

Review Article

Intellectual Disability and Ataxia: Genetic Collisions

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Intellectual disability (ID) is a common and highly heterogeneous neurodevelopmental disorder. The prevalence of ID is around 1%–3% in the general population. ID is associated with a wide range of additional neurological disabilities and the results of various studies have disclosed the co-morbidity of ID and ataxia. The aim of this review is elucidation of the common molecular and cellular pathways in the etiology of ID and ataxia. Categorization of these genes with various cellular functions indicates several genetic collisions in the co-occurrence of ID and ataxia.

Keywords: Ataxia, Ciliogenesis, Ion channels, Intellectual disability, Mitochondria

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Introduction

Intellectual disability (ID) is characterized clinically by substantial limitations in intellectual functioning, and social and adaptive behavior. Its age of onset is before 18 years. The global prevalence of ID varies between 1% and 3%.^{1,2} In terms of severity, ID can be divided into mild, moderate, severe, and profound categories affecting about 85%, 10%, 4%, and 2% of the population, respectively.³ Etiologically, ID can be caused by exogenous factors, such as infections, maternal alcohol abuse during pregnancy, childbirth problems, and severe malnutrition, and by genetic factors. The genetic causes of ID have been linked to more than 50% of ID patients.^{4,5} Based on clinical manifestations, ID can be split into non-syndromic and syndromic types, occurring in isolation or with other co-morbid traits such as dysmorphic features and malformations, or neurological abnormalities such as epilepsy, spasticity and ataxia.⁶ Ataxia is a neurological sign consisting of uncoordinated movements and lack of muscle control during voluntary movements; however, it can also affect speech, eye movement and swallowing.⁷

ID syndromes with ataxia are a clinically and genetically heterogeneous group of neurological disorders. With the introduction of high-throughput sequencing technology such as next-generation sequencing (NGS), new disease-causing genes and mutations are being identified at a rapid pace (Figure 1).⁸ Despite differences in clinical manifestations between ID and ataxia, the involvement of similar cellular functions and molecular pathways indicates a common role of genetic background in ID associated with ataxia.

In this review, we highlight the genes that cause ID syndromes with ataxia. We mainly focus on the molecular and cellular nature of these genes.

Genes Linked to Intellectual Disability and Ataxia

Functional classification of proteins encoded by ID and ataxia-associated genes led to identification of common pathways and cellular and molecular mechanisms underlying the pathophysiology of these genes. These categorizations are very useful for investigation of the potential pathogenicity of new candidate genes for ID syndromes with ataxia. Therefore, functional categorization of these genes results in marking of similar cellular functions that contribute to normal development of human cognition and coordination of muscle movements.

Many classes of molecules participate in several cellular processes and regulate neuronal morphology and structure, proliferation, migration and communication, thus playing a critical role in normal cognition and coordination of voluntary movements and balance.

Metabolic Pathway

Despite the relatively small size of brain in adult humans, it accounts for 2% of our body mass and its metabolism consumes about 20% of the energy produced by the body. Therefore, efficient energy supply is crucial for brain function.⁹ Evolutionary studies in different species have demonstrated that higher cognitive abilities in humans are associated with high level of expression of metabolic genes followed by increased glucose utilization

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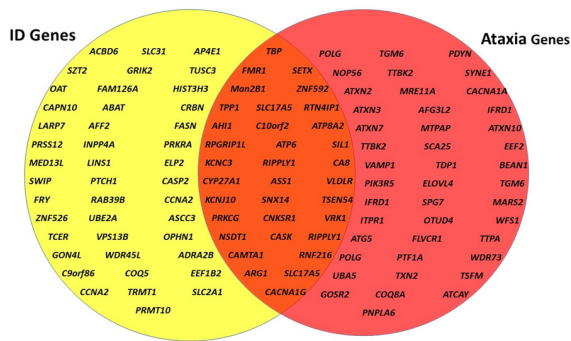


Figure 1. A number of intellectual disability (ID) genes, genes involved in cerebellar ataxia, and in the overlap, genes involved in both phenotypes/diseases.

in the brain. The bulk of the brain's energy budget is used in generating and maintaining ionic concentration gradients, and the release, uptake and recycling of neurotransmitters.^{10,11} Metabolic reprogramming is an essential and vital process during neuronal differentiation. Several enzymes such as CA8, GSS, NDST1 and TAT, accelerate, or catalyze, chemical reactions in metabolic pathways.^{12,13} However, as mentioned above, due to the

high metabolic rate of brain, genetic defects in several metabolic pathways such as amino acid, cholesterol, vitamin, pyrimidine and purine metabolism, and the urea cycle, are frequent causes of ID and other neurological signs such as ataxia (Table 1).

Urea Cycle

Deficiencies in any of the enzymes and cofactors involved in the metabolism of waste nitrogen in the urea cycle lead to urea cycle disorders (UCDs) (Figure 2). Almost 50% of children with neonatal onset UCDs suffer from ID because of accumulation of ammonia (hyperammonemia) in the blood and brain.¹⁴

Arginase is an enzymatic product of the *ARG1* gene. Mutations of the *ARG1* gene that lead to complete loss of enzyme function tend to cause one of the distal urea cycle defects called arginase deficiency.¹⁵ The neurologic symptoms and cerebral dysfunction of arginase deficiency caused by hyperammonemia, subsequently increase the amount of ammonia entering the brain.¹⁶ Unfortunately, no defense mechanism exists in neurons

