Repeat Expansions in Leukoencephalopathy

Adult onset leukoencephalopathy is a heterogeneous condition that often poses a diagnostic challenge. After infectious, inflammatory, neoplastic, drug-induced, and acquired demyelinating disorders have been excluded, the range of potential genetic causes is daunting. Even in this era of next-generation sequencing and targeted disease gene panels, the precise genetic diagnosis often remains elusive.[1,2] In this issue, Okubo and colleagues[3] report that a recently identified GGC repeat expansion in *NOTCH2NLC* (also known as *NBPF19*) may be a relatively common genetic cause of adult onset leukoencephalopathy. This newest repeat expansion disease also points to an exciting realization: a cluster of formerly unlinked disorders may well constitute a spectrum of age-related neurodegenerative diseases with shared clinical, radiographic, neuropathological, and molecular features.

The current report builds on the recent discovery that a GGC repeat expansion in *NOTCH2NLC*[4–7] is the major cause of neuronal intranuclear inclusion disease (NIID), a fatal neurodegenerative disorder that also involves peripheral organs. In patients, the diagnosis of NIID is made via skin biopsy, which reveals the neuropathological hallmark of disease, ubiquitin-positive intranuclear inclusions that occur in many organs and cell types, including neurons and glia of the central and peripheral nervous systems. Before skin biopsy became part of the workup, most cases of NIID were only discovered when brain autopsy revealed the characteristic neuropathological finding. Although NIID often runs in families with an autosomal dominant pattern of inheritance, sporadic disease in older persons is not infrequent. Clinical features of NIID vary greatly, with younger onset patients usually presenting with limb weakness and older onset patients with dementia.[8] Other common findings include neuropathy, movement disorder (most often ataxia), and signs of autonomic dysfunction, as well as white matter signal abnormalities on brain magnetic resonance imaging (MRI). In particular, high signal intensity at the corticomedullary junction in diffusion-weighted imaging is nearly always found.[8]

Given the white matter involvement in NIID, Okubo and colleagues asked whether this newly discovered GCC expansion might also be a cause of adult onset leukoencephalopathy in which other genetic causes had been excluded. They evaluated 101 Japanese patients, in 51 of whom a custom disease gene panel[1] for causes of leukoencephalopathy had proven negative; the remaining 50 newly recruited patients were first assessed by whole exome sequencing, which uncovered 7 pathogenic mutations, 6 of which were in the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) disease gene, *NOTCH3*. (A notable incidental finding of this study is that mutations in *NOTCH3* can manifest as adult onset leukoencephalopathy lacking the typical characteristics of CADASIL.) Remarkably, repeat-primed polymerase chain reaction analysis in the remaining 94 patients identified the NIID-associated GGC repeat expansion in 12 patients, making it perhaps the most common identified cause of adult onset leukoencephalopathy.

What does this collection of a dozen Japanese patients tell us about the characteristics of *NOTCH2NLC* repeat expansion-mediated leukoencephalopathy? Symptom onset ranged from ages 27 to 70 years, and nearly all patients manifested dementia, decreased deep tendon reflexes, neuropathy, and autonomic dysfunction. A minority developed tremor or experienced encephalitic episodes. The range of white matter changes detected by MRI varied greatly but was always accompanied by ventricular distention, implying a global neurodegenerative process. Skin biopsy was not part of the evaluation, but presumably many or all of the 12 individuals have NIID. Though it will be important to assess other ethnic populations, the writing appears to be on the wall: *NOTCH2NLC* repeat expansion disease should be considered in the differential diagnosis of patients displaying a progressive leukoencephalopathy with cognitive impairment, neuropathy, and autonomic dysfunction, with or without accompanying movement disorder or weakness.

