

Data Supplement: Detailed Descriptions of the 47 Cases in the Literature on Patients With Psychiatric Symptoms and Mitochondrial Disorders

Reference	Diagnosis	Sex	Age at Onset, years	Age at Psychiatric Diagnosis	Age at Physical Diagnosis	Psychiatric Symptoms	Medical History	Family History	Investigations
Ahn <i>et al.</i> , 2005 ¹³	Mitochondrial cytopathy	F	16	5	NR	Low IQ; developmental delay; mood lability, impulsivity, depression, self-harm. After treatment with risperidone, developed paranoid ideation, psychomotor retardation, depression, and fatigue. Resolved with discontinuation of risperidone.	Seizures	Family history of seizures	MRI : normal; Blood work: lactate elevated; Muscle biopsy: RRFs
Amemiya <i>et al.</i> , 2000 ¹⁴	C3256T	M	29	NR	36	Delusions, confusion, progressive dementia	Myoclonus, muscle atrophy, seizures, ataxia, ophthalmoplegia, paralytic ileus. Died of cardiac failure age 46	None	MRI: progressive brain atrophy; Blood work: lactate and pyruvate elevated; CSF lactate elevated; Muscle biopsy: RRFs, reduced COX activity
Apostolova <i>et al.</i> , 2005 ¹⁵	MELAS A3243G	F	58	58	58	Psychosis (paranoia and hallucinations), agitation, cognitive deterioration	CAD, cardiomyopathy, chronic fatigue, muscle weakness	Parents and brother: CAD	MRI : hyperintensities in a watershed distribution and bilaterally in the cerebellum; Blood work: normal lactate; Muscle biopsy: RRFs, COX–fibers

Ban et al., 1992 ¹⁶	MELAS A3243G	M	25	19	37	Psychosis (auditory hallucinations, delusions) diagnosed with schizophrenia; later, developed euphoria, progressive dementia, and akinetic mutism	Gastroparesis, weakness of extremities, dysarthria, myoclonus, rigidity, cardiac hypertrophy, bilateral sensorineural hearing loss, died of heart failure	Mother: heart disease from age 30; suicide at age 58	MRI: ischemia in parieto-occipital regions; Blood work: lactate and pyruvate elevated; Muscle biopsy: RRFs
Bhuvaneshwar et al., 2008 ⁵⁵	MELAS	F	NR	28	28	History of depression, psychosis (paranoid delusions)	Headaches, progressive decline in functioning, seizures, fatigue, ptosis	NR	MRI: focal posterior cerebral lesions with T2 hyperintensities and symmetrical basal ganglia calcifications associated with a stroke-like-episode that resolved
Clark et al., 1996 ¹⁷	MELAS A3243G	F	44	27	44	Psychosis (paranoid delusions), suicidal ideation, anxiety, cognitive deterioration	Weakness upper and lower extremities, bilateral sensorineural hearing loss, stroke, simple partial seizures, WPW, bowel symptoms	Mother: bilateral hearing loss; stroke in 40s; seizures; severe psychiatric illness; bowel obstruction. Maternal grandmother: bizarre behavior; died of stroke at 64. Maternal great-aunt: psychosis, episodes of unconsciousness; died at 45. Maternal aunt: depression. Maternal cousin: psychiatric	MRI: cortical hyperintensities; atrophy Blood work: lactate and pyruvate elevated; Muscle biopsy: RRFs, COX+ fibers