Table 1. Genes Involved in Metabolic Pathways

Gene (Gene/Locus MIM Number)	Function	Inheritance	Disease Phenotype (MIM Number)
<i>ABCD1</i> (300371)	ATP binding cassette subfamily D member 1, brings very long-chain fatty acids (VLCFAs) into peroxisomes	XLR	Adrenoleukodystrophy (300100)
<i>ABHD5</i> (604780)	Acyltransferase for the synthesis of phosphatidic acid	AR	Chanarin-Dorfman syndrome (275630)
<i>ADCK3</i> (606980)	Involved in coenzyme Q10 synthesis	AR	Coenzyme Q10 deficiency, primary, 4 (612016)
<i>ALG6</i> (604566)	Asparagine-linked glycosylation 6 enzyme	AR	Congenital disorder of glycosylation, type Ic (603147)
<i>ARG1</i> (608313)	Involved in urea cycle	AR	Argininemia (207800)
<i>ASS1</i> (603470)	Argininosuccinate synthase 1 enzyme participates in the urea cycle	AR	Citrullinemia (215700)
<i>BTD</i> (609019)	Hydrolysis of biocytin	AR	Biotinidase deficiency (253260)
<i>CA8</i> (114815)	Interconversion of carbon dioxide and water to bicarbonate and protons	AR	Cerebellar ataxia and intellectual disability with or without quadrupedal locomotion 3 (613227)
<i>CLN5</i> (608102)	Lysosomal enzyme	AR	Ceroid lipofuscinosis, neuronal, 5 (256731)
<i>CUL4B</i> (300304)	Component of cullin 4B-RING ubiquitin ligase (E3) complex	XLR	Mental retardation, X-linked, syndromic 15 (Cabezas type) (300354)
<i>DLD</i> (238331)	Component of ubiquitin ligase (E3) complex	AR	Dihydroliipoamide dehydrogenase deficiency (246900)
<i>GPI</i> (172400)	Function in glycolysis	AR	Glucose phosphate isomerase deficiency (613470)
<i>GRID2</i> (602368)	Glutamate receptors	AR	Spinocerebellar ataxia, autosomal recessive 18 (616204)
<i>GRM1</i> (604473)	Glutamate receptors	AR	Spinocerebellar ataxia, autosomal recessive 13 (614831)
<i>GSS</i> (601002)	Glutathione synthetase participates in a process called the gamma-glutamyl cycle, for the production of glutathione	AR	Glutathione synthetase deficiency (266130)
<i>HEXA</i> (606869)	Lysosomal enzyme breaks down GM2 ganglioside	AR	Tay-Sachs disease (272800)
<i>HEXB</i> (606873)	Lysosomal enzyme breaks down GM2 ganglioside	AR	Sandhoff disease (268800)
<i>HPD</i> (609695)	4-hydroxyphenylpyruvate dioxygenase, converts 4-hydroxyphenylpyruvate to homogentisic acid	AR	Tyrosinemia, type III (276710)
<i>KIAA0226</i> (613516)	Vesicular trafficking and late endosome maturation	AR	Spinocerebellar ataxia, autosomal recessive 15 (615705)
<i>MAN2B1</i> (609458)	lysosomal enzyme breaks down alpha-linked mannose residues from the nonreducing end of N-linked glycoproteins	AR	Mannosidosis, alpha (248500)
<i>NEU1</i> (608272)	Neuraminidase, or lysosomal sialidase participates in intralysosomal catabolism of sialatedglycoconjugates	AR	Sialidosis (256550)
<i>NDST1</i> (600853)	Heparan sulfate biosynthesis	AR	Intellectual disability, autosomal recessive 46 (616116)
<i>NPC1</i> (607623)	Lysosomal membrane protein performs function in movement of cholesterol	AR	Niemann-Pick disease, type C1 (257220)

Table 1. Continued

<i>NPC2</i> (601015)	Lysosomal membrane protein performs function in movement of cholesterol	AR	Niemann-Pick disease, type C2 (607625)
<i>PEX2</i> (601757)	Peroxisome biogenesis	AR	Peroxisome biogenesis disorder 9B (614879) Rhizomelic chondrodysplasia punctata, type 1 (215100)
<i>PMM2</i> (601785)	Phosphomannomutase enzyme for the synthesis of GDP-mannose	AR	Congenital disorder of glycosylation, type Ia (212065)
<i>PNKP</i> (605610)	Polynucleotide kinase 3-prime phosphatase	AR	Microcephaly, seizures, and developmental delay (613402)
<i>PRPS1</i> (311850)	Involved in salvage pathways of purine and pyrimidine biosynthesis	XLR	Arts syndrome (301835) Charcot-Marie-Tooth disease, X-linked recessive, 5 (311070) Gout, PRPS-related (300661)
<i>RNF216</i> (609948)	Functions as an E3 ubiquitin-protein ligase	AR	Cerebellar ataxia and hypogonadotropic hypogonadism (212840)
<i>SLC2A1</i> (138140)	Transports dehydroascorbic acid into the brain	AR	Dystonia 9 (601042) GLUT1 deficiency syndrome 1, infantile onset, severe (606777) GLUT1 deficiency syndrome 2, childhood onset (612126) Stomatin-deficient cryohydrocytosis with neurologic defects (608885) Epilepsy, idiopathic generalized, susceptibility to, 12 (614847)
<i>SLC9A6</i> (300231)	Monovalent sodium-selective sodium/hydrogen exchanger (NHE)	XLD	Intellectual disability, X-linked syndromic, Christianson type (300243)
<i>SLC17A5</i> (604322)	Vesicular excitatory amino acid transporter (VEAT)	AR	Salla disease (604369) Sialic acid storage disorder, infantile (269920)
<i>SMPD1</i> (607608)	Sphingomyelin phosphodiesterase 1, lysosomal enzyme for the conversion of sphingomyelin into ceramide	AR	Niemann-Pick disease, type A, type B (257200, 607616)
<i>SNX14</i> (616105)	Member of the sorting nexin family. Regulator of the G protein signaling (RGS)	AR	Spinocerebellar ataxia, autosomal recessive, 20 (SCAR20) (616354)
<i>TAT</i> (613018)	Tyrosine aminotransferase converts tyrosine into a byproduct called 4-hydroxyphenylpyruvate	AR	Tyrosinemia, type II (276600)
<i>TPP1</i> (607998)	Lysosomal exopeptidase	AR	Ceroid lipofuscinosis, neuronal, 2 (204500) Spinocerebellar ataxia, autosomal recessive 7 (609270)
<i>UBE3A</i> (601623)	E3 ligase in the ubiquitin proteasome pathway	IC	Angelman syndrome (105830)

Abbreviations: XLR, X-linked recessive; AR, autosomal recessive; XLD, X-linked dominant; IC, imprinting center.

against elevated ammonia concentration; therefore, high levels of ammonia impair the brain's function by altering nerve signal transmission.¹⁷ On the other hand, ammonia concentration can alter the gene expression profile of the

brain.¹⁸ Therefore, these alterations in gene expression in brain can be responsible for neurological signs of disease as a result of changes in structure, function and neurotransmitter activity of neuronal cells. Mutations in

