

Table S1. Genes associated to RTT spectrum disorders in case reports from the HGMD-Professional database (June 2021) compared with OMIM phenotypes. The table shows the Gene Symbol, the general inheritance pattern (Inh) associated to each gene (AD = Autosomal Dominant, AR = Autosomal Recessive, XLD = X-Linked Dominant; XLR = X-Linked Recessive, NA = Not Available), the RTT spectrum cases reported in HGMD professional and their phenotypic description, as well as the phenotypes described in OMIM associated to each gene (NA = No phenotypes described in OMIM).

Gene Symbol	Inh	HGMD		OMIM		
		RTT spectrum phenotypes	N	Phenotypes	Inh	MIM#
<i>ACTL6B</i>	AD/AR	Rett syndrome, atypical	1	Developmental and epileptic encephalopathy 76	AR	618468
		Intellectual disability, ambulation deficits, language impairment, hypotonia, Rett-like stereotypies and facial dysmorphism	2	Intellectual developmental disorder with severe speech and ambulation defects	AD	618470
<i>AGAP6</i>	NA	Rett-like syndrome	1	NA		
<i>ANKRD31</i>	NA	Rett-like syndrome	1	NA		
<i>ANXA11</i>	AD	Rett-like syndrome	1	Amyotrophic lateral sclerosis 23	AD	617839
<i>ATP6V0A1</i>	NA	Rett syndrome, atypical	1	NA		
<i>AUTS2</i>	AD	Rett syndrome, atypical	1	Mental retardation, autosomal dominant 26	AD	615834
<i>BRAF</i>	AD	Rett syndrome, atypical	1	Cardiofaciocutaneous syndrome	AD	115150
				LEOPARD syndrome 3	AD	613707
				Noonan syndrome 7	AD	613706
<i>BTBD9</i>	NA	Rett-like syndrome	1	NA		

<i>CACNA1A</i>	AD	Rett syndrome, atypical	1	Developmental and epileptic encephalopathy 42	AD	617106
				Episodic ataxia, type 2	AD	108500
				Migraine, familial hemiplegic, 1	AD	141500
				Migraine, familial hemiplegic, 1, with progressive cerebellar ataxia	AD	141500
				Spinocerebellar ataxia 6	AD	183086
<i>CACNA1D</i>	NA	Rett-like syndrome	1	Primary aldosteronism, seizures, and neurologic abnormalities	AD	615474
				Sinoatrial node dysfunction and deafness	AR	614896
<i>CACNA1G</i>	AD	Rett-like syndrome	1	Spinocerebellar ataxia 42	AD	616795
				Spinocerebellar ataxia 42, early-onset, severe, with neurodevelopmental deficits	AD	618087
<i>CACNA1I</i>	NA	Rett-like syndrome	1	NA		
<i>CAMK2B</i>	NA	Rett-like syndrome	1	Mental retardation, autosomal dominant 54	AD	617799
<i>CDKL5</i>	XLD	<i>CDKL5</i> deficiency disorder	102	Developmental and epileptic encephalopathy 2	XLD	300672
		Rett syndrome	10			
		Rett syndrome, atypical	23			
		Rett syndrome, Hanefeld variant	4			
		Rett syndrome, variant, with infantile spasms	18			
		Encephalopathy, early-onset, and atypical Rett syndrome	3			
		Rett-like syndrome	1			
<i>CHD4</i>	NA	Rett syndrome	1	Sifrim-Hitz-Weiss syndrome	AD	617159

<i>CHRNA5</i>	NA	Rett-like syndrome	1	NA		
<i>CLTC</i>	AD	Rett-like syndrome	1	Mental retardation, autosomal dominant 56	AD	617854
<i>COL4A1</i>	AD	Rett-like syndrome	1	Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps	AD	611773
				Brain small vessel disease with or without ocular anomalies	AD	175780
				Microangiopathy and leukoencephalopathy, pontine, autosomal dominant	AD	618564
<i>CTNNB1</i>	AD	Rett syndrome	1	Exudative vitreoretinopathy 7	AD	617572
		Rett-like syndrome	2	Neurodevelopmental disorder with spastic diplegia and visual defects	AD	615075
<i>CUX2</i>	NA	Rett-like syndrome	1	Developmental and epileptic encephalopathy 67	AD	618141
<i>DMXL2</i>	NA	Rett-like syndrome	1	?Deafness, autosomal dominant 71	AD	617605
				?Polyendocrine-polyneuropathy syndrome	AR	616113
				Developmental and epileptic encephalopathy 81	AR	618663
<i>DNMT3A</i>	AD	Rett-like syndrome	1	Acute myeloid leukemia, somatic		601626
				Heyn-Sproul-Jackson syndrome	AD	618724
				Tatton-Brown-Rahman syndrome	AD	615879
<i>EEF1A2</i>	NA	Rett-like syndrome	1	Developmental and epileptic encephalopathy 33	AD	616409
				Mental retardation, autosomal dominant 38	AD	616393
<i>EIF2B2</i>	AR	Rett-like syndrome	1	Leukoencephalopathy with vanishing white matter	AR	603896
				Ovarioleukodystrophy	AR	603896

