Molecular Base of “de novo” DRPLA

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Dentatorubropallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder, characterized by variable combinations of ataxia, involuntary movement including chorea and athetosis, myoclonic epilepsy, and dementia (1). Recent studies have identified an unstable expansion of CAG repeat in a gene located in chromosome 12 as a cause of DRPLA (2, 3). Although a clinical anticipation of the symptoms of DRPLA in successive generations has sometimes been found, the exact reason has not been understood. However, once the genetic abnormality of the disease was identified, it was revealed that the CAG repeat size showed a close relationship with the age at onset and disease severity (2, 3). Thus, clinically well-known phenomenon were clearly explained based on the expanded CAG repeat size. As with cases of Huntington’s chorea and spinocerebellar ataxias (SCA1-3, 6 and 7) that are also related to the expansion of CAG repeat, most cases of severe DRPLA with juvenile onset are inherited from their father (paternal transmission) with large expansions of more than 60 repeats, although some also had maternal anticipation (4).

The number of the normal CAG repeat of the DRPLA gene ranges from 6 to 35, and that of the disease, 49–79. CAG repeat between 36 and 48 is recognized as “intermediate expansion”. In the range of expanded size (49–79 repeats), there are two clinical subtypes depending on the expanded size. With larger expansion, patients usually develop epilepsy in younger ages (less than 20 years old), accompanied by myoclonus and progressive dementia. This type of DRPLA is called progressive myoclonic epilepsy (PME) type. On the other hand, with smaller expansion, patients usually develop chronic progressive cerebellar ataxia with chorea and/or athetosis. This type is called the non-PME type. Thus, the clinical phenotype is also closely related to the size of expansion (2–4).

DRPLA is relatively common in Japanese compared to Caucasian people (1, 5). Although the exact reason is still to be debated, a possible explanation is a racial difference of allele frequency of the intermediate allele or larger CAG size in the normal range. For example, a recent report describes a difference of allele frequency of normal CAG in DRPLA gene of more than 20 repeats (up to 35 repeats) between Japanese and Caucasian people, i.e., 8% and 1%, respectively (6). Of interest is that the same thing is found in spinocerebellar ataxia type 6 (SCA6) that is also more common in the Japanese, and the frequency is opposite in other spinocerebellar ataxias such as SCA1 and SCA2 more frequently seen in Caucasian than in Japanese. Thus, abnormal expansion of CAG could newly be provided from the intermediate allele or larger CAG size in the normal range, and the allele frequency could contribute to the racial difference of the frequency of the disease in each population.

Hattori et al (7) in this volume of Internal Medicine report a Japanese family with de novo DRPLA patents with 60 and 67 repeats of non-PME and PME types, respectively.

See also p 287.

The father is 81 years old with 51 CAG repeat, but does not show any neurological symptoms and signs so far. The father is considered as an asymptomatic carrier at this moment. The 51 CAG repeat is lower limit of the disease allele. Therefore, careful observation will be necessary to determine whether or not he will develop any symptom in the future. This kind of careful study may provide important information on the role of the intermediate allele, the upper limit of the normal allele, or the lower limit of the abnormally expanded allele in the development of the disease.

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References