Review Article

Huntington Disease in Asia

Miao Xu[1], Zhi-Ying Wu[1,2]

[1]Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China
[2]Department of Neurology and Research Center of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China

Abstract

Objective: The objective was to review the major differences of Huntington disease (HD) in Asian population from those in the Caucasian population.

Data Sources: Data cited in this review were obtained from PubMed database and China National Knowledge Infrastructure (CNKI) from 1994 to 2014. All the papers were written in English or Chinese languages, with the terms of Asia/Asian, HD, genotype, epidemiology, phenotype, and treatment used for the literature search.

Study Selection: From the PubMed database, we included the articles and reviews which contained the HD patients' data from Asian countries. From the CNKI, we excluded the papers which were not original research. Due to the language's restrictions, those data published in other languages were not included.

Results: In total, 50 papers were cited in this review, authors of which were from the mainland of China, Japan, India, Thailand, Taiwan (China), Korea, and western countries.

Conclusions: The lower epidemiology in Asians can be partly explained by the less cytosine-adenine-guanine repeats, different haplotypes, and CCG polymorphisms. For the physicians, atypical clinical profiles such as the initial symptom of ataxia, movement abnormalities of Parkinsonism, dystonia, or tics need to be paid more attention to and suggest gene testing if necessary. Moreover, some pathogenesis studies may help progress some new advanced treatments. The clinicians in Asian especially in China should promote the usage of genetic testing and put more effects in rehabilitation, palliative care, and offer comfort of patients and their families. The unified HD rating scale also needs to be popularized in Asia to assist in evaluating the progression of HD.

Key words: China; Genotype; Huntington Disease; Phenotype

Introduction

Huntington disease (HD) is a progressive neurodegenerative disease, characterized by movement disorder, progressive dementia, and psychiatric and behavior change. HD is an autosomal dominant disease associated with the expansion of cytosine-adenine-guanine (CAG) triplet repeats sequences in *Huntingtin* (*HTT*) gene which locates on 4p16.3 and encodes the protein of *HTT*. HD can be diagnosed by its typical clinical manifestations and genetic testing of *HTT*. But the disease is still incurable. Here, we reviewed HD patients' epidemiology, clinical characteristics, genotype and phenotype, recent mechanism researches, and treatment progression, with particular reference to Asia.

Epidemiology

Great geographic differences were seen in HD prevalence. The overall prevalence of HD in Asian was 0.40/100,000 (95% confidence interval [*CI*]: 0.26–0.61), much lower comparing with that of 5.70/100,000 (95% *CI*: 4.42–7.35) in European, North American, and Australia.[1] Recently, an epidemiologic study of HD in Taiwan (China) showed that the average annual incidence rate was 0.1/100,000, much lower than those of Caucasians (5–10/100,000).[2] Many studies have showed that HD prevalence is closely related to the different genotypes of population, which will be described later in this article.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.159359

Clinical Characteristics

The typical clinical profiles of HD disease are movement disorder, progressive dementia, and psychiatric and behavior change. Most clinical features of HD patients in Asia resembled those of the western population.[3-5] Of note, in terms of the atypical onset, juvenile HD (JHD) and sporadic HD, Asian patients bear their own characteristics, which will be deliberated in the following parts.

Huntington disease with an atypical onset

Some adult-onset HD patients have atypical onset symptoms

Address for correspondence: Dr. Zhi-Ying Wu, Department of Neurology and Research Center of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou,Zhejiang 310009, China
E-mail: zhiyingwu@zju.edu.cn

instead of chorea, behavioral of psychiatric disorders, and progressive dementia. Two western studies summarized the nonspecific onset movement including abnormalities of Parkinsonism, dystonia, ataxia, and tics[6,7] [Table 1]. In Chinese adult-onset HD patients, atypical initial symptom of ataxia was reported.[8] In their study, three out of seven patients developed chorea during follow-up visits, while the others did not. Their observations both confirm the clinical heterogeneity of HD in Chinese Han, and deserve the attention of clinicians since the combination of ataxia in the absence of chorea and an autosomal-dominant family history might lead to a misdiagnosis of spinocerebellar ataxia. Meanwhile, Kageyama *et al*. reported a Japanese adult-onset case of HD presenting with spasticity and cerebellar ataxia.[9] In conclusion, atypical onset of HD also occur in Asian population with HD and the first onset manifests were consistent with Caucasian population.

