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Neurogenetic disorders across the lifespan: from aberrant development to degeneration

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Abstract

Intellectual disability and autism spectrum disorder (ASD) are common, and genetic testing is increasingly performed in individuals with these diagnoses to inform prognosis, refine management and provide information about recurrence risk in the family. For neurogenetic conditions associated with intellectual disability and ASD, data on natural history in adults are scarce; however, as older adults with these disorders are identified, it is becoming clear that some conditions are associated with both neurodevelopmental problems and neurodegeneration. Moreover, emerging evidence indicates that some neurogenetic conditions associated primarily with neurodegeneration also affect neurodevelopment. In this Perspective, we discuss examples of diseases that have developmental and degenerative overlap. We propose that neurogenetic disorders should be studied continually across the lifespan to understand the roles of the affected genes in brain development and maintenance, and to inform strategies for treatment.

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Author contributions

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Intellectual disability and autism spectrum disorder (ASD) are common. In the USA, intellectual disability affects up to 3% of the population, and 1 in 54 children have ASD[1,2]. Advances in medical care have resulted in an increased lifespan for individuals with these conditions and, in some parts of the world, the life expectancy of an individual with mild intellectual disability is similar to that of the general population[3–6]. This increased longevity brings with it the contemporary health challenges associated with ageing, particularly degenerative dementias[7,8]. Both families and health-care providers want to know what to expect from these conditions and what symptoms to monitor if treatments are available. Information exists for some neurogenetic diseases such as Down syndrome (also known as trisomy 21), in which nearly every individual has some degree of intellectual disability, will develop the neuropathological changes of Alzheimer disease (AD) by 40 years of age and will often subsequently develop dementia[9–12]. However, for most diseases associated with intellectual disability and/or ASD, the future is uncertain. Initially, studies had suggested that individuals with intellectual disability not caused by Down syndrome were not at a higher risk of dementia than the general population[13,14]; however, more recent cohort studies have identified an increased risk of dementia in some individuals with intellectual disability[15–17].

CNS diseases are frequently classified into early-onset neurodevelopmental disorders and late-onset neurodegenerative disorders. Part of the reason for this dogmatic separation is that the neurodevelopmental phase of disease is treated by paediatricians whereas the later neurodegenerative phase is managed by adult physicians. However, we now recognize that both developmental and neurodegenerative disorders can involve shared cellular and molecular processes and that the pathogenesis of some classic neurodegenerative diseases is associated with developmental aberrations[18–22]. It is possible that both neurodevelopmental and neurodegenerative processes have their origins early in life and can be influenced throughout the life course. Therefore, accurately characterizing the long-term natural histories of rare neurogenetic conditions is critical as it could facilitate the identification of novel molecular targets that are relevant early in the disease course, enabling the subsequent development of true disease-modifying interventions. Although far from exhaustive, in this Perspective we have included selected examples of diseases, genes or proteins that have developmental and degenerative overlap to support the concept of a neurodevelopmental–degenerative continuum (TABLE 1).

Shared mechanisms

Protein aggregates.

Two common features of neurodegenerative diseases are the selective vulnerability of specific regional CNS cell types (neurons or glia) to dysfunction and death, and the presence of protein aggregates, such as phosphorylated tau that forms neurofibrillary tangles, α-synuclein that forms Lewy bodies and neurites and amyloid-β (Aβ) that aggregates to generate amyloid plaques. Although these aggregated proteins can be found in abundance at the end stages of neurodegenerative diseases, abnormal deposits can be observed in the CNS much earlier than the time of disease onset. For example, Braak et al. documented the presence of abnormal neuronal phosphorylated tau in AD, but also identified focal

tauopathic changes in childhood and early adulthood[23,24]. Similarly, PET imaging data and other biomarker studies have suggested that Aβ accumulation in late-onset AD occurs several decades before the onset of symptoms[25–28]. Although controversy remains as to whether these aggregated proteins are toxic to the CNS, their presence early in life indicates that many of these disease processes are likely to occur far ahead of symptom onset and might be happening closer to the developmental period than is often realized.