								problems; died at an early age	
Campos et al., 2001 ¹⁸	C3303T	F	Teens	Teens	33	Psychosis; recurrent episodes of depression	Fatigue, weakness, migraine	Maternal aunt: psychosis, bipolar disorder; maternal grandmother: psychosis; maternal great-uncle: psychosis	Not reported
Desnuelle et al., 1989 ¹⁹	KSS	F	24	18	46	Psychosis (auditory hallucinations) treated with neuroleptics and several psychiatric admissions; improvement in physical and psychiatric manifestations with coenzyme Q10 treatment	Ptosis, ophthalmoplegia, amenorrhea, amyotrophy with exercise intolerance, eventual respiratory failure requiring tracheostomy	Parental consanguinity; ptosis and ophthalmoplegia in a deceased maternal uncle; brother with ptosis and ophthalmoplegia who died from cardiomyopathy and cardiac conduction abnormalities; sister with epilepsy who died at 48	Blood work: lactate, pyruvate normal
Gardner et al., 2003 ²⁰	Mitochondrial cytopathy	M	22	34	61	Psychosis (auditory and visual hallucinations), treatment-resistant depression, suicide attempt	Fatigue, headaches, facial paresthesias, sensorineural hearing loss; excessive sweating; conduction block; DM	Maternal aunts: psychiatric symptoms; sister: depression; father: schizophrenia	SPECT : decreased rCBF; Muscle biopsy: no RRFs
Grover et al., 2006 ⁴⁵	Mitochondrial myopathy	M	16	16	16	Mania followed by catatonia; deterioration on psychotropic medications	Muscle rigidity and weakness	Paternal uncle: psychotic illness	MRI: hyperintensities of the basal ganglia bilaterally; SPECT: impaired perfusion, right thalamus; Muscle biopsy:

									subsarcolemmal accumulations of abnormal mitochondria
Hopkins et al., 2010 ⁴⁶	POLGI mutation (c.1550G>T)	F	16-21	16	NR	Depression, suicidal ideation, psychosis	DM; adrenal insufficiency; hypothyroidism; short stature; seizures; choreiform movements; encephalopathy	TWIN A	Blood work: elevated lactate; CT: basal ganglia hyperintensity; MRI: bilateral basal ganglia and thalamic hyperintensities; Muscle biopsy: mild chronic myopathic changes, increased central nuclei, and small myofibers
Hopkins et al., 2010 ⁴⁶	POLGI mutation (c.1550G>T)	F	17-22	17	NR	Depression, suicidal ideation, psychosis	DM; adrenal insufficiency; hypothyroidism; short stature; headache; left facial twitching; seizures; encephalopathy	TWIN B	Blood work: elevated lactate; CT: bilateral basal ganglia infarctions, right-frontal infarction
Inagaki et al., 1997 ²¹	MELAS A3243G	M	31	29	35	Psychosis (auditory hallucinations, persecutory delusions), odd behavior, frontal lobe syndrome, mutism, cognitive deterioration	Short stature, sensorineural hearing loss, WPW, DM	Family history DM and hearing loss	MRI : normal SPECT: normal Blood work: lactate and pyruvate elevated Muscle biopsy: no RRFs
Jaksch et al., 2001 ²²	MELAS A3274G	M	27	27	33	Psychosis, depression, suicidal ideation, cognitive deterioration	Bilateral hearing loss; gait instability; dysdiadochokinesis; vision loss with early-onset cataracts; dysarthria; dysmetria	No history of neurological disease	MRI: cerebral and cerebellar atrophy; hyperintensities in basal ganglia and periventricular white matter;

									Blood work: lactate elevated; Muscle biopsy: RRFs, COX activity reduced, complex I reduced
Kaido et al., 1996 ²³	MELAS A3243G	F	53	53	53	Apathy, psychosis (hallucinations)	Recurrent vomiting, anuresis, decreased level of consciousness, short stature, muscle atrophy, ileus	Mother: short stature	Blood work: lactate and pyruvate normal; CSF: lactate and pyruvate elevated; MRI: diffuse cerebral atrophy; Muscle biopsy: RRFs
Kiejna et al., 2002 ²⁴	MELAS	M	32	19	32	Psychosis (visual hallucinations, somatic delusions); hyperarousal anxiety, progressive dementia	Headache, stroke-like episodes, chronic tinnitus	Mother: seizures, episodic loss of consciousness, stroke; brother: unusual neurological episodes	MRI: cortical and subcortical atrophy; Blood work: lactate normal; Visual EVP: latencies in both eyes; Muscle biopsy: RRFs
Koene et al., 2009 ⁴⁷	MTND1 mutation (3460 G>A)	F	14	Teens	16	Recurrent suicidal ideation and major depression, treated with clomipramine	Fatigue, migraine, myopathy	Family history of depression	Blood work: elevated lactate
Koene et al., 2009 ⁴⁷	POLG1 mutation (1399G>A)	F	16	Teens	17	Major depression with dysphoria, apathy and food aversion, visual hallucinations	Migraine, epilepsy, encephalopathy, fulminant hepatic failure, death		Blood work: elevated lactate
Koene et al., 2009 ⁴⁷	MT DNA Del 4977 bp	F	12	Teens	14	Major depression	Muscle weakness, migraine, short stature, retinitis pigmentosa, DM, myopathy		Blood work: elevated lactate
Koene et al. 2009 ⁴⁷	MTTK mutation (8344A>G)	F	15	16	16	Major depression, mental retardation	Muscle weakness, fatigue	Family history of depression	Blood work: lactate normal