<i>EIF4G1</i>	AD	Rett-like syndrome	1	{Parkinson disease 18}	AD	614251
<i>FAM151A</i>	NA	Rett syndrome	1	NA		
<i>FAT3</i>	NA	Rett syndrome, atypical	1	NA		
<i>FOXP1</i>	AD	<i>FOXP1</i> syndrome	25	Rett syndrome, congenital variant	AD	613454
		Rett syndrome	36			
		Rett-like syndrome	10			
		Rett syndrome, atypical	6			
		Mental retardation, Rett-like	1			
		Rett syndrome features	1			
		Rett syndrome with hypoplastic hippocampus	1			
		Rett syndrome, congenital variant	1			
<i>GABBR2</i>	NA	Rett-like syndrome	1	Developmental and epileptic encephalopathy 59	AD	617904
				Neurodevelopmental disorder with poor language and loss of hand skills	AD	617903
<i>GABRA1</i>	AD	Rett-like syndrome	1	Developmental and epileptic encephalopathy 19	AD	615744
<i>GABRB2</i>	AD	Rett syndrome	1	Developmental and epileptic encephalopathy 92	AD	617829
		Rett syndrome, atypical	1			
<i>GABRD</i>	NA	Rett syndrome	1	{Epilepsy, generalized, with febrile seizures plus, type 5, susceptibility to}	AD	613060
				{Epilepsy, idiopathic generalized, 10}	AD	613060
				{Epilepsy, juvenile myoclonic, susceptibility to}	AD	613060

<i>GABRG2</i>	AD	Rett syndrome, atypical	1	Developmental and epileptic encephalopathy 74	AD	618396
				Epilepsy, generalized, with febrile seizures plus, type 3	AD	607681
				Febrile seizures, familial, 8	AD	607681
<i>GRIA3</i>	XLR	Rett-like syndrome	1	Intellectual developmental disorder, X-linked, syndromic, Wu type	XLR	300699
<i>GRIN1</i>	AD	Rett syndrome, atypical	1	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant	AD	614254
				Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal recessive	AR	617820
<i>GRIN2A</i>	AD	Rett syndrome, atypical	1	Epilepsy, focal, with speech disorder and with or without mental retardation	AD	245570
		Rett-like syndrome	1			
<i>GRIN2B</i>	AD	Rett syndrome, atypical	1	Developmental and epileptic encephalopathy 27	AD	616139
		Rett-like syndrome	1			
		Rett-like syndrome with encephalopathy	1	Intellectual developmental disorder, autosomal dominant 6, with or without seizures	AD	613970
		Atypical Rett syndrome & intractable epilepsy	1			
<i>HCN1</i>	NA	Rett-like syndrome	1	Developmental and epileptic encephalopathy 24	AD	615871
				Generalized epilepsy with febrile seizures plus, type 10	AD	618482
<i>HDAC1</i>	NA	Rett syndrome	1	NA		
<i>HDAC8</i>	XLD	Rett syndrome, atypical	1	Cornelia de Lange syndrome 5	XLD	300882
<i>HECW2</i>	NA	Rett-like syndrome	1	Neurodevelopmental disorder with hypotonia, seizures, and absent language	AD	617268