Many of the proteins that aggregate in neurodegenerative diseases have key developmental functions and have been implicated in ASD and/or intellectual disability. For example, amyloid precursor protein (APP) is an integral membrane protein that is a biological substrate for the formation of the Aβ peptides found in amyloid plaques. Mutations in the *APP* gene can cause early-onset familial AD, and this observation has formed the basis of the amyloid cascade hypothesis for the pathogenesis of AD[29–31]. However, in development and life, APP has crucial functions as a cell surface receptor that is necessary for synaptic plasticity, synaptogenesis, axonal guidance and neurite pruning[32]. Evidence from studies in animals and humans indicates that elevated levels of APP — specifically, secreted APPα — contribute to insufficient neurite pruning and the clinical findings associated with ASD[33–37].

Biomolecular condensates.

The study of biomolecular condensates is rapidly identifying mechanistic overlaps between neurodevelopment and neurodegeneration. The cytosol of a cell is not homogeneous, but instead is arranged by collections of biomolecular condensates, that is, non-membrane-bound organelles and organelle subdomains that act as functionally distinct units and form by a physical process called phase separation. These condensates enable biophysical modulation of the majority of neural processes during development, adult life and ageing as well as with respect to general subcellular, cellular, systems and complex genome functions[38,39]. These processes are universally deregulated in neurological disease states[40–42], and disease mutations that deregulate these condensates are frequently present in intrinsically disordered regions of effector proteins implicated in both neurodevelopment and neurodegeneration[43–47]. These include pleiotropic pathogenic proteins, mediators of cell identity and developmental signalling molecules (for example, via super-enhancers)[48], mutations in which can give rise to both the pre-manifest and the symptomatic stages of specific neurodegenerative diseases[49].

Phase transitions refer to an abrupt change in the physical state of a macromolecule (for example, from liquid to solid phase) and can allow the generation of intricate amalgams consisting of liquid–liquid demixing, gel and solid-state molecular organization[39]. These processes are dynamic and the amalgams can exhibit a wide spectrum of molecular architectures (from transient to metastable intermediates), orchestrate chromatin topologies, display robustness of biological signals, modulate cellular fitness, encompass emergent properties, show infinite tunability on the basis of initiating signals and thermodynamic properties, promote context-specificity, and operationalize normal as well as pathological phase transition thresholds. These contingencies suggest that a more integrated understanding of the roles of normal and pathogenic phase transitions will revolutionize our understanding of disease pathogenesis and remediation, and of the mechanisms that

mediate the broad continuum of neurodevelopmental and neurodegenerative diseases. These diseases include those involving a unitary pathogenic cascade — for example, Huntington disease (HD) — and those involving a sequential pathogenic cascade — for example, Down syndrome and AD or Gaucher disease and Parkinson disease (PD).

Development of neural networks.

How the CNS develops and maintains its neural network connections is relevant to both its development and subsequent degeneration, and abnormal development might be partly responsible for the selective vulnerability of neurons in degenerative diseases. Axon guidance molecules have an important function in directing axonal growth as well as influencing synaptic plasticity during development and later life. As such, numerous mutations in axonal guidance genes have now been implicated in both developmental conditions and neurodegenerative diseases[50]. Accumulating evidence indicates that inappropriate connectivity within and between brain regions owing to aberrant neuronal density, dendritic branching and/or cortical layering is one of the causes of ASD[51–53]. Defects in axonal guidance also affect the developing cortical connectivity and are likely to contribute to ASD[53]. Semaphorins are transmembrane proteins that are expressed during nervous system development and have important roles in axonal guidance, CNS patterning and neuronal migration via their receptors, which include plexins[54,55]. Rare homozygous deletions of the gene encoding plexin A1 (*PLXNA1*) can cause global developmental delay, and *PLXNA1* variants are associated with PD and frontotemporal dementia[56,57].

Genome-wide association studies have demonstrated that the ε4 allele of the gene encoding apolipoprotein E (*APOE* ε4) is the strongest risk factor for AD and reduces the age at onset of the disease[58–61]. Imaging studies in humans have shown that infants carrying *APOE* ε4 alleles have reduced grey matter volumes in cortical regions that are particularly affected by AD (for example, precuneus and occipitotemporal gyri), as well as abnormal myelination patterns, when compared with non-carrier infants[62,63]. In children and adolescents, the thickness of the entorhinal cortex, an area affected early in AD, is lower in individuals with the *APOE* ε4/4 genotype than in individuals with the *APOE* ε3/3 genotype and is highest in individuals with the *APOE* ε2/2 genotype — the genotype associated with the lowest risk of AD[64]. One hypothesis is that this abnormal thinning reflects early maldevelopment in the brain that is compensated for during early life but predisposes to the pathological changes of AD in later life via abnormal circuitry and degeneration. Similarly, abnormal striatocerebellar circuitry has been identified in individuals with expansions in the huntingtin (*HTT*) gene decades before the onset of motor symptoms of HD[65].

