic transmission (94). Furthermore, synapses with mitochondria can sustain repeated cycles of neurotransmitter release whereas the transport of mitochondria either in or out of the synapse dynamically modulates this synaptic strength (95–97). To halt the transport of mitochondria at a required destination such as the synapse requires a braking system. In this respect, synaptic firing renders synapses to be sites of high calcium influx. After synaptic firing the high (Ca^{2+}) acts to halt mitochondrial transport through the action of the Ca^{2+} sensitive GTPase of MIRO which is embedded within the outer mitochondrial membrane which then inactivates the molecular motor kinesin (**Figure 2**). To summarize, the precise location and relocation of mitochondria closely matches the site-specific requirements of the neuron including a rich supply of energy, in the form of ATP, to power the synaptic calcium ion pumps that expel calcium from the cell and for direct mitochondrial buffering of Ca^{2+} (98–100). Furthermore, mitochondria directly regulate the strength of synaptic transmission (94).

Motor proteins interact with mitochondria through adaptor and accessory proteins (98, 101) that determine the direction of mitochondrial transport (**Figure 2**). The mitochondrial transport adaptor proteins TRAK1 and TRAK2 link mitochondria to the motor proteins kinesin and dynein (102). TRAK1 and TRAK2 interact with the mitochondria through the Ca^{2+} sensitive GTPases MIRO1 and MIRO2 embedded within the outer mitochondrial membrane (**Figure 1**) (102–106). MIRO and TRAK work in concert with the transport accessory proteins DISC1 and NDE1 that determine the direction of mitochondrial movement (**Figure 2**). While no mutations in *MIRO* or *TRAK* have been identified (107) both *DISC1* and

TABLE 2 | GTS risk genes in mitochondrial dynamics, structure, and function.

Deleterious mutations
OPA1 (x2), MPV17, PDP1***, ME2, SLC1A3/EAAT1/GLAST, MRPL44 (x3), MRPL48, MRPL3 - Familial, PTCD3, GK2, DPP4, SLC25A26, SLC25A6, SLC52A2, ATP5B, AGK/TIMM22, ACOX3, DGAT2, UBE3A, BCKDHA, ENOSF1, ACOT12*
CNV duplications
SLC25A1(x3), SAP97- Familial duplicated mediated downregulation (14)
CNV deletions
IMMP2L (x12) (x9 in ASD), IMMP1L (x3 in ASD), GPD2 (x1 in ASD), RMRP, SLC25A1 and Txrnd2 (x3), TIMM13, NDUFA4 (Familial deletion), NDUFA13/ETC Complex I, SAP97—Duplication mediated downregulation (14)
Adjacent to deletion
ACOT12
Adjacent to duplication
MGME1 mitochondria DNA maintenance
***GTS linkage/association studies**
MPV17 Mutated and non parametric linkage analysis
PDP1 Mutated and Linked and Associated
SLC25A4 4q35Linkage region in Sib pairs
NDUFS3 D11S1377 in Africana families
SAP97 Parametric linkage in large Dutch pedigree
IMMP2L Autism linkage
Mitochondrial transport protein genes
NDE1 (x2 deletions), *DISC1* (x3 deletions), *DNAH6, DNAH5, and DYNC2H1*, *KIF6 and KLC2* have been mutated, *KIF7* deleted and *KIF16B* is adjacent to a GTS deletion breakpoint at 20p12.1
Mitochondrial dynamics regulators
OPA1 (x2), PRKAB2 (x 2 deletions + adjacent to deletion), *ADCY2 (x2), RCAN1 (duplicated), DGKB (x2 duplications), PLPP2 and PLPP4, PI4K2A and ITPR3* all mutated
Microtubule associated genes
TUBB2A and TUBB2B tubulin genes (duplicated), *TTLL1, TTLL2 and TTLL5* tubulin ligase genes mutated, *MICAL2 and MICAL3* microtubule regulators mutated, *KANK1* microtubule polymerization (x2 duplications), *CCT6A, BRPF1, SKA2, SPAST, KATNAL2, MARK2, TUBGCP5* and *CAMSAP1* which regulates microtubule dynamics and neurite outgrowth and *CAMD1* involved in microtubule stability and radial neuronal cell migration in the developing cerebral cortex lies immediately adjacent to the deletion of the Titin gene in GTS
Ubiquitin ligase genes
UBE3A (duplicated), UBE4A, DTX3, RNF41, RNF213 (x2), SH3RF3, SHPRH, WWP2, UBR4 and TRIM37 all mutated
Ubiquitin modifying genes
UBE4B ubiquination factor, *USP1 and USP47 and USP34* ubiquitin peptidases, *CYLD and BIRC6* all mutated
Cellular energy metabolism
HK2, ME1 (from GTS associated 33 metabolic enzyme gene set)