Koller et al., 2003 ²⁵	MELAS 3243	M	34	22	37	Frontal lobe syndrome with apathy, loss of interest, aggressive behavior, personality change	Short stature, hearing loss, migraines, seizures, ataxia, WPW, hypertrophic cardiomyopathy, azoospermia	No neurological or psychiatric history	MRI: disseminated WML; Blood work: lactate elevated; Muscle biopsy : RRFs, COX– fibers
Komulainen et al., 2010 ⁴⁸	POLG mutation (c.2447G>A and c.2243 G>C)	F	Teens	11	NR	Learning difficulties and cognitive deterioration, depression, aggressivity, suicidality, psychotic episodes	Epilepsy, ptosis, cardiac arrhythmia	Sister: mental retardation, ptosis, psychiatric problems (depression, aggressivity, and suicidality)	CT: normal
Lacey et al., 2008 ²⁶	MELAS 3243	M	30	25	30	OCPD, treatment-resistant OCD	Headache, seizures, left homonymous hemianopia, sensorineural deafness, short stature	None	MRI: WML temporal and occipital lobes; Blood work: lactate elevated
Lacey et al., 2008 ²⁶	MELAS 3243	M	49	51	51	Treatment-resistant OCD, agitation	Stroke-like episodes, seizures, DM, short stature, sensorineural deafness	Mother: short stature, sensorineural deafness, congenital heart valve abnormality	MRI: moderate atrophy, multiple areas of infarction
Mancuso et al., 2008 ⁴⁹	Multiple mtDNA deletions	F	12	15	63	Recurrent depression without psychotic features, cognitive impairment	Migraines, exercise intolerance initially diagnosed as fibromyalgia, short stature, muscle atrophy	Multiple maternal family members with bipolar disorder, depression, schizophrenia, and “nervous breakdowns;” some members with lower-limb motor difficulties	Blood work: elevated lactate; MRI: normal; Muscle biopsy: RRFs and COX– fibers
Miyaoka et al., 1997 ²⁷	MELAS A3243G	M	47	Not reported	52	Recurrent depression	DM	Not reported	MRI: normal; SPECT: hypoaccumulation bilateral