Somatic mutations.

Non-germline, postzygotic somatic mutations in the CNS have attracted increasing attention among researchers studying neural development, ASD and neurodegenerative disease[66–69]. During neurogenesis, an estimated 5.1 single nucleotide variants occur per neural progenitor cell per day, and postmitotic neurons accrue around 20 somatic mutations per year[69–71]. This mosaicism contributes to neuronal diversity but can also result in disease-causing mutations that lead to neural developmental abnormalities and/or neurodegeneration[71]. In diseases that result from deficient nucleotide excision repair, such as Cockayne syndrome

or xeroderma pigmentosa, a substantial increase in somatic single nucleotide variants occurs and is associated with neurodegeneration[72]. Genetic data in AD are mixed: some — but not all — studies have found that neuronal somatic mutations in genes related to familial AD are more common in individuals with AD than in controls (reviewed elsewhere[73]). The results of a study of post-mortem hippocampal tissue indicated that compared with controls, neurons in the brains of individuals with AD acquire a higher frequency of somatic mutations that are enriched in cancer-related genes, such as those involved in the PI3K–AKT, MAPK and AMPK pathways[68]. These mutations are in pathways that are recognized to contribute to the tau hyperphosphorylation and neurofibrillary tangle formation that occur in AD[74–78]. Further work is needed in larger cohorts to better assess the accumulation of somatic mutations within cells of the CNS and establish the effect of these mutations on the cellular dysfunction that leads to neurodegeneration.

Mitochondrial dysfunction.

Mitochondrial dysfunction has been implicated in both neurodevelopmental and neurodegenerative diseases, including those with primary mitochondrial mutations and those that are nuclear genetic disorders (for example, fragile X syndrome and HD). Broadly speaking, the deficits in mitochondrial function not only include problems with mitochondrial respiration but also extend to issues of mitochondrial trafficking, interactions between mitochondria and other organelles, and maintenance of the mitochondria themselves (reviewed comprehensively elsewhere[79,80]). Neurodevelopmental disorders associated with pathogenic mutations in mitochondrial DNA (mtDNA) include Alpers–Huttenlocher syndrome, Leigh syndrome and myocerebrohepatopathy spectrum, which are associated with developmental encephalopathy, failure to thrive, hypotonia, hepatic disease and metabolic abnormalities[81–83]. Alpers–Huttenlocher syndrome and myocerebrohepatopathy spectrum, as well as some cases of Leigh syndrome, are caused by mutations in the gene encoding polymerase-γ (*POLG*), which is involved in mtDNA replication. Mutations in *POLG* have been linked to early-onset and levodopa-responsive parkinsonism, and some evidence suggests that *POLG* mutations are also involved in mitochondrial dysfunction in PD and other neurodegenerative diseases[84–86]. Several pathophysiological mechanisms are likely to contribute to the development of parkinsonism in the setting of mitochondrial dysfunction, and one hypothesized pathogenic mechanism includes abnormalities in mitochondrial electron transport chains, with neurons within the substantia nigra pars compacta being particularly susceptible to such oxidative damage[87–90].

Down syndrome and Alzheimer disease

The archetypal example of a neural developmental disease that is associated with ASD and intellectual disability, and later neurodegeneration, is Down syndrome. However, this syndrome, also known as trisomy 21, is complex, as chromosome 21 contains many genes that could contribute to neurodevelopment and/or neurodegeneration. Estimates indicate that 10–15% of individuals with Down syndrome have ASD — 10–25 times higher than the risk in the general population[91–93]. The brains of individuals with Down syndrome classically show various developmental anomalies of brain morphology, including anteroposterior foreshortening of the cerebrum with a sharpened occipital contour, a small cerebellum and

narrow superior temporal gyri[10]. Many of these anomalies are apparent early in development and can be observed at 6 months of age. Indeed, pathological changes such as reduced neurogenesis and increased cell death have been observed during gestation[94,95].