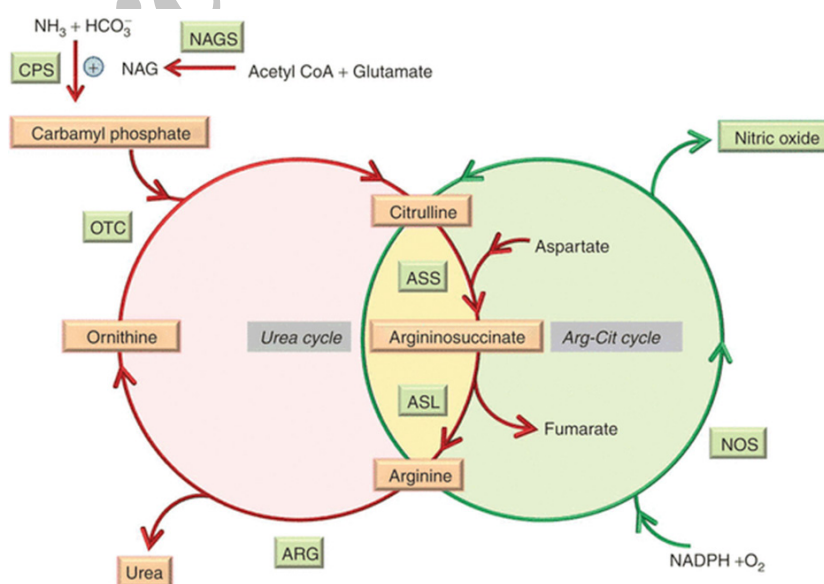


Figure 2. The urea and Krebs Cycle. The urea-cycle functions to facilitate ammonia excretion, a ubiquitous waste product of protein metabolism in mammals. ASS (argininosuccinatesynthetase) and ARG (Arginase) deficiencies are associated with ID and ataxia. Adopted from Erez et al.⁸

the *ASS1* gene are associated with another UCD with ID and ataxia called citrullinemia type I. This gene provides instructions for an enzyme, argininosuccinate synthase1 that is responsible for one step of the urea cycle. Mutations in the *ASS1* gene disrupt the production of the enzyme leading to accumulation of ammonia during the first few days of life and subsequently cause neuronal damage as discussed above.¹⁹

Pyrimidine and Purine Metabolism

In addition to their role in “genetic information storage”, purine and pyrimidine nucleotides are energy carriers in metabolic pathways. Several inherited disorders of nucleotide metabolism indicate the importance of this class of small organic molecule as neurotransmitters in neuronal differentiation and function.²⁰ In addition, nucleotides play a critical role in neuron–glia communication and this reciprocal communication is essential for axonal conduction, synaptic transmission, and information processing.^{21,22}

Phosphoribosyl pyrophosphate synthetase 1 (*PRPS1*) catalyzes the phosphoribosylation of ribose 5-phosphate to 5-phosphoribosyl-1-pyrophosphate which is necessary for purine metabolism and nucleotide biosynthesis. Missense mutations in *PRPS1* lead to X-linked Charcot-Marie-Tooth disease-5 (*CMTX5*), Arts syndrome, gout, *PRPS*-related and X-linked nonsyndromic sensorineural deafness (*DFN2*). Notably, some neurological symptoms such as ataxia and ID are reported in patients with *PRPS1* superactivity or impaired activity.²³ Because of the high level of metabolism and large demand for ATP in neuronal cells, maintaining the appropriate level and balance of nucleotides is essential for DNA integrity and preventing neurodegeneration.²⁴

Lysosomal enzyme

Membrane-enclosed organelles called lysosomes that contain a wide array of enzymes are responsible for the physiologic turnover of all types of cell constituents. More than 50 lysosomal protein deficiencies have been described. Lysosomal storage diseases are inherited metabolic diseases that are characterized by accumulation of undigested or partially digested macromolecules and various toxic materials in body cells.²⁵ The blood–brain barrier plays a critical role in deterioration of both intellect and neurological functions in lysosomal storage diseases.²⁶

Alpha-mannosidase is a lysosomal enzyme encoded by *MAN2B1* gene. The absent or deficient activity of the enzyme alpha-mannosidase causes autosomal recessive lysosomal storage disorder, alpha-mannosidosis. As a result, vacuolated neurons and morphological changes are seen in different parts of the nervous system and

cerebral cortex. Eventually, abnormal accumulations of mannose-containing oligosaccharide vacuoles lead to cell death.^{27,28}

Recent findings indicate the essential role of sorting nexin 14 (*SNX14*) gene in neural development and function, especially in the cerebellum. According to recent findings, mutations in *SNX14* lead to distinctive autosomal-recessive cerebellar ataxia and ID syndrome and a syndromic form of cerebellar atrophy and lysosome-autophagosome dysfunction. *SNX14* encodes a ubiquitously expressed cellular protein localized to lysosomes. *SNX14* contains Phox (PX) and regulator of G protein signaling (RGS) domains and is associated with phosphatidylinositol (3,5)-bisphosphate, which plays a key role in vesicle trafficking in eukaryotic cells.^{29,30}

Mitochondrial Metabolism

The indispensable role of mitochondria in energy metabolism indicates that this organelle has enormous potential to influence health factors. The tremendous energy demands of cells in the nervous system are met by the powerhouse of the cell, mitochondria. On the other hand, mitochondria act as a gatekeeper in apoptotic and non-apoptotic cell death. Therefore, mitochondrial disorders (MCDs) are multi-organ disorders with clinically heterogeneous features, and neurons are one of the most commonly affected cells in MCDs. Consequently, impaired mitochondrial function (mitochondrial fusion/fission, morphology, size, transport/trafficking, and movement) contributes to neurodevelopmental manifestations and neurologic signs that present in about 45% of these patients.^{31,32} Mutations in some of the mitochondrial and nuclear genes (Table 2) underlie mitochondrial syndrome, expressed as ID and ataxia.