Juvenile-Huntington disease

Huntington disease is mostly adult onset. However, there are approximately 10% of the cases with age at onset (AAO) younger than 21. They are referred as JHD. JHD cases have been reported in the mainland[10] and Taiwan of China,[11] whose characteristics were similar to those in Caucasians. In China, the initial symptoms of JHD were seizures, intellectual decline, walking instability, and tics in limbs[10] [Table 1]. In Caucasian population, onset symptoms of JHD were different from adult-onset ones, and JHD patients were more susceptible to have imprint fathers than mothers (67–100%).[12] Most JHD had CAG repeats lengths >60, and those with onset before 10 commonly had CAG repeats lengths >80.[13] In Chinese JHD patients, the CAG repeats expansions were all beyond 60 (mean CAG repeats = 80.8, ranging from 68 to 104). In addition, most of them were found of paternal transmission.[10,14]

Sporadic Huntington disease

Most HD patients have family history. But there also exists sporadic HD cases reported all around the world.[15,16] Wang and Zhang[17] and Liu *et al*.[10] reported six sporadic HD patients in China, all of which had been diagnosed by genetic testing with no family history. Their average onset age was 40.8, with mild chorea but no significant mental disorder at diagnosis. The characteristics of Chinese sporadic HD patients are consistent with observations on HD patients all over the world. However, these reports failed to exclude the existence of family history of these sporadic cases since the parents of them might either harbor an intermediary allele or die before the onset.

Homozygous Huntington disease

Since it is rare that both parents are heterozygous for *HTT*, the frequency of homozygous HD patients is low, ranging from 0.1 to 0.4%.[18,19] Squitieri *et al*.'s studies in the Caucasian population suggested that homozygosity in the expanded alleles did not lead to an earlier onset of the disease, but increased severity and rapid progression.[2,18] Up to date, only one Chinese pedigree with a homozygous individual was reported,[20] suggesting that the homozygosity of HD seemed quite rare in Chinese Han population. The homozygote was 38-year-old and was, to the published date, free of symptoms. It was possible that symptoms in this individual might become apparent with increasing age. Therefore, because of the low incidence, it is difficult to assess the differences of homozygous HD between western and Asian population.

Genotype and Phenotype

Cytosine-adenine-guanine triplet repeats

Several studies consistently reported that the average CAG repeats size in western population was larger than that in Asian and African population. From the results of these studies, mean CAG repeats length of normal western population was 18.4 ± 3.7, while CAG size was 16.2 ± 2.5 in normal population of Africa, 16.4 ± 1.5 in the mainland of China, 16.6 ± 1.5 in Japan, 17.75 ± 1.95 in Taiwan of China,[21,22] 16.8 ± 2.1 in India[23] and 16.5 ± 1.9 in Thailand[2,24] [Table 2]. Previous studies demonstrated the wild-type (WT) CAG repeats size was significantly larger in population with a higher prevalence of HD.[25] The expanded CAG repeats number in HD patients was inversely correlated with AAO.[26] Larger CAG repeats the expansion was also reported associated with the course of illness, such as severity or progression of motor, cognitive, and function.[27]

Pulkes *et al*.'s study showed that in Thai HD patients, pathological CAG-repeat alleles ranged from 39 to 48 repeats (43.5 ± 3.0).[24] This range was documented to be 36–95 in Japanese and 40–58 in Korean population with HD.[4,5,25] In a large Chinese HD cohort in China, triplet repeats in the shorter allele were between 8 and

Table 1: Profiles of HD with an atypical onset

Asian adult-patients[8,9]	Chinese JHD[10,11]	Caucasian HD patients[6,7]
Ataxia	Seizure	Parkinsonism
Spasticity	Intellectual decline	Dystonia
	Walking instability	Ataxia
	Tics in limbs	Tics

JHD: Juvenile Huntington disease.

Table 2: Distribution of CAG repeats in the *Huntingtin* gene in normal individuals and HD patients in population of different geographical origins

Geographical origins	CAG repeats of normal population (mean ± SD)	CAG repeats of HD patients
Western countries (479 cases)[2]	18.4 ± 3.7	>36
The mainland of China[28]	16.4 ± 1.5	36–120
Taiwan of China (35 cases)[21,22]	17.75 ± 1.95	38–109
Japan (110 cases)[5,35]	16.6 ± 1.3	36–95
Thailand (18 cases)[24]	16.5 ± 1.9	39–48
Korea (36 cases)[4]	No data	40–58
India (28 cases)[23]	16.8 ± 2.1	41–56

HD: Huntington disease; CAG: Cytosine-adenine-guanine.

37 (17.7 ± 1.6). In the longer allele, a range between 36 and 120 was found[28] [Table 2]. These studies in Asia also made a conclusion of a negative correlation (−0.65, r = 0.42 in China,[28] Pearson correlation coefficient = −0.757, P = 0.001 in Korea[4]) between AAO and CAG repeats in the larger allele. In summary, different CAG repeats between western and Asian population do have effects on their different manifests.