By the fifth decade of life, nearly all individuals with Down syndrome harbour the neuropathological changes of AD, and cerebrospinal fluid (CSF) biomarker data suggest that these neurodegenerative changes are likely to occur when individuals are in the third decade of life[10,96–99]. Oxidative stress might accelerate these changes, as differences in susceptibility seem to be mediated in part through variants or expression levels of superoxide dismutase 1 (REFS[100,101]). Amyloid PET imaging has also identified amyloid accumulation, for example, in the striatum, in the fourth decade of life in a subset of individuals with Down syndrome without dementia[102,103].

Theories regarding the aetiology of AD in Down syndrome have historically centred on the increased gene dosage of *APP*, which is found on chromosome 21 band q21.3 (REFS[96,104]). Supporting this gene dosage hypothesis, and consistent with the amyloid cascade hypothesis of AD, rare familial duplications of *APP* cause early-onset AD, and promoter mutations that increase *APP* expression have been associated with an increased risk of AD[105,106]. Furthermore, in the two instances of partial trisomy 21 without triplication of *APP* that have been reported in the literature, the affected individuals (aged 72 and 78 years) had mild intellectual impairment without substantial AD neuropathological changes[107,108]. Interestingly, APP and APP-related proteins have been implicated in neural development with functions in neurogenesis, including neural progenitor cell differentiation and neuronal migration[109].

Nevertheless, the pathogenesis of AD and the earlier developmental defects in Down syndrome are far more complex than the overexpression of *APP*. Studies have now shown that trisomy 21 is associated with widespread epigenetic changes to the genome, which result in the upregulation of more than 600 genes[110,111]. One of these upregulated genes is *DYRK1A*, which encodes a kinase and is one of many genes located within the Down syndrome critical region (DSCR) on chromosome 21. Genes located within the DSCR are thought to contribute to many of the phenotypes observed in Down syndrome, including neural developmental defects and the hyperphosphorylation of tau that causes neurofibrillary tangles[112–115]. Genes such as those encoding the cell adhesion molecule DSCAM and the transcription factor ETS2 have been implicated in the neural developmental aberrations observed in Down syndrome[116–119]. Together, the evidence indicates that the combined genetic changes and downstream effects of trisomy 21 affect numerous biological pathways that influence both neural development and AD via alterations of neurogenesis and/or neuronal differentiation, changes to neuronal migration, dysfunction of endocytosis, altered phosphorylation of cytoskeletal proteins and Aβ deposition[120].

Fragile X

Fragile X syndrome and fragile X-associated tremor/ataxia syndrome (FXTAS) are caused by abnormal trinucleotide (CGG) repeat expansions in the *FMR1* gene on the X chromosome. Fragile X syndrome is caused by expansions consisting of more than 200

CGG repeats, whereas FXTAS is caused by more modest expansions of between 55 and 200 CGG repeats[121]. Fragile X syndrome is considered to be the most commonly inherited cause of intellectual disability and ASD, with an estimated 1.4 per 10,000 people harbouring the pathogenic expansion[122,123]. By contrast, FXTAS is conventionally thought to be more of a neurodegenerative condition that presents with parkinsonism and ataxia as a result of Purkinje cell loss and white matter disease[124,125]. Interestingly, some individuals with 55–200 CGG repeats in *FMR1* also have neurodevelopmental problems, including ASD, which affects around 50% of males and 20% of females with FXTAS[126]. Furthermore, data have shown that around 30% of individuals with fragile X syndrome develop movement disorders; for example, PD has been reported in 6.5% of individuals with fragile X syndrome aged 40 years or over[121,127–129]. These observations suggest that both fragile X syndrome and FXTAS rest on a developmental–degenerative continuum.

Intellectual disability and parkinsonism

Numerous genetic conditions have now been found to cause both neurodevelopmental abnormalities and early-onset parkinsonism. For example, around 0.5% of individuals with early-onset PD have 22q11.2 deletion syndrome, also known as velocardiofacial syndrome[130]. This syndrome is characterized by multiple congenital anomalies including cardiac defects, skeletal anomalies, cleft palate, learning disabilities and/or intellectual disabilities and schizophrenia. Approximately 5.9% of individuals with 22q11.2 deletion syndrome develop early-onset parkinsonism[131–135]. Neuropathological examination of a subset of these individuals identified loss of dopaminergic neurons within the substantia nigra as well as the presence of α-synuclein-positive Lewy bodies and neurites; these changes are consistent with PD[131].