NDE1 display recurrent hemizygous deletion in GTS, ASD and SCZ (**Table 2**) (58–62). DISC1 is localized predominantly to mitochondria and in synapses, centrosomes, nuclei, endoplasmic reticulum and the Golgi (108, 109). DISC1 forms oligomers that interact with kinesin (110) and dynein (111), MIRO and TRAK, and the mitochondrial transport accessory proteins LIS1, GSK3β, NDE1 and its homolog NDEL1 (**Figure 2**) (112). DISC1 promotes anterograde and retrograde mitochondrial transport in a dose dependent manner in both axons and dendrites (112–114) possibly through blocking SNPH-mediated anchoring of mitochondria (115). DISC1 is also directly linked to anomalies in mitochondrial fission, fusion, structure and function (112–114).

NDE1 interacts with DISC1, TRAK1, NDEL1, LIS1, and with the dynein motor protein to promote retrograde axonal transport (**Figure 2**) (112). NDE1, and its close homolog NDEL1 form a complex with LIS1 that regulates neuronal proliferation, differentiation, and migration within the brain (116). NDE1 is a centrosomal protein with a crucial role in the growth of the cerebral cortex (116). Homozygous frame shift mutations in NDE1 are associated with extreme microlissencephaly (117, 118), whereas heterozygous deletions (LOH) in NDE1 are associated with GTS, ASD, and SCZ (62). Interestingly, the subcellular localization of NDE1, its protein-protein interactions and its regulation of retrograde mitochondrial transport, are all modulated through its phosphorylation by AMP-activated protein kinase A (AMPK/PKA) (**Figure 2**) (119). This regulatory association between NDE1 and PKA is note-worthy on many counts. Firstly, the gene encoding beta subunit 2 of PKA (PRKAB2) is recurrently deleted in GTS (**Table 2**) (58, 63, 120, 121) and PKA activity is greatly decreased in the frontal cortex of

