

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		

CACNA1A	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
CACNA1D	NA	Rett-like syndrome	1	Primary aldosteronism, seizures, and neurologic abnormalities	AD	615474
				Sinoatrial node dysfunction and deafness	AR	614896
CACNA1G	AD	Rett-like syndrome	1	Spinocerebellar ataxia 42	AD	616795
				Spinocerebellar ataxia 42, early-onset, severe, with neurodevelopmental deficits	AD	618087
CACNA1I	NA	Rett-like syndrome	1	NA		
CAMK2B	NA	Rett-like syndrome	1	Mental retardation, autosomal dominant 54	AD	617799
CDKL5	XLD	CDKL5 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			
CHD4	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>FOXG1</i>	AD	<i>FOXG1</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

GABRG2	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
GRIA3	XLR	Rett-like syndrome	1	Intellectual developmental disorder, X-linked, syndromic, Wu type	XLR	300699
GRIN1	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
GRIN2A	AD	Rett syndrome, atypical	1	Epilepsy, focal, with speech disorder and with or without mental retardation	AD	245570
		Rett-like syndrome	1			
GRIN2B	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			
HCN1	NA	Rett-like syndrome	1	Developmental and epileptic encephalopathy 24	AD	615871
				Generalized epilepsy with febrile seizures plus, type 10	AD	618482
HDAC1	NA	Rett syndrome	1	NA		
HDAC8	XLD	Rett syndrome, atypical	1	Cornelia de Lange syndrome 5	XLD	300882
HECW2	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

KCNQ2	AD	Rett syndrome	1	Developmental and epileptic encephalopathy 7	AD	613720
				Myokymia	AD	121200
				Seizures, benign neonatal, 1	AD	121200
KIF1A	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
KIF4B	NA	Rett-like syndrome	1	NA		
LAMB2	AR	Rett syndrome	1	Nephrotic syndrome, type 5, with or without ocular abnormalities		614199
				Pierson syndrome	AR	609049
LRRC40	NA	Rett syndrome	1	NA		
MAST1	NA	Rett syndrome, atypical	1	Mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical malformations	AD	618273
MAST3	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
				Parangangliomas 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		

SMC1A	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
STXBP1	AD	Rett syndrome	1	Developmental and epileptic encephalopathy 4	AD	612164
		Rett syndrome, atypical	1			
		Rett-like syndrome	2			
		Rett syndrome features	1			
SYNGAP1	AD	Rett-like syndrome	1	Mental retardation, autosomal dominant 5	AD	612621
TBL1XR1	AD	Rett-like syndrome	1	Mental retardation, autosomal dominant 41	AD	616944
				Pierpont syndrome	AD	602342
TCF4	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
TRRAP	AD	Rett syndrome, atypical	1	?Deafness, autosomal dominant 75	AD	618778
				Developmental delay with or without dysmorphic facies and autism	AD	618454
UBE3A	AD	Rett-like syndrome	1	Angelman syndrome	AD	105830
USP8	NA	Rett syndrome, atypical	1	Pituitary adenoma 4, ACTH-secreting, somatic	NA	219090
WDR45	XLD	Rett syndrome	2	Neurodegeneration with brain iron accumulation 5	XLD	300894
		Rett syndrome, atypical	2			
		Rett-like syndrome	2			
ZNF620	NA	Rett-like syndrome	1	NA		