A genetic mutation in *PPP2R5D* (c.598G>A (p.E200K)), which is known to cause developmental delay and/or intellectual disability associated with macrocephaly, can also cause early-onset parkinsonism[136,137]. Post-mortem neuropathological examination of one individual with this mutation demonstrated subtotal loss of neurons within the substantia nigra in the absence of Lewy body pathology. Other genetic factors that have been associated with both intellectual disability and parkinsonism include variants in the gene *NR4A2* and loss-of-function mutations in *RAB39B*, a gene that codes for a vesicular trafficking protein[138–141]. Many more genes that, when mutated, are causative for PD have also been implicated in intellectual disability and ASD and are reviewed elsewhere[134,142].

Germline *H3F3A and H3F3B* mutations

In 2020, a condition was described that is caused by germline mutations in genes encoding H3.3 variant histones and is associated with both neurodevelopmental abnormalities and later neurodegeneration[143]. The report described a series of 46 individuals with *H3F3A* and *H3F3B* mutations who had shared features of developmental delays, congenital anomalies and brain imaging abnormalities. Furthermore, 21% of these individuals developed neurological decline and neurodegeneration within the first two decades of life.

KIF1A-associated neurological disorder

KIF1A-associated neurological disorder (KAND) encompasses a group of rare neurodegenerative conditions caused by genetic variants in *KIF1A*, a gene that encodes an anterograde neuronal microtubule motor protein[144–146]. KIF1A is responsible for anterograde transport of multiple protein cargoes, including synaptic vesicle precursors and dense core secretory vesicles, along axonal and dendritic microtubules[144]. This transport is required for both development of the brain and maintenance of neurons.

KAND has a broad phenotypic spectrum, which can include spasticity, neurodevelopmental delay, intellectual disability, ASD, microcephaly, progressive spastic paraplegia, autonomic and peripheral neuropathy, optic nerve atrophy, cerebral and cerebellar atrophy, and seizures[145]. Heterozygous variants in *KIF1A* have been associated with: neurodegeneration and spasticity with or without cerebellar atrophy or cortical visual impairment (NESCAV syndrome); progressive encephalopathy with oedema, hypsarrhythmia, and optic atrophy (PEHO syndrome); and complicated hereditary spastic paraplegia with peripheral nerve degeneration and severe distal sensory loss with distal motor involvement[147–149]. Depending on the variant in *KIF1A*, the evolution from neurodevelopmental disorder to neurodegenerative disorder can occur over a few years or decades.

Huntington disease

Pathogenic trinucleotide repeat expansion in *HTT* causes HD, and has also been identified in around 0.1% of individuals with amyotrophic lateral sclerosis (ALS)[150,151]. ALS and HD are not associated with ASD or intellectual disability and have traditionally been considered purely neurodegenerative diseases; however, evidence has begun to challenge this viewpoint in HD. Onset of motor symptoms of HD frequently commences in mid-life (30–50 years of age), but psychiatric symptoms can precede motor onset by decades[152]. In one study, CSF and plasma levels of neurofilament light chain — a marker of axonal damage — were higher in young adults with pre-manifest HD than in age-matched control participants[153]. The mean age of the participants with pre-manifest HD was 29 years and they were predicted to be up to 24 years away from clinical disease onset at the time of the study. Other studies have found slower overall brain growth in children with pathogenic *HTT* gene expansion than in control participants[154–156]. The striatum is the subcortical structure most affected by neurodegeneration in HD, and neuroimaging of children with pathogenic *HTT* gene expansion has identified initial hypertrophy of striatal structures followed by rapid atrophy compared with control participants, further highlighting the association between altered developmental growth trajectories and *HTT* gene expansion[157]. This altered circuitry is postulated to contribute to the development of HD later in life[65].