									parieto-occipital areas
Miyaoka et al., 1997 ²⁷	MELAS A3243G	F	37	Not reported	62	Panic disorder with agoraphobia	DM	Not reported	MRI: normal; SPECT: hypoaccumulation right occipital area
Miyaoka et al., 1997 ²⁷	MELAS A3243G	F	25	NR	69	Social phobia	DM	Not reported	MRI: WML; SPECT: normal
Miyaoka et al., 1997 ²⁷	MELAS A3243G	M	35	NR	61	Phobias	DM, transient atonic bladder	Not reported	MRI: WML; SPECT: hypoaccumulation bilateral occipital areas
Odawara et al., 1997 ³⁰	MELAS	F	23	21	52	Treatment-resistant schizophrenia; progressive dementia	Muscle wasting, DM, episodes of LOC, bilateral sensorineural hearing loss	Mother: schizophrenia; Maternal uncle: schizophrenia	Muscle biopsy: RRFs
Onishi et al., 1997 ³¹	MELAS A3243G	M	22	NR	23	Treatment-resistant depression, anxiety	Fatigue, sensorineural hearing loss, WPW	Mother, maternal grandmother - DM	MRI :normal SPECT: decreased rCBF
Prayson and Wang, 1998 ³²	MELAS 3243	F	27	27	47	Paranoid schizophrenia	Peptic ulcer disease, malnutrition, seizure, constipation requiring hemicolectomy, migraines, deafness, stroke	Not reported	MRI: bilateral calcification, basal ganglia; left temporal lobe infarction; Blood work: lactate and pyruvate elevated; Muscle biopsy: RRFs, COX- fibers
Rantamaki et al., 2001 ⁵¹ and Van Goethem et al., 2004 ⁵⁰	POLG mutation (c.2243G>C and c.3428A>G))	M	30	30	47	Fatigue, social withdrawal, lack of concentration considered to reflect mental illness; treated with antipsychotics that worsened his difficulty with movement, cognitive	Ataxia, dysarthria, nystagmus, ophthalmoplegia, hyperreflexia, decreased vibration sense, muscle weakness and atrophy	Cousin: severe psychiatric symptoms and alcoholism; died at 42; possibly of a seizure; 2 sisters with ataxia, 1 with epilepsy	NR

						impairment			
Sartor et al., 2002 ³⁴	MELAS A3243G	M	28	28	34	Acute psychosis, psychomotor slowing, social withdrawal and odd behavior, frontal lobe syndrome	TIA, headache, ataxia, seizures	None reported	MRI: atrophy, cortical and subcortical lesions; Blood work: lactate elevated; Muscle biopsy: RRFs
Shinkai et al., 2000 ³⁶	MELAS 3243	F	48	30	48	Psychosis (paranoid ideation), aggression, cognitive deterioration	Hearing loss, DM, small stature, stroke-like episode	Hearing loss in mother, younger sister, father	MRI: hyperintensities of the temporo-parietal lobes bilaterally and bilateral caudate calcification
Siciliano et al., 2003 ⁵²	ANT1 mutation (c.293T>C)	F	Teens	40	44	Bipolar disorder with frequent psychotic episodes and little response to lithium	Ptosis, bilateral facial weakness, migraines	Sister: bipolar disorder, exercise intolerance; Sister: facial weakness, ataxia, bipolar disorder; Mother: ptosis, cognitive impairment, migraines, bipolar disorder, ataxia, hearing loss, ophthalmoplegia	Blood work: lactate normal; Muscle biopsy: RRF and COX-fibers
Spellberg et al., 2001 ³⁷	MELAS A3243G	M	21	21	36	Psychosis	Seizures, sensorineural hearing loss, wide-based gait, weakness, intention tremor	Multiple siblings and maternal family members: DM, heart disease, psychiatric problems (bipolar disorder and psychosis), hearing loss	Blood work: lactate normal; Muscle biopsy: no RRFs
Stewart and Naylor, 1990 ³⁸	KSS	F	23	20	44	Bipolar disorder, cognitive deterioration	Myasthenia, bilateral ptosis, ophthalmoplegia, proximal muscle weakness, cerebellar	None	CT : normal; Blood work: lactate elevated; Muscle biopsy: RRFs

