Table S2. Molecular functions and disease mechanisms associated with recessive cerebellar ataxia genes and encoded proteins, grouped by main clinical phenotype.

Gene	Protein	Subcellular localization	Molecular function(s)	Associated disease(s)	Disease mechanim(s)	References
Spastic ataxia						
SACS	Sacsin	Cytoplasm; Mitochondria	Co-chaperone of Hsp70 chaperone machinery; regulator of mitochondria dynamics; maintenance of cytoskeleton network	ARSACS	Loss-of-function: reduced chaperone activity, and altered mitochondria and neurofilament networks caused by sacsin depletion	[1-4]
KIF1C	Kinesin family member 1C (KIF1C)	Cytoskeleton/ microtubules	Anterograde movement of vesicles; retrograde transport from Golgi to ER	SPAX2; SPG58	Loss-of-function / gain-of-function? (functional studies are needed for confirmation)	[5-7]
ANO10	Anoctamin-10 (ANO10)	Plasma membrane	Regulates intracellular calcium signals	SCAR10/ ARCA3	Loss-of-function? (functional studies are needed for confirmation)	[8,9]
SPG11	Spatacsin	Cytoplasm; ER; Vesicles	Role in neuronal axonal growth, intracellular cargo trafficking and lysosome function	SPG11; ALS5; CMTD	Loss-of-function: impaired axonal transport and neurite outgrowth, and endolysosomal abnormalities due to spatacsin dysfunction	[10-14]
SYNE1	SYNE1/Nesprin-1	Nuclear envelope	Structural protein that links the nuclear envelope to the actin cytoskeleton (LINC complex)	ARCA1/ SCAR8; AMC; EDMD	Loss-of-function: nuclear morphology defects and defective synaptic transmission caused by nesprin-1 insufficiency	[15-18]
Ataxia and neuropathy						
POLG	DNA polymerase subunit gamma 1 (POLG)	Mitochondria	Involved in the replication of mtDNA and mtDNA repair	SANDO; SCAE; MDS; PEO	Loss-of-function: reduced POLG DNA polymerase activity and DNA-binding	[19-24]
Ataxia with oculomotor apraxia (AOA)						
SETX	Senataxin	Nucleus; Cytoplasm	Probable RNA/DNA helicase involved in transcription regulation, mRNA splicing and DNA damage response	AOA2; ALS4	Loss-of-function: altered gene expression and mRNA processing caused by senataxin disrupted function; Toxic gain-of-function: increased susceptibility to DNA-damaging agents	[25-28]

Gene	Protein	Subcellular localization	Molecular function(s)	Associated disease(s)	Disease mechanim(s)	References
PNKP	Polynucleotide kinase 3' phosphatase (PNKP)	Nucleus	Involved in DNA damage repair and cell cycle regulation	AOA4; MCSZ; CMTD	Loss-of-function: impaired DNA repair and cell cycle dynamics caused by hypomorphic PNKP	[29-32]
Ataxia and dystonia						
HEXB	Hexosaminidase subunit beta (HEXB)	Lysosome	Catalyzes the degradation of the GM2 ganglioside, and other molecules, in the lysosome	Sandhoff disease	Loss-of-function: accumulation of GM2 gangliosides and lysosomal abnormalities	[33,34]
Ataxia with cognitive impairment						
FA2H	Fatty acid 2-hydroxylase (FA2H)	ER membrane	Catalyzes the synthesis of 2-hydroxysphingolipids (myelin lipids)	SPG35	Loss-of-function: decreased hydroxylation of myelin lipid components	[35,36]

AMC3, arthrogryposis multiplex congenita; ALS, amyotrophic lateral sclerosis; AOA, ataxia and oculomotor apraxia; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; CMTD, Charcot-Marie-Tooth disease; EA, episodic ataxia; EDMD, Emery-Dreifuss muscular dystrophy; ER, endoplasmic reticulum; LINC, linker of nucleoskeleton and cytoskeleton; MCSZ, microcephaly, seizures, and developmental delay; MIRAS, mitochondrial recessive ataxia syndrome; MDS, mitochondrial DNA depletion syndrome; mtDNA, mitochondrial DNA; OA, oculomotor apraxia; SANDO, sensory ataxic neuropathy with dysarthria and ophthalmoparesis; SCAE, spinocerebellar ataxia with epilepsy; SPG, spastic paraplegia; PEO, progressive external ophthalmoplegia; WT, wild-type.

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