Huntingtin has pleiotropic intracellular functions including mitotic spindle formation, vesicle and organelle trafficking, ciliogenesis and possibly even DNA repair[158–161]. With such a multitude of vital roles that are important for brain development, one would expect *HTT* expansion to influence the early stages of human neurodevelopment. Barnat et al. compared cortical tissues from human fetuses carrying the *HTT* expansion with those from healthy control fetuses, and identified a wide variety of neurodevelopmental abnormalities

associated with *HTT* expansion, including aberrant ciliogenesis, neural progenitor cell polarities and mislocalization of junctional complexes[162]. In a post-mortem study, the results of which were published in 2021, we found that brain malformations were up to eight times more frequent in individuals with HD than in control participants without HD, providing further evidence of an association between neuronal migration defects and HD[163]. Malformations were more common in women with HD than in men with this condition, which is suggestive of sexual dimorphism. Single unilateral heterotopias were the most frequent malformation observed in this study and one putative underlying mechanism would be mutations in genes involved in neuronal migration.

In a study using a using knock-in mouse model of HD, multiple abnormalities in regional developmental stem cell-mediated and progenitor cell-mediated neurogenesis were identified[164]. These abnormalities differentially affected medium spiny neurons in the striosome and the matrix of the striatum; the latter is the neuronal cell type most vulnerable to neurodegeneration in HD. Moreover, mouse models with conditional loss-of-function mutations in *Htt* targeting inhibitory interneuron subtypes of the developing ventral forebrain phenocopied the late-onset neurodegenerative disease[165,166]. In another study, selective loss of *Htt* expression during development, but not thereafter, was associated with the classic hallmarks of late-onset HD[167]. This observation indicates that developmental alterations are inextricably linked to HD.

Discussion and conclusions

The aetiologies of intellectual disability, ASD, AD and PD are heterogeneous and include both genetic and non-genetic factors. Over 400 monogenetic factors have been identified for highly penetrant conditions associated with intellectual disability, ASD, epilepsy or some combination thereof[168–170]. Although children with intellectual disability undergo genetic testing, adults with neurodevelopmental disorders are not frequently offered such testing because the results are not considered relevant to clinical care; these individuals also rarely participate in genetic research studies because of their disabilities. Similarly, most individuals with neurodegenerative disorders such as AD and PD are not tested for genetic conditions unless there is a strong family history of AD or PD. If these individuals do receive genetic testing, they usually only undergo targeted testing, such as testing of *APOE* or *PS1* for AD, which does not include the known neurodevelopmental genes. Asymptomatic children or young adults are largely not genetically or clinically assessed for genetic determinants of later-onset degenerative conditions, even when a highly penetrant monogenic cause is documented in the family. If therapeutic interventions for the condition are not yet available, children are not tested for ethical reasons and adults must make a personal choice to undergo testing. As a result, a large gap exists in our knowledge of the natural history of the neurogenetic disorders associated with intellectual disability and ASD. This foundational understanding will be necessary if we are to determine the most productive windows of time for therapeutic intervention.

The gaps in our knowledge of the natural history of these neurogenetic disorders could be addressed by studies that assess population-based cohorts over the life course. Such studies should include comprehensive genomic analyses, and researchers should have the option to

recall participants of a specific genotype for targeted neurobehavioural assessments. Lack of participant retention in research studies is an important challenge, and strategies for retention must be considered in the early stages of planning[171]. Large cohorts such as the UK Biobank and All of Us in the USA represent initial attempts to recruit and retain large disease-agnostic cohorts with genomic data. Disease-specific cohorts and/or cohorts enriched for a family history of disease can be used to complement such population-based cohorts. Studies should be inclusive and include individuals with disabilities, as well as children, while ensuring that research is undertaken in an ethical manner. Studies should also include contingencies for participation when a change in status of capacity occurs over the life course, for example, when a minor reaches 18 years of age and requires re-consent or when a participant loses capacity for consent owing to neurological decline.