Haplotype

Several studies showed that the difference in prevalence can be largely explained by *HTT* haplotypes.[29,30] These studies showed that differences in frequency of *HTT* haplotype might account for geographic and ethnic differences in HD prevalence. The European general population chromosomes could be grouped into three major haplotypes including A, B, and C. The majority of HD chromosomes in Europe contain haplotype A. However, in the East-Asian population of China and Japan, the majority of HD chromosomes belong to haplotype C, and in Thailand the majority being to haplotype A5 and C.[24] Moreover, the highest risk HD haplogroup variants (A1 and A2) are absent from the general and HD population of China, Japan, and Thailand, while the frequency of the protective haplogroup variant A5 is very high in Asian general population. In contrast, variants A1 and A2 are found up to 20% of the general population in Europe.[31] Therefore, there is another explanation besides CAG repeats length to the low prevalence of HD in East Asia.

CCG polymorphisms

CCG repeats the region is a genetic polymorphism in the full-length *HTT*, locating in the first proline-rich fragment. It is still unknown whether the CCG polymorphism takes part in the pathogenesis of HD. In Caucasian population, expanded CAG repeats alleles were strongly associated with CCG7 alleles[2,32] [Table 3]. CCG7 alleles were present in 67.8% of WT *HTT* and 94.4% of mutant type (MT) *HTT*. In contrast, studies of Japanese and Chinese population showed strong linkage disequilibrium between CAG expansion and CCG10 allele.[5,33,34] In the mainland of China, several studies showed that CCG10 alleles presented in approximately 60.0% of HD patients (MT *HTT*) and 41.3% of normal controls (WT *HTT*).[33,34] The percentage of CCG10 was 82.2% in Japanese HD patients and 37.3% in Japanese normal individuals.[5,35] Furthermore, in population of Taiwan (China), CCG10 alleles were present in 69.4% of MT *HTT* and 39.2% of WT *HTT*.[21] These studies suggest that HD mutations in Asian and Caucasian population might arise from different ancestral lineages. However, there is an exception. In Indian HD patients, the percentage of CCG7 is much higher than that of CCG10.[23] If CCG polymorphic region predisposes to CAG repeat expansion, the relative lower frequency of the predisposing CCG repeat size in Asian population, compared to western population, may be another explanation for the lower prevalence of HD.[1] Furthermore, CCG repeats number of four was first identified in an HD patient in India.[23] So far, there has been no evidence suggesting an association between CCG repeats region and clinical features.[2,30]

Pathogenesis

The pathogenesis of HD is still not elucidated. Many possible mechanisms are being explored. In particular, factors promoting apoptosis, phenomena causing the toxic aggregation of proteins, the blockage of trophic factors, mitochondrial dysfunction, and excitotoxicity have been studied.[36] In Asia, recently, there are some studies aiming to help explain the pathogenic mechanism of HD and even explore a new approach to HD therapy. Wu *et al*.'s study had found that onjisaponin B, which was on component derived from radix polygalae, one type of Chinese medicinal herbs, was able to induce autophagy and accelerate both the removal of mutant Huntington and A53T α-synuclein and onjisaponin B induced autophagy via the adenosine monophosphate protein kinase-mammalian target of rapamycin signaling pathway.[37] Besides, Xiao *et al*.'s study had showed that altered expression of genes involved in copper metabolism significantly modulated the HD progression via using a *Drosophila* model of HD. From their studies, they concluded that HD entail two levels of toxicity: The copper-facilitated protein aggregation as conferred by a direct copper binding in the exon 1 and the copper-independent polyQ toxicity.[38] These findings may help provide us detailed insights into the pathogenic mechanism of HD.

Diagnosis

The guideline of HD diagnosis is consistent with the western one. The diagnosis of HD depends on both clinical manifestations and genetic testing of *HTT*.[39,40]

Clinical evaluations

Combined with the description of Asian clinical characteristics above, the clinicians should focus on some atypical manifestations, such as the initial symptom of ataxia,

Table 3: Frequency of CCG alleles in normal individuals and HD patients in population of different geographical origins (*n* (%))

Alleles	Western countries (n = 479)[2]		The mainland of China (n = 85)[33,34]		Japan (n = 73)[5,35]		Taiwan (China) (n = 36)[21]		India (n = 28)[23]	
	WT *HTT**	MT *HTT*†	WT *HTT*	MT *HTT*	WT *HTT*	MT *HTT*	WT *HTT*	MT *HTT*	WT *HTT*	MT *HTT*
CCG7	325 (67.8)	168 (94.4)	151 (45.2)	31 (36.5)	115 (62.2)	69 (17.8)	199 (57.9)	11 (30.6)	276 (72.6)	25 (89.3)
CCG10	130 (27.1)	10 (5.6)	138 (41.3)	51 (60.0)	69 (37.3)	60 (82.2)	135 (39.2)	25 (69.4)	76 (20.0)	3 (10.7)

n means number of HD patients. *WT *HTT*: wild-type *Huntingtin*, normal individuals; †MT *HTT*: mutant-type *Huntingtin*, HD patients; HD: Huntington disease.

movement abnormalities of Parkinsonism, dystonia, and tics, even some sporadic cases, or juvenile patients with initial symptom of seizures, intellectual decline, walking instability or tics and so on. These profiles may imply that HD gene testing is helpful.