The *CYP27A1* gene encodes for cytochrome P450 oxidases, a mitochondrial member of the cytochrome P450 gene family. The protein product of *CYP27A1* gene, often known as sterol 27-hydroxylase, is ubiquitously expressed and is located in mitochondria. Mutations in this gene cause an autosomal recessive disorder, cerebrotendinous xanthomatosis. The main role of this enzyme is oxidation of cholesterol intermediates for the biosynthesis of bile acids.³³ Cholesterol is a multifaceted molecule. Various studies have confirmed the structural (the major lipid of myelin is cholesterol) and functional role of cholesterol in the brain for synapse development and stability.³⁴⁻³⁶ Analysis of hedgehog signaling pathway demonstrates that cholesterol plays a vital role in cellular metabolism and postnatal CNS development.³⁷ A recent study indicated that cholesterol overload impairs cerebellar function.³⁸

Mutations in the *DNAJC19* gene cause a novel autosomal recessive Barth syndrome-like condition,

Table 2. Genes Involved in Mitochondrial Metabolism

Gene	Function	Inheritance	Disease Phenotype (MIM Number)
<i>ACO2</i> (100850)	Mitochondrial enzyme, interconversion of citrate to isocitrate in the Krebs cycle	AR	Infantile cerebellar-retinal degeneration (614559)
<i>ALDH5A1</i> (610045)	Mitochondrial enzyme, aldehyde dehydrogenase 5 family, member A1 involved in breakdown of gamma-amino butyric acid (GABA) neurotransmitter	AR	Succinic semialdehyde dehydrogenase deficiency (271980)
<i>ATP6</i> (516060)	Complex V (ATP synthase) of the mitochondrion	Mit	Leigh syndrome (256000) NARP syndrome
<i>ATP8A2</i> (605870)	P(4)-ATPase subfamily of P-type ATPases	AR	Cerebellar ataxia, intellectual disability, and disequilibrium syndrome 4 (615268)
<i>C10orf2</i> (606075)	Binds to mitochondrial DNA and catalyzed DNA unwinding	AR	Mitochondrial DNA depletion syndrome 7 (Hepatocerebral type) (271245)
<i>COX1</i> (516030)	Cytochrome c oxidase subunit I	Mit	Leber Hereditary Optic Neuropathy; LHON
<i>COX10</i> (602125)	Cytochrome c oxidase (COX) assembly protein involved in the mitochondrial heme biosynthetic pathway	AR	Leigh syndrome (256000)
<i>CYP27A1</i> (606530)	Sterol 27-hydroxylase, a mitochondrial cytochrome P450, breaks down cholesterol to form a bile acid called chenodeoxycholic acid	AR	Cerebrotendinousxanthomatosis (213700)
<i>DNAJC19</i> (608977)	Transport other proteins into and out of mitochondria and protein assembly	AR	3-methylglutaconic aciduria, type V (610198)
<i>LRPPRC</i> (607544)	Leucine-rich PPR-motif containing, plays a role in cytoskeletal organization, vesicular transport, or in transcriptional regulation of both nuclear and mitochondrial genes	AR	Leigh syndrome, French-Canadian type (220111)
<i>MRPL10</i> (611825)	Components of mitochondrial ribosomes	AR	Intellectual disability, ataxia
<i>ND5 (MTND5)</i> (516005)	Subunit of mitochondrial NADH, complex I	Mit	Leber hereditary optic neuropathy (LHON); (535000), MELAS syndrome (540000), Leigh syndrome (256000), complex I deficiency (252010)
<i>NDUFA1</i> (300078)	Subunit of mitochondrial NADH, complex I	XLD	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>NDUFS1</i> (157655)	NADH-ubiquinone oxidoreductase fe-s protein 1, a subunit of mitochondrial NADH, complex I	AR	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>NDUFS2</i> (602985)	NADH-ubiquinone oxidoreductase fe-s protein 2, a subunit of mitochondrial NADH, complex I	AR	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>NDUFS4</i> (602694)	NADH-ubiquinone oxidoreductase fe-s protein 4, a subunit of mitochondrial NADH, complex I	AR	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>NDUFS7</i> (601825)	NADH-ubiquinone oxidoreductase fe-s protein 7, a subunit of mitochondrial NADH, complex I	AR	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>NDUFS8</i> (602141)	NADH-ubiquinone oxidoreductase fe-s protein 8, a subunit of mitochondrial NADH, complex I	AR	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>NDUFV1</i> (161015)	NADH-ubiquinone oxidoreductase flavoprotein1, a subunit of mitochondrial NADH, complex I	AR	Leigh syndrome due to mitochondrial complex I deficiency (256000)
<i>PDHA1</i> (300502)	Nuclear-encoded mitochondrial matrix enzyme, converts pyruvate into acetyl-CoA	XLD	Pyruvate dehydrogenase E1-alpha deficiency (312170)
<i>PDHX</i> (608769)	Component X of the pyruvate dehydrogenase (PDH) complex	AR	Lacticacidemia due to PDX1 deficiency (245349)
<i>PDP1</i> (605993)	Catalyzes the dephosphorylation reactivation of the mitochondrial pyruvate dehydrogenase multienzyme complex	AR	Pyruvate dehydrogenase phosphatase deficiency (608782)
<i>RARS2</i> (611524)	Mitochondrial arginine-tRNAsynthetase	AR	Pontocerebellar hypoplasia, type 6 (611523)
<i>RTN4IP1</i> (610502)	Mitochondrial protein interacts with reticulon 4	AR	Optic atrophy 10 with or without ataxia, intellectual disability, and seizures (616732)
<i>SDHA</i> (600857)	Succinate dehydrogenase complex, subunit A	AR	Mitochondrial respiratory chain complex II deficiency (252011) Leigh syndrome (256000)
<i>SURF1</i> (185620)	Assembly factor of mitochondrial complex IV	AR	Charcot-Marie-Tooth disease, type 4K (616684) Leigh syndrome, due to COX IV deficiency (256000)
<i>TIMM8A</i> (300356)	Transports proteins across the intermembrane space to the mitochondrial inner membrane	XLR	Mohr-Tranebjaerg syndrome (304700)
<i>TRNK</i> (590060)	Mitochondrial tRNA for lysine	Mit	Myoclonic Epilepsy Associated with Ragged-Red Fibers; MERRF (545000)
<i>TRNL1</i> (590050)	Mitochondrial tRNA for leucine	Mit	Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes; MELAS (540000)
<i>TRNS1</i> (590080)	Mitochondrial tRNA for serine	Mit	MERRF (545000)
<i>TRNV</i> (590105)	Mitochondrial tRNA for valine	Mit	MELAS (540000)

Abbreviations: AR, autosomal recessive; Mit, mitochondrial; XLD, X-linked dominant; XLR, X-linked recessive.

dilated cardiomyopathy with ataxia (DCMA) syndrome. The protein product of *DNAJC19* gene (DnaJ heat shock protein family [Hsp40] member C19) is a component of the mitochondrial protein import system. Neuropathological examination of DCMA patients has revealed a minor diffuse atrophy of brain stem which could explain the ataxia in those patients.³⁹

Regulation of Gene Expression

Sophisticated techniques and a wide range of mechanisms are used by cells to adjust gene expression levels. The regulation of gene expression has multiple aspects, from transcriptional initiation to post-translational modification of a protein so that all steps in this process can be modulated by various factors.⁴⁰ Brain is the most complex organ in human body. The gene-expression profile of human brain indicates that more than 80% of human genes are active in brain. This explains the complexity of brain-related diseases and the importance of gene expression regulation factors.⁴¹ Many types of

gene expression factor are listed in Table 3.