As knowledge is gained through the research studies described above, the clinical utility of genetic information in individuals with neurodevelopmental and/or neurodegenerative disorders should become clearer. In the future, this information might be useful for refining prognosis, for identifying effective or ineffective treatment options and their windows of therapeutic efficacy, for identifying clinical trial opportunities, for defining other associated clinical features such as obesity[172] and cancer[173], for informing family members at risk, and for reproductive planning. Refining prognosis and our understanding of associated medical conditions is important, as many individuals with intellectual disability are unable to adequately access routine health surveillance and frequently experience delays in diagnosis of common adult-onset conditions[174]. In addition, some symptoms of neurodegeneration might respond to treatment with existing medications (for example, levodopa-responsive parkinsonism in individuals with the c.598G>A mutation in *PPP2R5D*), and hopefully in the future genetic treatments will be available for some neurogenetic conditions. Ideally, those participating in the studies proposed here would be the first to benefit from the findings, with return of this genetic and clinical information to the participants included as a component of research participation.

Once diagnosed, it is crucial for individuals with these rare neurogenetic conditions to share their experiences with others through natural history studies such as Simons Searchlight and the National Organization for Rare Disorders (NORD)–FDA Natural History Study Project. This sharing will enable individuals with rare disorders, their health-care providers and scientists to learn as quickly as possible from each other, to improve clinical care by monitoring for symptoms and diagnosing conditions that emerge over the life course, and, when possible, to prevent or provide tailored care for conditions that emerge later in life. Life is a continuum, and we should strive to remove boundaries between providers and support individuals with rare neurogenetic conditions along this lifelong journey.

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Glossary

Intrinsically disordered
An intrinsically disordered protein or region that lacks a dominant 3D structure and adopts a range of conformational states

Liquid–liquid demixing
A process that generates membraneless compartments within the subcellular space, in which certain components are enriched while others are excluded

Metastable
A kinetically trapped structure (for example, a protein or other molecule) that maintains a local free energy minimum within a dynamic system

Pleiotropic
When one gene influences two or more seemingly unrelated phenotypic traits

Population-based cohorts
Epidemiological studies in which a defined population is followed and observed longitudinally

Super-enhancers
Transcriptional enhancers that drive expression of genes that define cell identity

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Table 1 |

Neurogenetic conditions with developmental and degenerative phases

genetic alteration	Condition	Neurodevelopmental phenotype	Developmental brain pathology	Degenerative phenotype	Degenerative brain pathology
Trisomy 21	Down syndrome	Autism, intellectual disability	Small cerebrum, small cerebellum, dendritic spine abnormalities	Alzheimer disease	Alzheimer disease neuropathological changes
FMR1 full mutation (>200 repeats)	Fragile X syndrome	Autism, intellectual disability, attention deficit hyperactivity disorder	Heterotopias, enlarged caudate nucleus, dendritic spine abnormalities	Parkinsonism, ataxia	Largely unknown
FMR1 pre-mutation (55–200 repeats)	Fragile X-associated tremor/ataxia syndrome	Autism, anxiety, attention deficit hyperactivity disorder in a subset	–	Ataxia, intention tremor, parkinsonism	White matter degeneration, Purkinje cell loss, eosinophilic inclusions within neurons and glia
22q11.2 deletion	Velocardiofacial syndrome	Learning disabilities, intellectual disability, schizophrenia	Variable: polymicrogyria, heterotopias, developmental microvasculopathy	Early-onset parkinsonism	Nigral degeneration with Lewy body formation
c.598G>A mutation in *PPP2R5D*	NA	Intellectual disability	Macrocephaly	Early-onset parkinsonism	Nigral degeneration in the absence of Lewy body pathology
NR4A2 variants	NA	Intellectual disability	–	Early-onset parkinsonism	Yet to be studied post-mortem
RAB39B variants	NA	Intellectual disability	–	Early-onset parkinsonism	Nigral degeneration with Lewy body formation
H3F3A and H3F3B variants	NA	Intellectual disability	Yet to be studied post-mortem	Global neurodegeneration	Yet to be studied post-mortem
KIF1A variants	*KIF1A*-associated neurological disorder	Intellectual disability, seizures, spastic paraplegia	Microcephaly	Optic nerve atrophy, cerebral and cerebellar atrophy	Cerebellar atrophy, dentate nucleus and inferior olivary neuronal loss
HTT expansions	Huntington disease	Reduced brain growth compared with control individuals, epilepsy in ~25% individuals with juvenile-onset Huntington disease (age of onset <20 years)	Brain malformations in a subset, usually single unilateral heterotopias	Psychiatric disease, cognitive decline, chorea	Striatal degeneration, diffuse brain atrophy, formation of huntingtin aggregates

NA, not applicable.