The list of repeat expansion diseases continues to grow (Table), and the use of new methods that can rapidly pinpoint disease-linked simple tandem repeats[9,10] suggests more likely will be discovered soon. As scientists explore the underlying mechanisms of various repeat expansion diseases, it has become increasingly clear that they cluster in groups sharing clinical and molecular features.[11] Many features of *NOTCH2NLC* repeat-mediated disease indicate

that it belongs to one such cluster: neurodegenerative disorders caused by GC-rich repeats residing in nonprotein coding regions of the respective disease genes. Well-known members of this class include fragile X–associated tremor ataxia syndrome (FXTAS) and *C9ORF72*-mediated frontotemporal dementia/amyotrophic lateral sclerosis (FTD/ALS). It was the similarity of NIID to FXTAS, including characteristic white matter changes, that led investigators[5] to search for repeat expansions in NIID and 2 similar conditions, oculopharyngeal myopathy with leukoencephalopathy (OPML) and oculopharyngodistal myopathy (OPDM). State-of-the-art techniques uncovered separate GGC(CGG) repeat expansions in all 3 diseases: in the 5′ untranslated region (UTR) of *NOTCH2NLC* (NIID), 5′ UTR of *LRP12* (OPDM), and the bidirectionally transcribed long noncoding RNAs *LOC642361* and *NUTM2B-AS1* (OPML).

TABLE. Repeat Expansions and Associated Neurologic Disorders

CAG	At least 10 diseases (HD, SBMA, DRPLA, 7 SCAs)
CTG	Myotonic dystrophy type 1, HD-like 2, SCA8, Fuchs corneal dystrophy
GAA	Friedreich ataxia
GCC, CCG	*FRAXE* mental retardation, other fragile sites (GCC, CCG)
CGG	Fragile X syndrome, FXTAS
GCG	Oculopharyngeal muscular dystrophy (OPMD)
CGG[a]	OPML, OPDM[a]
GGC/CGG[a]	NIID, leukoencephalopathy[a]
CCTG	Myotonic dystrophy type 2
AAGGG	Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)
TTTCA	Benign adult familial myoclonic epilepsies (BAFME 1, 6, and 7)
ATTCT	SCA 10
TGGAA	SCA 31
GGCCTG	SCA 36
GGGGCC	*C9ORF72* FTD/ALS
CCCCGCCCCGCG	*EPM1* myoclonic epilepsy

Microsatellite expansions of the indicated repeat sequences are associated with a wide range of neurological diseases.
[a]GGC/CGG expansions were recently identified in NIID/leukoencephalopathy and 2 similar, rare neurodegenerative diseases, OPML and OPDM. Together with FXTAS, these diseases, which are all caused by noncoding expansions consisting only of G and C, constitute a spectrum of related neurodegenerative disorders with shared clinical, radiographic, and neuropathological features.
DRPLA = dentatorubral–pallidoluysian atrophy; FTD/ALS = frontotemporal dementia/amyotrophic lateral sclerosis; FXTAS = fragile X–associated tremor ataxia syndrome; HD = Huntington disease; NIID = neuronal intranuclear inclusion disease; OPDM = oculopharyngodistal myopathy; OPML = oculopharyngeal myopathy with leukoencephalopathy; SBMA = spinal bulbar muscular atrophy; SCA = spinocerebellar ataxia.

How do noncoding GC-rich repeats in *NOTCH2NLC* and these other new repeat expansion genes cause disease? The inheritance pattern in families with NIID favors a dominant gain-of-function mechanism. Moreover, the ubiquitin- and p62-positive inclusions found throughout the brain in NIID are reminiscent of similar inclusions in FXTAS and *C9ORF72* FTD/ALS. Perhaps, as in these well-studied diseases,[12] repeat associated non-ATG (RAN) translation across the GGC repeat generates aggregation-prone RAN proteins. A second nonexclusive possibility is that the repeat expansion sequesters RNA binding proteins, thereby disrupting RNA homeostasis. Stay tuned as studies of these newly identified repeat expansions test these hypotheses.

On a final note, white matter disturbances are a frequent finding in progressive dementing disorders. Although late-life dementia often carries a strong neurovascular component, many patients have white matter changes that seem disproportionate to their known cerebrovascular risk factors. In the right setting, we already screen for *NOTCH3* mutations when the radiographic appearance, clinical characteristics, and family history suggest CADASIL. For most neurologists, however, NIID has not been on their radar. This new report suggests that screening for the *NOTCH2NLC* repeat expansion will aid in the genetic evaluation of age-related cognitive impairment accompanied by leukoencephalopathy, especially—but not only—when there is a family history of similar disease.

Potential Conflicts of Interest

Nothing to report.

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