<i>HNRNPU</i>	AD	Developmental delay and Rett-like syndrome with acute encephalopathy and intractable epilepsy	1	Developmental and epileptic encephalopathy 54	AD	617391
<i>HTT</i>	AD	Rett-like syndrome	3	Huntington disease	AD	143100
				Lopes-Maciel-Rodan syndrome	AR	617435
<i>IMPDH2</i>	NA	Rett syndrome, atypical	1	[IMPDH2 enzyme activity, variation in]	NA	617995
<i>IQGAP3</i>	NA	Rett syndrome, atypical	1	NA		
<i>IQSEC2</i>	XLD	Rett syndrome	2	Mental retardation, X-linked 1/78	XLD	309530
		Rett syndrome, atypical	1			
		Rett syndrome features	1			
		Rett-like syndrome	1			
<i>IRF2BPL</i>	NA	Rett-like syndrome	1	Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures	AD	618088
<i>ITPR1</i>	AD/AR	Rett-like syndrome	1	Gillespie syndrome	AD/AR	206700
				Spinocerebellar ataxia 15	AD	606658
				Spinocerebellar ataxia 29, congenital nonprogressive	AD	117360
<i>JMJD1C</i>	AD	Rett syndrome	1	NA		
<i>KCNA2</i>	AR	Rett-like syndrome with infantile onset seizures	1	Developmental and epileptic encephalopathy 32	AD	616366
<i>KCNB1</i>	AD	Rett syndrome, atypical	1	Developmental and epileptic encephalopathy 26	AD	616056
<i>KCNJ10</i>	AR	Rett syndrome	1	Enlarged vestibular aqueduct, digenic	AR	600791
				SESAME syndrome	AR	612780

<i>KCNQ2</i>	AD	Rett syndrome	1	Developmental and epileptic encephalopathy 7	AD	613720
				Myokymia	AD	121200
				Seizures, benign neonatal, 1	AD	121200
<i>KIF1A</i>	AR	Rett syndrome	2	NESCAV syndrome	AD	614255
				Neuropathy, hereditary sensory, type IIC	AR	614213
		Rett-like syndrome	1	Spastic paraplegia 30, autosomal dominant	AD/AR	610357
				Spastic paraplegia 30, autosomal recessive	AD/AR	610357
<i>KIF4B</i>	NA	Rett-like syndrome	1	NA		
<i>LAMB2</i>	AR	Rett syndrome	1	Nephrotic syndrome, type 5, with or without ocular abnormalities		614199
				Pierson syndrome	AR	609049
<i>LRRC40</i>	NA	Rett syndrome	1	NA		
<i>MAST1</i>	NA	Rett syndrome, atypical	1	Mega-corpor-callosum syndrome with cerebellar hypoplasia and cortical malformations	AD	618273
<i>MAST3</i>	NA	Rett-like syndrome	1	NA		

MECP2	XLD	Rett syndrome	719	{Autism susceptibility, X-linked 3}	XL	300496
				Encephalopathy, neonatal severe	XLR	300673
		Rett syndrome, atypical	22	Mental retardation, X-linked syndromic, Lubs type	XLR	300260
		Rett syndrome, preserved speech variant	5	Mental retardation, X-linked, syndromic 13	XLR	300055
		Rett-like syndrome	3	Rett syndrome	XLD	312750
		Rett syndrome, variant	1	Rett syndrome, atypical	XLD	312750
		Rett syndrome, variant, with autism	1	Rett syndrome, preserved speech variant	XLD	312750
MEF2C	AD	Rett syndrome	4	Chromosome 5q14.3 deletion syndrome	AD	613443
		Rett like features	1			
		Rett like intellectual disability	1	Mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations	AD	613443
		Rett/rett-like syndrome and/or non-syndromic intellectual disability	1			
MEIS2	NA	Rett syndrome, atypical	1	Cleft palate, cardiac defects, and mental retardation	AD	600987
MGRN1	NA	Rett-like syndrome	1	NA		
NALCN	AD/AR	Rett-like syndrome	1	Congenital contractures of the limbs and face, hypotonia, and developmental delay	AD	616266
				Hypotonia, infantile, with psychomotor retardation and characteristic facies 1	AR	615419
NCOR2	NA	Rett syndrome, atypical	1	NA		
		Rett-like syndrome	2			
NR2F1	AD	Rett-like syndrome	1	Bosch-Boonstra-Schaaf optic atrophy syndrome	AD	615722
NTNG1	NA	Rett syndrome	1	NA		