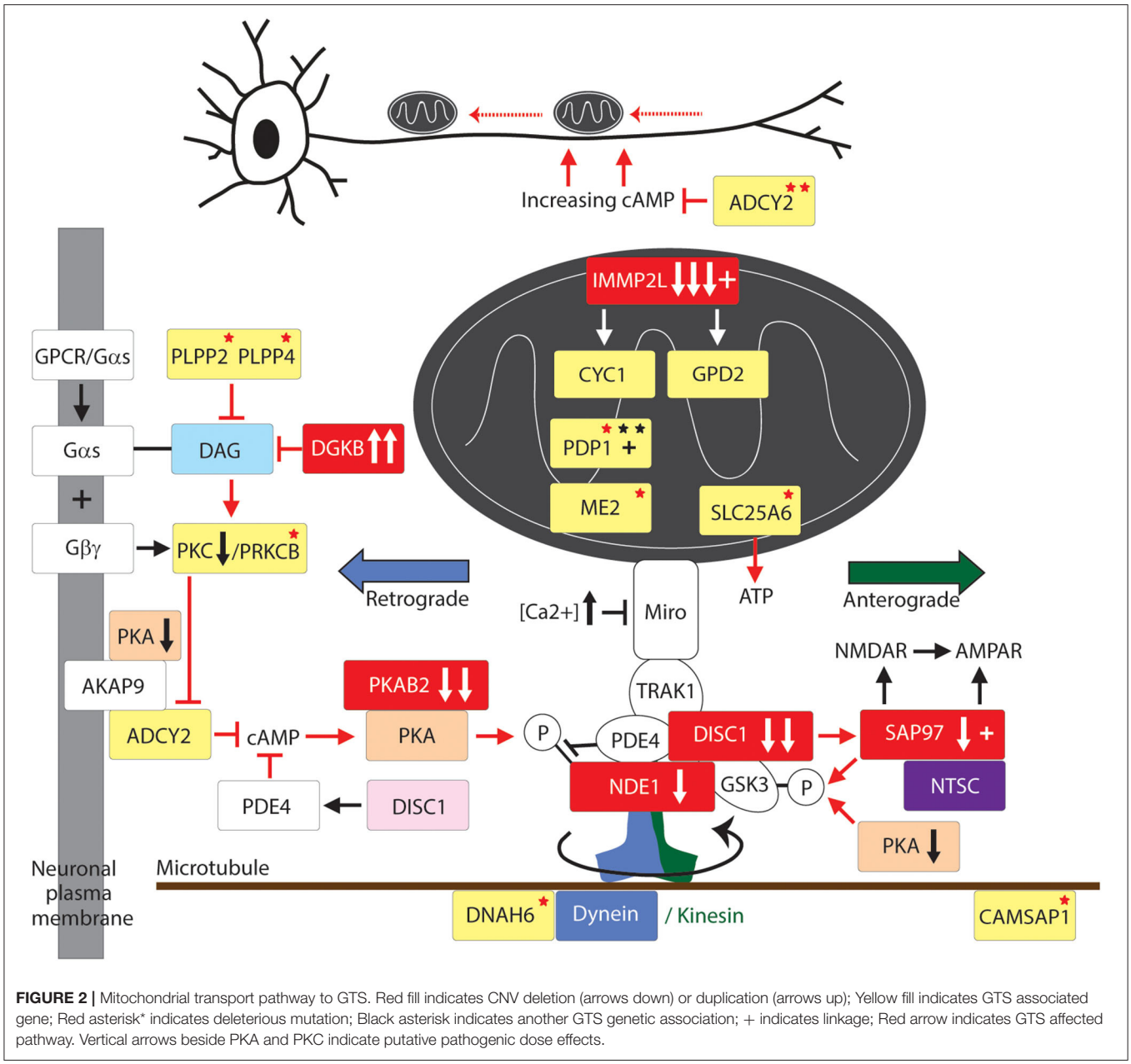

FIGURE 2 | Mitochondrial transport pathway to GTS. Red fill indicates CNV deletion (arrows down) or duplication (arrows up); Yellow fill indicates GTS associated gene; Red asterisk* indicates deleterious mutation; Black asterisk indicates another GTS genetic association; + indicates linkage; Red arrow indicates GTS affected pathway. Vertical arrows beside PKA and PKC indicate putative pathogenic dose effects.

subjects with regressive autism (122). Secondly, cAMP mediated PKA phosphorylation of NDE1 at threonine residue 131 regulates NDE1's all-important interactions with NDEL1 and LIS1 that are thought to activate dynein and facilitate its ability to move high-load cargo like mitochondria (123, 124). Thirdly, PKA's activation by rising cAMP levels provides a mitochondrial transport switch that can be activated on depletion of cellular ATP. Finally, DISC1 modulates the phosphorylation of NDE1 by PKA through its regulation of PDE4, a cAMP-hydrolyzing enzyme which creates a co-complex with DISC1 and NDE1 (**Figure 2**) and LIS1 and NDEL1 (112, 119, 125).

Mitochondria also localize to sites of neuronal branching. During development of neuronal circuitry the axons are guided to their target sites by extracellular guidance molecules like DSCAM, ROBO1, SLIT2 and SLIT3. *SLIT3* has been recurrently associated with GTS (2, 45, 46) as has *SLIT2* with ASD (2, 68, 69). Moreover, *DSCAM* and *ROBO1* have been recurrently mutated in ASD as have *DSCAM's* DNA regulatory elements (21, 22).

Neuronal growth cone navigation also relies on intracellular changes to microtubule and F-actin architecture downstream of these guidance cues (126), for example CAMSAP1 which was mentioned above in relation to its regulation of microtubule dynamics and neurite outgrowth (**Table 2** and **Figure 2**) (58, 93). Furthermore, AMPK/PKA regulates F-actin cytoskeletal dynamics (127). After extension to their target sites axons undergo local branching to establish the appropriate functional connections between pre- and postsynaptic neuronal termini. The intracellular mechanism that regulates this axonal branching

also involves PKA through its regulation of mitochondrial transport and recruitment to sites of future axon branching (128). Here, neuronal depolarization-induced rebalance of mitochondrial motility between anterograde and retrograde transport underlies the formation of axonal branches (128). Axon branching is formed in an ATP-depletion dependent manner through an increase in activated/phosphorylated PKA—a function which can be recapitulated by the pharmacological activation of PKA (128). Following neuronal depolarization there is an increase in anterograde transport of mitochondria into axons thus providing a mechanism for mitochondrial relocation and recruitment to sites of high energy demand that would appear to include sites of future branching. Moreover, the continued localization of mitochondria at branch points correlates with the longevity of axonal branches indicating a probable role for mitochondrial localization in the maintenance of axon branches (128). To summarize, a role for mitochondria in neuronal function and neurological disease has been established. Moreover, the role of mitochondrial transport in GTS is greatly strengthened by the interacting roles of the dynein motor protein, DISC1, NDE1, and PKA in mitochondrial transport and the complementary nature of their deleterious mutations in GTS and ASD (**Table 2**) (61–63, 112).