ZNF592 is a zinc-finger protein, and includes 13 classical C2H2-type ZnF domains. Mutations of the *ZNF592* gene cause CAMOS (cerebellar ataxia with ID, optic atrophy and skin abnormalities) (SCAR5). ZNF592 acts as a transcription regulator by DNA, RNA and protein binding and plays a critical role in various processes, such as transcription, translation, metabolism, and the signaling pathway. *ZNF592* expressed ubiquitously in all human adult tissues and significantly in the nervous system and skeletal muscle. Elevated levels of cyclin D1 and cyclin D2 in CAMOS patients lead to disruption of the proliferation and differentiation processes in cerebellar granule neuron precursors.⁴²

NKX2 mutations are responsible for about 50% of benign hereditary chorea (BHC) disease. This disease demonstrates genetic heterogeneity and remarkable intra- and inter-familial phenotypic variability such as dysarthria, gait disturbances, mental impairment or axial dystonia, and progression in adulthood. The NKX2-

Table 3. Genes Involved in Regulation of Gene Expression

Gene	Function	Inheritance	Disease Phenotype (MIM Number)
<i>ATN1 (DRPLA)</i> (607462)	Transcriptional co-repressor in nerve cells	AD	Dentatorubro-pallidoluyisian atrophy (125370)
<i>ATXN1</i> (601556)	Transcriptional repression by binding to RNA	AD	Spinocerebellar ataxia 1 (164400)
<i>CAMTA1</i> (611501)	Calmodulin Binding Transcription Activator 1	AD	Cerebellar ataxia, non-progressive, with intellectual disability (614756)
<i>CHMP1A</i> (164010)	Chromatin-modifying protein	AR	Pontocerebellar hypoplasia, type 8 (614961)
<i>EXOSC3</i> (606489)	Subunit of RNA exosome complex	AR	Pontocerebellar hypoplasia, type 1B (614678)
<i>EXOSC8</i> (606019)	Subunit of RNA exosome complex	AR	Pontocerebellar hypoplasia, type 1C (616081)
<i>FMR1</i> (309550)	RNA-binding protein involved in translation	XLD	Fragile X tremor/Ataxia syndrome (300623)
<i>FOXP2</i> (605317)	Forkhead Box P2, putative transcription factor containing a polyglutamine tract and a forkhead DNA binding domain	AD	Speech-language disorder-1
<i>MECP2</i> (300005)	Binds methylated CpGs, chromatin-associated protein	XLD	Rett syndrome (312750)
<i>NKX2-1 (TTF1)</i> (600635)	Transcription factor	AD	Chorea, hereditary benign (BHC)(118700) Choreoathetosis and congenital hypothyroidism with or without pulmonary dysfunction (CAHTP) (610978)
<i>POLR3B</i> (614366)	Subunit of RNA polymerase (pol) III	AR	Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism (614381)
<i>PTRH2</i> (608625)	Prevents the accumulation of dissociated peptidyl-tRNAs	AR	Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (616263)
<i>RIPPLY1</i> (300575)	Transcriptional repressor	AR	Intellectual disability, ataxia
<i>SACS</i> (604490)	Sacsin molecular chaperone	AR	Spastic ataxia, Charlevoix-Saguenay type (270550)
<i>SETX</i> (608465)	Involved in transcription and RNA processing	AR	Spinocerebellar ataxia, autosomal recessive 1 (606002)
<i>SPG11</i> (610844)	Controls gene expression	AR	Spastic paraplegia 11, autosomal recessive (604360)
<i>STUB1</i> (607207)	Cochaperone	AR	Spinocerebellar ataxia, autosomal recessive 16 (615768)
<i>TBP</i> (600075)	TATA box binding protein, DNA-binding subunit of TFIID	AD	Spinocerebellar ataxia 17 (607136)
<i>TSEN2</i> (608753)	Subunit of tRNA splicing endonuclease complex	AR	Pontocerebellar hypoplasia type 2B (612389)
<i>TSEN34</i> (608754)	Subunit of tRNA splicing endonuclease complex	AR	Pontocerebellar hypoplasia type 2C (612390)
<i>TSEN54</i> (608755)	Subunit of tRNA splicing endonuclease complex	AR	Pontocerebellar hypoplasia type 2A (277470)
<i>VWA3B</i> (614884)	Functions in transcription and DNA repair	AR	Spinocerebellar ataxia, autosomal recessive 22 (616948)
<i>ZNF592 (KIAA0211)</i> (613624)	Zinc finger protein 592, regulatory function involved in cerebellar development	AR	Spinocerebellar ataxia autosomal recessive 5

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant.

1 (*TITF1*) gene encodes thyroid-specific transcription factor-1 (TTF-1). The protein regulates the expression of thyroid-specific genes by binding to thyroglobulin promoter and eventually engages the production of thyroglobulin, thyroid peroxidase and thyrotropin.⁴³ *NKX2* is expressed in early embryonic stages in brain, but is not detected in adult humans. *Nkx2* plays a major role in healthy development of nervous system by regulation of neuronal fate in progenitor cells and directs neuronal migration. Downregulation of postmitotic *Nkx2* expression is an indispensable event for promoting migration of interneurons – a nerve cell found entirely within the central nervous system that acts as a link between sensory neurons and motor neurons – to the striatum (part of the basal ganglia) and cerebral cortex.⁴⁴⁻⁴⁶ Of note, dysfunction of the vestibular system of cerebral cortex can cause vestibular ataxia and ID.