							ataxia, pigmentary retinopathy, heart block		
Suomalainen et al., 1992 ³⁹	Autosomal dominant PEO, Twinkle mutation	F	19	29	29	Recurrent depression with severe psychomotor retardation, apathy, mutism, fatigue, insomnia, negativism, loss of initiative and appetite; at age 60: psychosis (paranoid delusions)	Bilateral ptosis, ophthalmoplegia, muscle weakness and atrophy, short stature, amenorrhea, cardiac arrhythmias	Mother: progressive ptosis; 4 siblings: PEO and muscle weakness; Brother: arrhythmias	Blood work: lactate elevated; Muscle biopsy: RRFs
Suzuki et al., 1989 ⁴⁰ Suzuki et al., 1990 ⁴¹ Mizukami et al., 1992 ²⁸	MELAS	M	25	19	35	Psychosis, psychomotor excitement, impulsive behavior with progressive cognitive deterioration, and akinetic mutism	Short stature, muscle atrophy, disturbances of consciousness, dysarthria, myoclonus, short stature, paralytic ileus, hypertrophic cardiomyopathy, bilateral sensorineural hearing loss, seizures	Not reported	MRI :WML left parieto-occipital area; Blood work: lactate and pyruvate elevated; Muscle biopsy: RRFs
Sweeney et al., 1993 ⁴²	MELAS 3251	F	29	NR	After death	Psychotic depression	Neck muscle weakness; died at 36	Multiple family members with progressive myopathy with weakness of neck and respiratory muscles; early death	Not reported
Sweeney et al., 1993 ⁴²	MELAS 3251	F	25	20	39	Anorexia and agoraphobia	Muscle weakness of neck and arms, diplopia, external ophthalmoplegia, idiopathic thrombocytopenia	As above (sisters)	CT: normal; Muscle biopsy: RRFs
Thomeer et al., 1998 ⁴³	MELAS A3243G	F	22	14	27	Treatment-resistant psychosis; aggression, suicidal behavior,	Short stature, headaches, confusional state;	No history of neurological or psychiatric illness	CT: hypodensity left temporo-occipital area;

						cognitive deterioration	aphasia and apraxia, WPW, deafness, seizures; died suddenly at 31 secondary to heart failure		Blood work: lactate elevated; Muscle biopsy: RRFs
Van Goethem et al., 2004 ⁵⁰	POLG mutation (c.1399G>A)	M	23	18	39	Acute psychiatric illness	Epilepsy; Todd paralysis, left arm and face; intestinal pseudo-obstruction, anorexia, gait and limb ataxia, areflexia, generalized dystrophy, loss of vibration sense, dysarthria, left-sided Babinski, positive Romberg	Sister: acute encephalopathy; myoclonus; seizures, left hemianopsia; cortical blindness; stupor and sudden death	CSF: lactate normal; Blood work: lactate elevated; MRI: normal; SPECT: normal; Muscle biopsy: no RRFs
Verhoeven et al., 2011 ⁵³	Novel POLG mutation (c.2207A>G)	F	37	35	52	Recurrent episodes of depression with melancholic features, one episode of major depression with paranoid ideation, resistant to treatment with multiple psychotropic medications	Ataxia, cataracts, dysarthria, cardiomyopathy, fatigue, incomplete left bundle branch block, all cerebellar tests impaired, hyperreflexia with bilateral positive Hoffman and Babinski signs, positive snout reflex	Brother died in 50s of gastric hemorrhage; son mentally retarded; mother died at 55 of cardiac arrest; father died at 80 of cerebral hemorrhage	CT: moderate cerebellar atrophy; MRI: marked cerebellar atrophy
Yamazaki et al., 1991 ⁴⁴	MELAS	M	29	19	37	Psychosis with diagnoses of schizophrenia and dementia, NMS during Haldol treatment	Muscle weakness and atrophy	Not reported	Muscle biopsy: RRFs, COX ⁻ fibers
Young et al., 2010 ⁵⁴	Novel MTF mutation (m.586G>A)	F	57	45	NR	Referred to psychiatry for self-neglect, weight loss, cognitive deterioration, psychosis (paranoid delusions and auditory hallucinations)	Deafness, worsening mobility with falls, facial grimacing, dysarthria, ataxia, hyperreflexia, positive Babinski responses	Father died of multiple strokes; Mother died of metastatic breast cancer	Blood work: lactate normal; MRI: generalized cerebral, cerebellar, and brainstem atrophy

NR: not reported; CAD: coronary artery disease; COX: cytochrome oxidase; CT: computed tomography; DM: diabetes mellitus; KSS: Kearns-Sayre syndrome; LOC: loss of consciousness; MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; PEO: progressive external ophthalmoplegia; RRFs: ragged red fibers; SPECT: single photon emission computed tomography; TIA: transient ischemic attack; WML: white-matter lesions; WPW: Wolff-Parkinson-White syndrome.