The master regulator glycogen synthase kinase 3β (GSK3β) is phospho-deactivated by another master regulator AMPK/PKA (129–131). This is important given that GSK3β associates with both DISC1 and TRAK1 in the regulation of mitochondrial transport (**Figure 2**) (112). In the synapse GSK3β is also deactivated by SAP97 downstream of DISC1 (132) (**Figure 2**). *SAP97* is linked to GTS (12) and downregulated in GTS and ASD (11) and forms part of the high-risk NTSC pathway to GTS (**Figure 1**) (2, 12). As such, SAP97 functions at the intersection of the NTSC, DISC1 and mitochondrial transport pathways to GTS (**Figures 1**, **2**) (2, 11, 12). GSK3β is also translocated into the mitochondria where it regulates mitochondrial homeostasis (112, 129, 133, 134). In the mitochondria GSK3β regulates the structure and function of the inner mitochondrial membrane (134). This is noteworthy given that the LOH and/or downregulation of *SAP97*, *DISC1,* and *PRKAB2* in GTS (2, 11, 12, 58, 61–63) are all consistent with stronger activation of GSK3β which is in turn consistent with the success of lithium chloride in the treatment of psychosis through its highly selective phospho-deactivation of GSK3 in both the cytosol and mitochondria (12, 134).

Mitochondrial Fusion and Fission

The constant optimisation of mitochondrial function requires mitochondria to undergo fusion and fission. Fusion of suboptimal mitochondria with healthy mitochondria creates larger healthier mitochondria where the damage is diluted (98, 135). Fission of mitochondria can rapidly increase the number of healthy mitochondria to allow for their wider distribution in the extended network of neuronal branches and boutons (98, 135). Fission can also help separate out damaged mitochondrial components for clearance by mitophagy (98, 102, 135). Conversely, if transport of mitochondria is retarded or otherwise defective mitochondria are less likely to merge thereby decreasing the clearance of damaged mitochondria and the overall health of the mitochondrial pool (39, 86).

Mitochondrial Fusion

Fusion of the outer mitochondrial membrane is coordinated by Mitofusins 1 and 2 (Mfn1/2) whereas fusion of the inner mitochondrial membrane is regulated by Optic Atrophy 1 (OPA1) (136, 137). This is most relevant as *OPA1* is recurrently mutated in GTS (**Table 2** and **Figure 3**) (58) and the levels of MFN1, MFN2, and OPA1 are decreased in the temporal lobe of the autistic brain, and there are deficits in MFN1 and MFN2 in Fragile X syndrome (**Figure 3**) (58, 77, 83). Mfn1/2 and OPA1 act through the formation of complexes both within and across the membranes (136, 137). Mfn2 coding mutations appear to inhibit mitochondrial fusion by forming a complex, in a dominant-negative fashion, with wild-type Mfn1 and Mfn2 (138). Mutations in Mfn2 cause Charcot Marie Tooth Disease Type 2A, a severe and early onset motor and sensory peripheral neuropathy with autosomal dominant inheritance (111, 139). These Mfn2 mutations promote mitochondrial fragmentation in dorsal root ganglion neurons and impair axonal mitochondrial transport which is suggestive of a link between mitochondrial fission/fusion equilibrium and mitochondrial transport (140). This link is supported further by the physical interaction between Mfn2 and the MIRO complex (141) and the finding that Purkinje-neuron-specific deletion of Mfn2 in mice (total knockout of Mfn2 is embryonic lethal) impairs mitochondrial fusion and the dendritic localization of mitochondria, dendrite development, degeneration of Purkinje neurons (142, 143). Similar to the situation in mice, Mfn2 loss-of-function in zebrafish reduces mitochondrial transport and depletes mitochondria from distal axons (144). Acting in a similar dominant-negative fashion to Mfn2, hypomorphic mutations in OPA1 cause dominant optic atrophy (DOA), the most common cause of hereditary blindness. Dominant optic atrophy is characterized by the early loss of retinal ganglion cells and degeneration of the optic nerve (145). Moreover, DOA patients often present with neurological disorders, including ataxia, myopathy, deafness and peripheral neuropathy, indicating an essential neurological role for OPA1 (146, 147). Like Mfn2, knockout of Opa1 in mice is embryonic lethal (141) whereas Opa1 LOH in mice recapitulates the DOA seen in patients, including early-onset degeneration of the optic nerve and vision loss (148). *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 ETC components, mitochondrial DNA content, dendritic outgrowth and synapse formation (149). As such, the characterization of mitochondrial phenotypes in those GTS patients identified with recurrent *OPA1* mutations is eagerly anticipated (**Figure 3**) (58).