The nervous system is the most complicated network in human body. Recent evidence indicates that other aspects of gene regulation, such as alternative pre-mRNA splicing, play a critical role in neuronal development by altering the diversity of the transcripts.⁴⁷ The evolutionarily conserved *FOXP2* gene is a forkhead-domain gene which encodes for a distinctive transcription factor with a forkhead DNA-binding domain and polyglutamine tract. *FOXP2* expressed in human fetal and adult brain as well as in other tissues such as lung and gut. The significant dysregulation of alternative splicing has been confirmed by the loss of *FOXP2* as indicated in splicing-sensitive microarray profiling experiments. Improperly spliced mRNAs, particularly sodium channel transcript splicing, in *FOXP2* mutants disrupt cerebellar development and mature motor function.⁴⁸

Rett syndrome is a type of neurodevelopmental disorders which occurs practically exclusively in young females. Mutations in methyl DNA binding protein 2 (*MeCP2*) cause the majority of cases of Rett syndrome. *MeCP2* protein is a crucial epigenetic factor that acts as a multifunctional nuclear protein, with an important role in chromatin architecture, activation of transcription and regulation of RNA splicing.⁴⁹ A recent study indicated the functional role of *MeCP2* in dendritic morphology, synaptic plasticity and excitatory neurotransmission. Magnetic resonance imaging (MRI) detected cerebellar degeneration and other neuroanatomic changes in patients with Rett syndrome.^{50,51}

Cytoskeleton Dynamics, Cell Adhesions and Migration

An outstanding neuropathological feature of patients with ID is altered dendritic spine morphogenesis. The polarized morphology of neurons, the normal structure and branching of dendrites, spines and cell adhesion components are important for sorting and trafficking

of cargos between axons and dendrites, transmission of neural signals and cell migration. The cytoskeletal, cell adhesion components and signaling molecules are vital elements in neuronal architecture (Table 4).⁵²⁻⁵⁴

Microtubules are one of the important heterodimer components of the cytoskeleton. *TUBA1A* gene encodes for alpha-tubulin (α -tubulin) protein. *TUBA1A* is a member of tubulin superfamily, which is composed of six distinct families. Mutations in *TUBA1A* gene affect brain development and cause lissencephaly with cerebellar hypoplasia (LCH). LCH appears with ID, ataxia, epilepsy and hypertonia. Several reports have shown that *TUBA1A* defects are associated with impaired neuronal migration, differentiation and axonal transport.^{55,56}

Signaling molecules and pathways that regulate actin-cytoskeleton organization play an important role in the structure and function of neurons. Members of the family of small Rho GTPase are key regulators of actin dynamics.⁵⁷ Rho proteins belong to guanine nucleotide-binding proteins, so cycling between active and inactive states of these pathways is controlled by several positive and negative regulators: GEFs (guanine nucleotide exchange factors), GAPs (GTPase activating proteins), and GDIs (guanine nucleotide disassociation inhibitors).⁵⁸ Patients with mutations in several genes from these pathways, such as *OPHN1*, *ARHGEF6* and *ARHGEF9* suffer from ID.⁵⁹⁻⁶³

The *CNKSR1* gene encodes for connector enhancer of kinase suppressor of Ras 1, acts as a scaffold component for receptor tyrosine kinase signaling, and acts as a mediator of crosstalk between Rho, Ras and Raf signal transduction pathways. Najmabadi et al identified a novel frameshift mutation in *CNKSR1* gene in a family with syndromic autosomal recessive ID, with severe ID, cerebellar atrophy, ataxia and quadrupedal gait. On the other hand, a novel mutation in *RALGDS* gene was also identified by Najmabadi and colleagues.⁶⁴ *Ral* guanine nucleotide dissociation stimulator encoded by *RALGDS* gene is a guanine nucleotide dissociation stimulator. This protein acts as an effector of the Ras-related GTPase *Ral*, and stimulates the dissociation of GDP from the Ras-related *RalA* and *RalB* GTPases, thereby allowing GTP binding and activation of the GTPases. *RALGDS* protein is in direct interaction with *CNKSR1* protein in the Ras/Rho signaling network. It is interesting that ataxia occurred along with ID in one of the other families investigated in the study by Najmabadi et al. A recent study showed that cell mobility increases by RhoA-dependent activation of C-Jun N-terminal kinase (JNK) as a result of phosphorylation-independent ephrinB1 interaction with *CNKSR1* protein.^{64,65}

VLDLR gene, which codes for the very low-density lipoprotein receptor, plays a vital role in the reelin signaling

Table 4. Genes Involved in Cytoskeleton Dynamics, Cell Adhesions and Migration

Gene	Function	Inheritance	Disease Phenotype (MIM Number)
<i>ATM</i> (607585)	DNA repair and cell cycle control	AR	Ataxia-telangiectasia (208900)
<i>APTX</i> (606350)	Member of the histidine triad (HIT) superfamily, an ancient superfamily of nucleotide hydrolases and transferases	AR	Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia (208920)
<i>CASK</i> (300172)	Calcium/calmodulin-dependent serine protein kinase associated with intercellular junctions	XLD	Mental retardation and microcephaly with pontine and cerebellar hypoplasia (300749)
<i>CNKSR1</i> (603272)	Scaffold protein in MAPK pathway	AR	Intellectual disability, microcephaly, ataxia
<i>FGF14</i> (601515)	Subclass of fibroblast growth factors involved in MAPK signaling pathway	AD	Spinocerebellar ataxia 27 (609307)
<i>GFAP</i> (137780)	Intermediate-filament (IF) protein	AD	Alexander disease (203450)
<i>ITPR1</i> (147265)	Inositol 1,4,5-triphosphate (IP3) receptor	AD	Spinocerebellar ataxia 15 (606658) Spinocerebellar ataxia 29, congenital non-progressive (117360)
<i>OPHN1</i> (300127)	Rho GTPase-activating protein	XLR	Intellectual disability, X-linked, with cerebellar hypoplasia and distinctive facial appearance (300486)
<i>PLP1</i> (300401)	Main proteins found in myelin	XLR	Pelizaeus-Merzbacher disease (312080) Spastic paraplegia 2, X-linked (312920)
<i>PPP2R2B</i> (604325)	Heterotrimeric serine/threonine phosphatase	AD	Spinocerebellar ataxia 12 (604326)
<i>PRKCG</i> (176980)	Member of the protein kinase C (PKC) gene family	AD	Spinocerebellar ataxia 14 (605361)
<i>PRRT2</i> (614386)	Involved in signaling between nerve cells	AD	Episodic kinesigenic dyskinesia 1 (128200)
<i>RALGDS</i> (601619)	Ral guanine nucleotide dissociation stimulator	AR	Intellectual disability, ataxia
<i>SIL1</i> (608005)	Nucleotide exchange factor	AR	Marinesco-Sjogren syndrome (248800)
<i>SPTBN2</i> (604985)	Links to short actin filaments	AR	Spinocerebellar ataxia, autosomal recessive 14 (615386)
<i>SYT14</i> (610949)	Encodes membrane-trafficking proteins	AR	Spinocerebellar ataxia, autosomal recessive 11 (614229)
<i>TUBA1A</i>	Member of tubulin family protein, main components of microtubules	AD	Lissencephaly 3 (611603)
<i>VLDLR</i> (602529)	Very low density lipoprotein receptor, part of the reelin signaling pathway	AR	Disequilibrium syndrome (224050)
<i>VRK1</i> (602168)	Involved in the regulation of cell division	AR	Pontocerebellar hypoplasia type 1A (607596)
<i>WDR81</i> (614218)	Inhibit sphosphoinositide 3-kinase (PI3K) pathway	AR	Cerebellar ataxia, mental retardation, and disequilibrium syndrome 2 (610185)
<i>WWOX</i> (605131)	Involved in TGFβ1 signaling and TGFβ1-mediated cell death	AR	Spinocerebellar ataxia, autosomal recessive 12 (614322)