<i>NTNG2</i>	NA	Rett-like syndrome with areflexia	1	Neurodevelopmental disorder with behavioral abnormalities, absent speech, and hypotonia	AR	618718
<i>OSBP</i>	NA	Rett-like syndrome	1	NA		
<i>PDE2A</i>	NA	Rett syndrome, atypical	1	Intellectual developmental disorder with paroxysmal dyskinesia or seizures	AR	619150
<i>PDHA1</i>	XLD	Rett syndrome, atypical	1	Pyruvate dehydrogenase E1-alpha deficiency	XLD	312170
<i>PDLIM7</i>	NA	Rett-like syndrome	1	NA		
<i>PPT1</i>	AR	Rett syndrome, atypical	1	Ceroid lipofuscinosis, neuronal, 1	AR	256730
<i>PTPN4</i>	NA	Rett-like syndrome	1	NA		
<i>RHOBTB2</i>	NA	Rett-like syndrome	5	Developmental and epileptic encephalopathy 64	AD	618004
<i>RRN3</i>	NA	Rett-like syndrome	1	NA		
<i>SATB2</i>	AD	Rett-like syndrome	2	Glass syndrome	AD	612313
<i>SCN1A</i>	AD	Rett syndrome	2	Developmental and epileptic encephalopathy 6B, non-Dravet	AD	619317
				Dravet syndrome	AD	607208
				Epilepsy, generalized, with febrile seizures plus, type 2	AD	604403
		Rett-like syndrome	1	Febrile seizures, familial, 3A	AD	604403
				Migraine, familial hemiplegic, 3	AD	609634
<i>SCN2A</i>	AD	Rett syndrome	1	Developmental and epileptic encephalopathy 11	AD	613721
				Episodic ataxia, type 9	AD	618924
				Seizures, benign familial infantile, 3	AD	607745

SCN8A	AD	Rett syndrome, atypical	1	?Myoclonus, familial, 2	AD	618364
				Cognitive impairment with or without cerebellar ataxia	AD	614306
		Rett syndrome features	1	Developmental and epileptic encephalopathy 13	AD	614558
				Seizures, benign familial infantile, 5	AD	617080
SDHA	AD	Rett syndrome	1	Cardiomyopathy, dilated, 1GG	AR	613642
				Mitochondrial complex II deficiency, nuclear type 1	AR	252011
				Neurodegeneration with ataxia and late-onset optic atrophy	AD	619259
				Parangliomas 5	AD	614165
SEMA6B	NA	Rett-like syndrome	1	Epilepsy, progressive myoclonic, 11	AD	618876
SHANK3	AD	Rett syndrome	2	{Schizophrenia 15}	AD	613950
		Rett syndrome, atypical	1	Phelan-McDermid syndrome	AD	606232
		Rett-like syndrome	2			
SLC35A2	XLD	Rett-like syndrome	1	Congenital disorder of glycosylation, type II _m	SMo, XLD	300896
SLC39A13	AR	Rett syndrome, atypical	1	Ehlers-Danlos syndrome, spondylodysplastic type, 3	AR	612350
SLC6A1	AD	Rett syndrome	1	Myoclonic-atonic epilepsy	AD	616421
		Rett-like syndrome	2			
SMARCA1	NA	Rett syndrome	1	NA		

<i>SMC1A</i>	XLD	Rett syndrome	1	Cornelia de Lange syndrome 2	XLD	300590
		Rett-like syndrome	2	Developmental and epileptic encephalopathy 85, with or without midline brain defects	XLD	301044
<i>STXBP1</i>	AD	Rett syndrome	1	Developmental and epileptic encephalopathy 4	AD	612164
		Rett syndrome, atypical	1			
		Rett-like syndrome	2			
		Rett syndrome features	1			
<i>SYNGAP1</i>	AD	Rett-like syndrome	1	Mental retardation, autosomal dominant 5	AD	612621
<i>TBL1XR1</i>	AD	Rett-like syndrome	1	Mental retardation, autosomal dominant 41	AD	616944
				Pierpont syndrome	AD	602342
<i>TCF4</i>	AD	Rett syndrome, atypical	2	Corneal dystrophy, Fuchs endothelial, 3	AD	613267
		Rett syndrome, variant / Pitt-Hopkins syndrome	1			
		Rett-like syndrome	1	Pitt-Hopkins syndrome	AD	610954
<i>TRRAP</i>	AD	Rett syndrome, atypical	1	?Deafness, autosomal dominant 75	AD	618778
				Developmental delay with or without dysmorphic facies and autism	AD	618454
<i>UBE3A</i>	AD	Rett-like syndrome	1	Angelman syndrome	AD	105830
<i>USP8</i>	NA	Rett syndrome, atypical	1	Pituitary adenoma 4, ACTH-secreting, somatic	NA	219090
<i>WDR45</i>	XLD	Rett syndrome	2	Neurodegeneration with brain iron accumulation 5	XLD	300894
		Rett syndrome, atypical	2			
		Rett-like syndrome	2			
<i>ZNF620</i>	NA	Rett-like syndrome	1	NA		