Mitochondrial Fission Regulatory Genes in GTS

The number and the complementary nature of the deleterious GTS mutations identified in mitochondrial fission pathways provide compelling evidence for mitochondrial fission deficiency

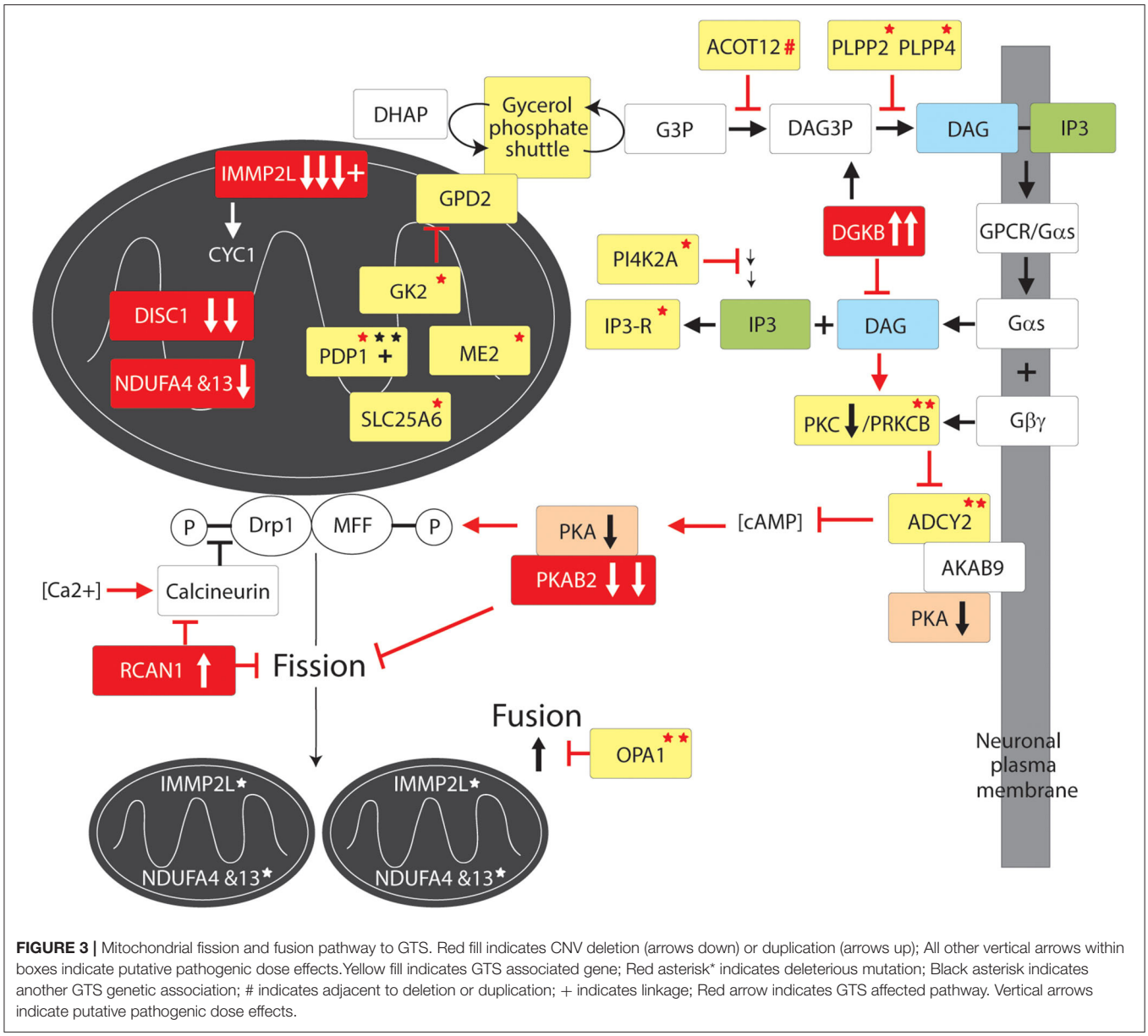

FIGURE 3 | Mitochondrial fission and fusion pathway to GTS. Red fill indicates CNV deletion (arrows down) or duplication (arrows up); All other vertical arrows within boxes indicate putative pathogenic dose effects.Yellow fill indicates GTS associated gene; Red asterisk* indicates deleterious mutation; Black asterisk indicates another GTS genetic association; # indicates adjacent to deletion or duplication; + indicates linkage; Red arrow indicates GTS affected pathway. Vertical arrows indicate putative pathogenic dose effects.