Abbreviations: AR, autosomal recessive; AD, autosomal dominant; XLD, X-linked dominant; XLR, X-linked recessive.

pathway. Reelin is a large secreted extracellular matrix glycoprotein. Autosomal recessive mutations of the *VLDLR* gene, which are associated with cerebellar ataxia and ID, lead to cerebellar hypoplasia and disequilibrium syndrome (DES). The reelin pathway plays vital roles in axonal branching, synaptogenesis, and neuroblast migration in the cerebral cortex and cerebellum.^{66,67}

Ciliogenesis

Cilia are polarized, hair-like cellular extensions emanating from the cell surface of almost all vertebrate cells. They are composed of microtubules and are derived from the mother centriole and they are anchored by the basal body to the cell surface. In the recent past, cilia were considered exclusively a vestigial organelle without critical biological function but research over the past decade has demonstrated that cilia perform a critical role as a regulator of alterations of cellular shape in response to environmental factors, hence regulating differentiation, migration, and cell growth during development and in adulthood (Table 5).^{68,69} Some neurological manifestations

such as ID, hydrocephalus, cerebellar malformation, ataxia and oculomotor apraxia are more prevalent in the spectrum of ciliopathy diseases.⁷⁰ Most ciliopathies, such as Joubert syndrome (JBTS), Meckel-Gruber syndrome (MKS), and Bardet-Biedl syndrome (BBS), are classified as genetic syndromes. The association of ataxia with ID is a common feature of Joubert syndrome in ciliopathies (Figure 3).⁷¹

Jouberin is encoded by Abelson helper integration site 1 (*AHI1*) gene at the JBTS3 locus. *AHI1* mutations are a cause of Joubert syndrome 3 (JBTS3). To characterize the function of Jouberin in mouse brain, it has been suggested that Jouberin is strongly expressed in mouse brain during periods of both cortical and cerebellar development. On the other hand, *AHI1* is expressed in cells that play a critical role in crossing of neurons in the nervous system therefore abnormal axonal decussation has been seen in individuals with Joubert syndrome.^{72,73} Jouberin is an element of the tectonic-like complex that is embedded in the transition zone of primary cilia as an obstacle to prevent transmembrane protein diffusion

Table 5. Genes Involved in Ciliogenesis

Gene	Function	Inheritance	Disease Phenotype (MIM Number)
<i>AHI1</i> (608894)	Component of a protein complex in the basal body, functions in the transition zone at the base of cilia	AR	Joubert syndrome-3 (608629)
<i>CEP290</i> (610142)	Plays an important role in cell structures called centrosomes and cilia	AR	Joubert syndrome 5 (610188)
<i>INPP5E</i> (613037)	Hydrolyzes Ins (1,4,5) P ₃ , which acts as a second messenger mediating cell by mobilizing intracellular calcium	AR	Joubert syndrome 1 (213300)
<i>KIF7</i> (611254)	Cilia-associated protein belonging to the kinesin family that plays a role in the hedgehog signaling pathway	AR	Joubert syndrome 12 (200990)
<i>RPGRIP1L</i> (610937)	Colocalized at the basal body-centrosome complex with nephrocystin-4	AR	Joubert syndrome 7 (611560)
<i>TMEM67</i> (609884)	Transmembrane protein 67 functions in centriole migration to the apical membrane and formation of the primary cilium	AR	Joubert syndrome 6 (610688)

Abbreviation: AR, autosomal recessive.

within the cilia and plasma membranes.⁷⁴

Disruption of protein–protein interactions occurs in the ciliary and basal body protein network involved in the pathogenesis of nephronophthisis (NPHP), Leber congenital amaurosis, Senior-Løken syndrome (SLSN) or Joubert syndrome (JBTS).⁷⁵

Meckelin protein is encoded by the *TMEM67* gene in human. The homozygous or compound heterozygous mutations of *TMEM67* gene are associated with Joubert syndrome 6, Meckel syndrome 3, Bardet-Biedl syndrome 14, COACH syndrome and Nephronophthisis 11. All Joubert syndrome patients with *TMEM67* mutations have ataxia associated with ID. Meckelin localizes to the

plasma membrane and to the primary cilium in association with centriole migration to the apical membrane and formation of the primary cilium.⁷⁶

Subcellular localization of ubiquitously expressed *RPGRIP1L* protein in basal body–centrosome complex establishes the main role of this protein in cilia and basal bodies in cells. Analysis of the molecular mechanisms of the basal body protein network indicates interaction of *RPGRIP1L*, *CEP290* and nephrocystin-4 in mammalian cells, and various studies have revealed the association of these proteins with JBTS. Defects in *RPGRIP1L* (KIAA1005) are involved in the pathogenesis of Cerebello-oculo-renal syndrome (CORS), also called Joubert syndrome type B.⁷⁷