in the etiology of GTS. The fission of the mitochondrial membranes is dependent on Dynamin-related protein1 (Drp1) (150–160) which is downregulated in the brain of patients with ASD (78–81). Drp1 also regulates peroxisomal fission and proliferation (161). Primarily a cytosolic enzyme, Drp1 translocates to the outer mitochondrial membrane when dephospho-activated by the Ca^{2+}-activated phosphatase calcineurin/PPP3CA (**Figure 3**) (162, 163). Conversely, calcineurin is inhibited by RCAN1 which blocks Drp1 translocation to the mitochondria (164, 165) and hence it is of immense interest that *RCAN1* has been duplicated in GTS and *Calcineurin* is downregulated in the cerebral cortex of patients with ASD (**Figure 3**) (47, 63, 80, 81, 166). Calcinueurin activated Drp1 is then recruited to the outer mitochondrial membrane by phospho-activated mitochondrial fission factor (MFF). MFF is phospho-activated in neurones by PKA in response to increasing levels of cAMP (**Figure 3**) (167, 168). Activated Drp1 then assembles into spirals around the mitochondrion, which constrict and ultimately divide the organelle in two while dynamin-2 catalyzes the final membrane scission event (169). As mentioned earlier, the gene for beta subunit 2 of cAMP activated PKA (*PRKAB2*) is recurrently deleted in GTS (58, 63). Furthermore, cAMP levels in the brain are largely regulated by *ADCY2* (170), the adenylate cyclase gene recurrently mutated in GTS including the loss of an *ADCY2* intron/exon splice site in GTS (58). *ADCY2* is also mutated in bipolar disorder and a mutation in the ADCY2 binding site of the AKAP9 synaptic scaffolding protein has been found associated with SCZ (54, 170). This is fascinating since AKAP9 acts as a synaptic membrane anchor for ADCY2 and PKA which keeps this primary target of

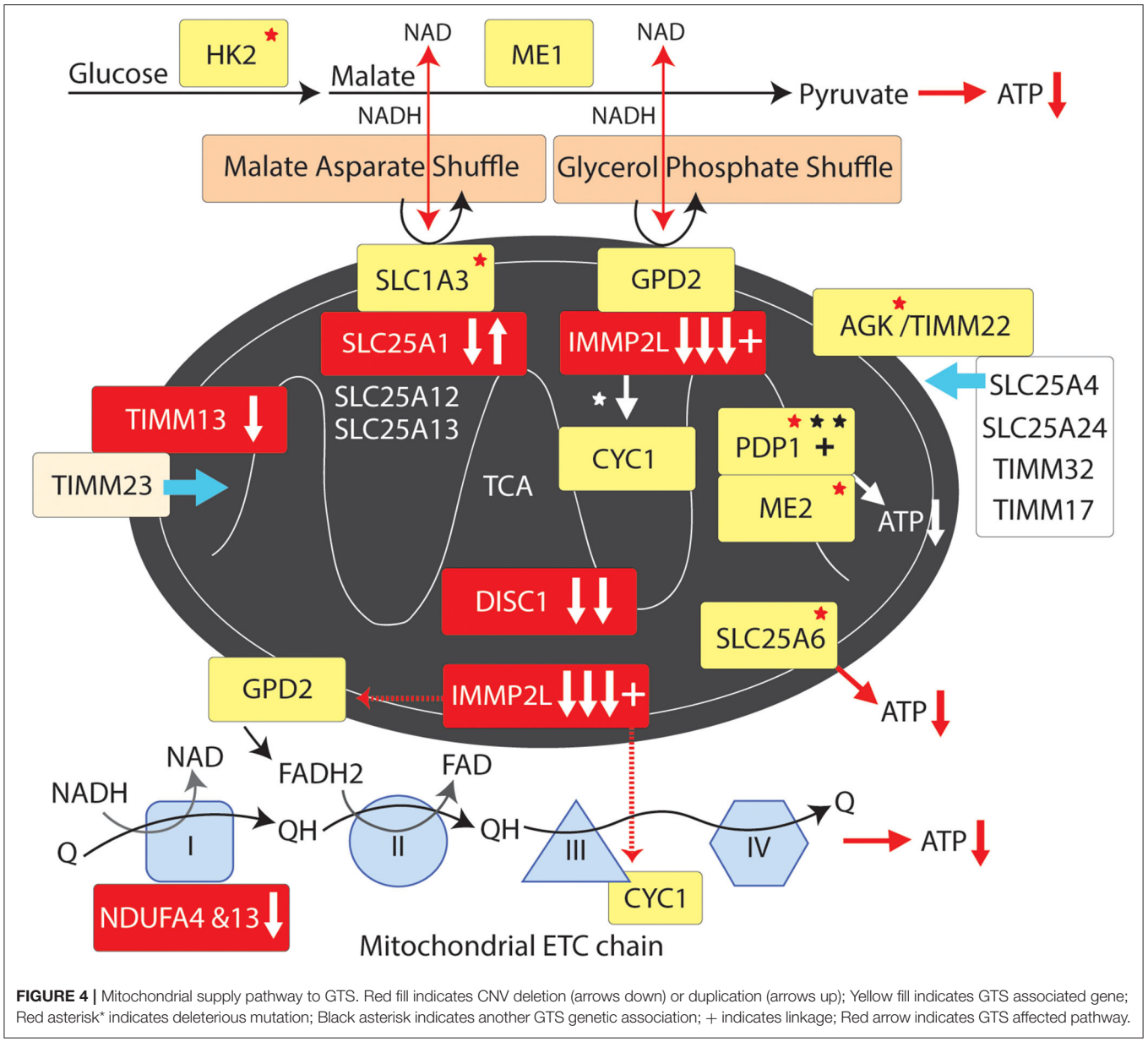

FIGURE 4 | Mitochondrial supply pathway to GTS. Red fill indicates CNV deletion (arrows down) or duplication (arrows up); Yellow fill indicates GTS associated gene; Red asterisk* indicates deleterious mutation; Black asterisk indicates another GTS genetic association; + indicates linkage; Red arrow indicates GTS affected pathway.

cAMP (PKA) in close proximity to the primary cAMP generator ADCY2 (170–173).

ADCY2 is activated by G-protein signaling through release of the alpha subunit of trimeric G protein (Gαs) (170, 174). Gαs is released when the G protein coupled receptor (GPCR) in the plasma membrane is bound by an extracellular regulatory molecule such as the neurotransmitter dopamine (**Figure 3**) (174, 175). When released, Gαs activates Phospholipase-C which in turn acts on phospholipid (phosphatidylinositol-triphosphate) within the plasma membrane cleaving off the inositol triphosphate (IP3) second messenger which frees yet another important second messenger diacylglycerol (DAG) (175). DAG activates Protein Kinase C (PKC), which in turn activates ADCY2 and other proteins (**Figure 3**) (175). Notably, the gene encoding PKC subunit B (PRKCB1) is mutated in GTS (**Figure 3**) (58) as well as being both linked and strongly associated with ASD, moreover, PKC activity is significantly reduced in the frontal cortex of subjects with regressive autism (55, 56, 82). *PRKCB1* is also associated with nominal autistic-like traits in the general population (176). Another compelling finding that links the PKCB/ADCY2 pathway to GTS is the recurrent duplication of the DAG kinase gene in GTS (DGKB) (58). DGKB terminates DAG-based signals by reducing DAG levels by converting DAG to diacylglycerol-3-phosphate (DAG3P) (**Figure 3**). Moreover, the phosphatases PLPP2 and PLPP4 which convert DAG3P back to DAG are both mutated in GTS (**Figure 3**) (58). It is also worthy of mention here that PI4K2A, an enzyme in the synthesis pathway

of phosphatidylinositol-triphosphate with the potential to limit the bioavailability of both the IP3 and DAG second messengers, is mutated in GTS. This together with a GTS mutation in the IP3 receptor ITPR3 (**Figure 3** and **Table 2**) (58) suggests the potential for an IP3 signaling affect in GTS notwithstanding ambiguity with regards to the calcium sensitivity of ACDY2 (170, 174, 175). To summarize, there is an impressive number of GTS gene mutations with the potential to limit the activation of Drp1, or the MFF-mediated recruitment of Drp1, for mitochondrial fission (**Figure 3**).

Optimisation of Mitochondrial Supply

Many of the genes mutated in GTS regulate mitochondrial function. Most notable is the *IMMP2L* gene commonly disrupted/deleted in GTS (64, 72–75, 84). *IMMP2L* encodes a mitochondrial peptidase (inner mitochondrial membrane peptidase-2-like protein) which processes other mitochondrial proteins within the inner mitochondrial membrane (**IMM**) (**Figure 4** and **Table 2**) (84). The *IMMP2L* association with GTS was first reported in a GTS family with a balanced *t* (7;18) (q22–q31; q22.3) translocation that disrupted the *IMMP2L* gene (72). More recently a Danish study reported 5′-end intragenic deletions in *IMMP2L* in seven out of a cohort of 188 GTS patients (3.7%) which was significantly higher than that of the control population (64). The IMMP2L gene has been repeatedly linked to ASD inheritance at the Autism 1 (AUTS1) locus (48–52). In addition, *IMMP2L* has demonstrated haplotype sharing in multiple ASD populations and deleterious exon deletions have been identified in ASD individuals and families (22, 52, 65, 66, 71, 74, 177) at significantly higher frequency than in control populations. Furthermore, reducing Immp2l dose in mice causes behavioral changes relevant to GTS behavioral deficits (85).

IMMP2L cleaves IMM signature signal peptides from a number of IMM proteins including cytochrome C1 (CYC1) and mitochondrial glycerol-3-phosphate dehydrogenase (GPD2) (84). CYC1 (oxidative phosphorylation complex 111 subunit 4) is a heme-containing subunit of the cytochrome complex of the electron transport chain (ETC). CYC1 has an important role in accepting electrons from the Rieske protein and transferring them to Cytochrome C in the respiratory chain. On the other hand GPD2 functions as part of the glycerol phosphate shuttle (**Figure 4**). GPD2, which is activated by IMMP2L, is located on the outer surface of the inner mitochondrial membrane where it catalyzes the interconversion of glycerol-3-phosphate (G3P) to dihydroxyacetone phosphate. Interestingly, mitochondrial glycerol kinase (GK2) which generates G3P is also mutated in GTS (58). Together, GPD1 and GPD2 constitute the glycerol phosphate shuttle, which generates $FADH_2$ for the mitochondrial ETC and NAD+ for glycolysis in the cytosol. The coordinated action of GPD1 and GPD2 results in the transfer of two reducing equivalents from G3P to the mobile electron carrier ubiquinone (Coenzyme Q10) which in turn passes these electrons to CYC1 located downstream in the ETC (80, 81, 178–180).