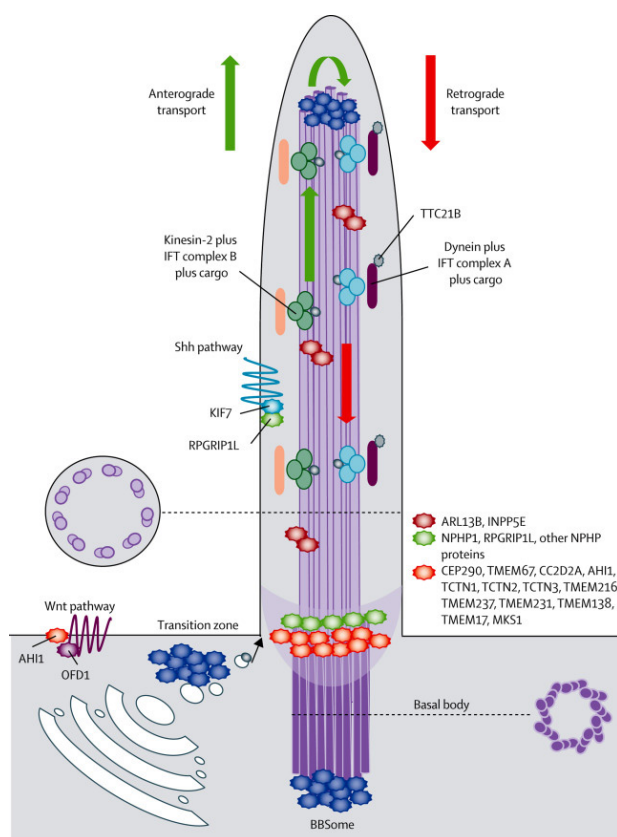


Figure 3. Cilia Structure and Protein Complexes. Large multiprotein complexes at the basal body and transition zone of the cilium participate in ciliogenesis and regulation of vital signaling pathways. Adopted from Romani et al.⁷¹

Ion Channels

Ion channels provide small pores for passive diffusion of ions across cellular membranes depending on the electrochemical gradient by a process called gating. They perform a pivotal role in chemical signaling, adjustment of cell volume, regulation of cytoplasmic ion concentration and pH regulation. In addition to the plasma membrane, ion channels are located in membranes of intracellular organelles such as mitochondria, lysosomes and endoplasmic reticulum; therefore, channel dysfunction can cause health problems in many tissues. The sequential opening of ion channels along the neurons gives rise to action potentials at the nerve terminals leading to neurotransmitter release into the microscopic gap between the neurons called a “synaptic cleft”. Sophisticated imaging techniques have demonstrated that the membranes of neuronal subcellular regions such as dendrites, axons, and presynaptic terminals carry high numbers of ion channels. Mutations of most of these crucial channel molecules can cause health problems (Table 6).^{78,79}

Voltage-dependent T-type calcium channel protein is encoded by the *CACNA1G* gene. *CACNA1G* gene mutations can lead to autosomal dominant spinocerebellar ataxia 42. High level expression of *CACNA1G* gene in the cerebellum can explain the association of this gene

Table 6. Genes Involved in Ion Channels

Gene	Function	Inheritance	Disease Phenotype (MIM Number)
<i>ANO10</i> (613726)	Member of calcium-activated chloride channel family	AR	Spinocerebellar ataxia, autosomal recessive 10 (613728)
<i>CACNA1G</i> (604065)	Calcium channel, voltage-dependent, T type, alpha-1G subunit	AD	Spinocerebellar ataxia 42 (616795)
<i>KCNC3</i> (176264)	Voltage-gated potassium channels	AD	Spinocerebellar ataxia 13 (605259)
<i>KCTD7</i> (611725)	Potassium channel tetramerization domain containing 7, functions in the voltage-gated potassium channel	AR	Epilepsy, progressive myoclonic 3, with or without intracellular inclusions (611726)
<i>KCND3</i> (605411)	Voltage-gated potassium channels	AD	Spinocerebellar ataxia 19 (607346)
<i>KCNJ10</i> (602208)	Potassium inwardly-rectifying channel, subfamily J, member 10 responsible for the potassium buffering action of glial cells in the brain	AR	SESAME syndrome (612780)
<i>NALCN</i> (611549)	Voltage-independent, nonselective, non-inactivating cation channel permeable to Na ⁺ , K ⁺ , and Ca ²⁺	AD	Congenital contractures of the limbs and face, hypotonia, and developmental delay (616266)

Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

with cerebellar ataxia. Transcriptional analysis in neuronal cells indicates the pivotal role of *CACNA1G* in neuronal maturation and differentiation.^{80,81}

The *KCNJ10* gene encodes for Potassium voltage-gated channel subfamily J member 10 protein, a member of the inward rectifier type potassium channel family (these permit potassium ions to flow into the cell rather than out of it). The protein of *KCNJ10* plays a critical role in the potassium buffering function of glial cells in the brain and kidney. *KCNJ10* stimulates oligodendrocyte differentiation and *in vivo* myelination of the central nervous system. *KCNJ10* gene mutations can lead to a complex syndrome comprising seizures, sensorineural deafness, ataxia, ID, and electrolyte imbalance, called SESAME syndrome or EAST syndrome.^{82,83}

Defects in the *KCTD7* gene cause severe and early onset autosomal recessive disease called Epilepsy, Progressive Myoclonic 3 (EPM3), with or without intracellular inclusions. The protein product of *KCTD7* is a member of the potassium channel tetramerization domain-containing protein family. *KCTD7* is in direct interaction with cullin-3 (*CUL3*), a component of the ubiquitin ligase complex. The expression of *KCTD7* reduces the excitability of cortical neurons by hyperpolarization of the cell membrane.⁸⁴

In conclusion, the advent of high-throughput sequencing technologies has led to an exponential increase in deciphering of novel disease-causing genes in highly heterogeneous diseases. Several studies have demonstrated the existence of genetic collisions in the co-occurrence of ID and ataxia. Investigations into gene-pathway coherence, pathway-pathway interactions, and disease-disease relationships indicate which similar elements participate in the normal development of human cognition and the coordination of voluntary movements and balance. Exploring the common genes and pathways in various heterogeneous diseases such as ID and ataxia can clarify the sophisticated puzzle of

ID and ataxia comorbidity, and is also useful for clinical diagnosis and pharmacological management.

Authors' Contribution

KK and HN conceived the original idea. SK wrote the manuscript in consultation with KK.

Conflict of Interest Disclosures

The authors declare that they have no competing interests.

Ethical Statement

Not applicable.

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