A recurrent functional variant in the glutamate aspartate transporter GLAST/*SLC1A3* has been identified in GTS (181) (**Table 2**). SLC1A3 is also of interest as it imports glutamate from the cytosol into the mitochondrial matrix and exports aspartate from the matrix to the cytosol at varying levels in different cell types including astrocytes and neurons (178, 181). In addition to reducing glutamate signaling within the synapse the malate aspartate shuttle, like the glycerol phosphate shuttle, provides NADH to the ETC to generate ATP and NAD+ for another round of glycolysis (**Figure 4**) (178). In addition, the mitochondrial ADP/ATP exchange transporter SLC25A6 is mutated in GTS as is the mitochondrial ATPase ATP5B (**Table 2**) (58). SLC25A4 is a nuclear encoded protein located at the 4q35 GTS linkage locus (2, 46) (**Table 1**). SLC25A4 is transported into the mitochondria by the TIMM22 mitochondrial translocase complex inclusive of AGK, a vital component of TIMM22 involved in its assembly and function, and which is downregulated in the cerebral cortex of autism sufferers (80, 81). Importantly, *AGK* is mutated in GTS as is the *TIMM13* (**Table 2** and **Figure 4**) (58, 182, 183). TIMM13 facilitates translocation of the TIMM23 translocase into the IMM which in turn forms a translocase complex with TIMM17A/B, which itself is translocated into the IMM by TIMM22 (184). Importantly, TIMM17A/B facilitates the translocation of two additional glutamate/aspartate exchange transporters into the IMM, namely SLC25A12 and SLC25A13 (**Figure 4**) with the former being downregulated in the brain of patients with ASD (78, 79).

Mitochondrial Maintenance

The MPV17 channel protein (53, 58) that regulates the transmembrane potential of the IMM and mitochondrial DNA maintenance has been mutated in GTS (**Table 2**), moreover, the *MPV17* gene is located at the 2p23.2 non-parametric linkage locus identified in GTS (53) (**Table 2**). *MGME1* which also regulates mitochondrial DNA maintenance is located immediately adjacent to a genomic DNA duplication at 20p11 in GTS (**Table 2**) (58). *RMRP*, a gene which regulates mitochondrial RNA processing, is deleted in GTS as is the *PTCD3* gene which regulates translation in the mitochondria (**Table 2**). In addition, a number of mitochondrial ribosomal protein genes are mutated in GTS: *MRPL44* was found mutated in 3 unrelated GTS patients (**Table 2**) (58), a mutation in *MRPL3* was found segregating with GTS in a large affected family (67) and *MRPL48* was found mutated in another GTS patient (**Table 2**) (58). Together these findings are reminiscent of the *MRPL19* gene association with ASD, Dyslexia and Reading Disorder (57).

CONCLUSION

The mitochondrial pathways involved in GTS overlap and interact making it possible to trace these pathways to common endpoints in mitochondrial dynamics and supply. While it is unlikely that all of the genes cited in this study are causative in GTS, or that they all act alone in GTS etiology, we present convincing weight of evidence that mitochondria are implicated in GTS. Notwithstanding, the deleterious mutation of genes directly involved in mitochondrial dynamics and supply (**Figure 4**) have the potential to limit neurodevelopment and neurotransmission during periods of peak demand. The exact

mitochondrial mechanism implicated in GTS has not been identified as there is no evidence of mitochondrial mediated increases in ROS or ROS related neurodegeneration in GTS as is commonly the case in neurodegenerative disorders. A deficit in neuronal energy supply during development is one possible contributing factor in the etiology of GTS, however, the waning of tic severity in GTS over time appears more consistent with a deficit in neurotransmission possibly compensated for at later ages (185–189). We have no non-molecular evidence of a mitochondrial pathway to GTS at this time, notwithstanding, this is the 1st study to report a mitochondrial pathway to GTS and we are confident it will not be the last. The mitochondrial pathways identified in this study (**Figures 2–4**) have roles in neuronal circuitry development, synaptic connectivity and neurotransmission (**Figure 1**) (2, 11). The NTSC and DISC1 and mitochondrial pathways to GTS all intersect around the pivotal role of SAP97 in regulating synaptic signaling downstream of the NTSC and mitochondrial transport downstream of DISC1 thus providing compounding support for a GTS deficit in mitochondrial supply affecting neurotransmission.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.