Accessory evaluations

For another, though genetic testing can confirm CAG repeats expansion in *HTT*, it cannot precisely predict the AAO, as a result, the precise onset time of gene-positive individuals was still hard to predict. There were substantial studies so far suggesting that a variety of additional data was predictive of pending diagnosis, including cognitive decline, subtle motor signs, reduced white matter volumes, and subjective complaints of noticeable change.[41,42] Large studies of gene-positive individuals, most notably PREDICT-HD and TRACK-HD, have provided abundant evidences that changes of brain imaging and cognitive testing were detectable years before the expected clinical diagnosis.[43-45] In addition, new approaches have been utilized to detect the time of clinical onset, for instance, functional magnetic resonance imaging (MRI), structural-MRI, electroencephalography, and event-related potentials.[46,47] However, research in this area is still blank in Asia.

Management

Gene therapy

Since the discovery of *HTT*, it has proposed possibilities for treatment based on silencing of the disease-causing allele or with compounds that reduce the production of disease-causing mRNA and/or protein. Therapies aiming at blocking toxicity theoretically were conceptually more complicated, as this requires an accurate understanding of the cellular location and the specific molecular dysfunctions that cause the phenotypes of HD. However, that was not yet available.[48] Gene therapy for HD is promising, yet a long way remains from preclinical studies to clinical trials. We hope the great advances in understanding the pathogenesis of HD could help explore the effective disease-modifying therapy.

Clinical management

Currently, there is no disease-altering treatment. What we are capable of at present is merely symptomatic treatment, which means to ameliorate the symptoms of chorea, depression, irritability, obsessiveness, and other behavioral symptoms. However, symptomatic therapy has limited benefits. Palliative care, even in the terminal stages of the disease may comfort the patients and their families.[49] Tetrabenazine showed a clear efficacy for the control of chorea,[50] but it is absent in Chinese pharmacies. Moreover, there is a need for our clinicians to promote the usage of genetic testing and provide more directions in rehabilitation, palliative care, and offer comfort and psychiatric therapies to the patients and their families. The unified HD rating scale (UHDRS) also needs to be popularized in Asia to assist in evaluating the HD progression.

In conclusion, increasing attention has been drawn to HD in Asia. Most clinical manifestations and CAG repeat expansion in *HTT* in Asian HD were similar to those in the Caucasian population. The HD haplotype and CCG polymorphisms have some differences between Asian and Caucasian population. Hence, there might be some difference in modifying single nucleotide polymorphisms which have never been reported in Asian before. Furthermore, the clinicians in Asia especially in China should promote the usage of genetic testing and put more effects in rehabilitation, palliative care and offer comfort of patients and their families. UHDRS scale also needs to be popularized in Asia to assist in evaluating the progression of HD. The progression of researches on pathogenesis could give an assistant to the therapy of HD. Though HD still remains a genetic hereditary incurable disease, we can make arduous efforts to progress the effective disease-modifying treatments technology.

References

1. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: A systematic review and meta-analysis. Mov Disord 2012;27:1083-91.
2. Squitieri F, Andrew SE, Goldberg YP, Kremer B, Spence N, Zeisler J, *et al.* DNA haplotype analysis of Huntington disease reveals clues to the origins and mechanisms of CAG expansion and reasons for geographic variations of prevalence. Hum Mol Genet 1994;3:2103-14.
3. Zheng Z, Burgunder JM, Shang H, Guo X. Huntington's like conditions in China, A review of published Chinese cases. PLoS Curr 2012;4:RRN1302.
4. Shin CW, Choi YJ, Kim M, Jeon BS. Preliminary analysis of Huntington's disease in South Korea. J Huntingtons Dis 2013;2:83-7.
5. Morovvati S, Nakagawa M, Osame M, Karami A. Analysis of CCG repeats in Huntingtin gene among HD patients and normal populations in Japan. Arch Med Res 2008;39:131-3.
6. Becker N, Munhoz RP, Raskin S, Werneck LC, Teive HA. Non-choreic movement disorders as initial manifestations of Huntington's disease. Arq Neuropsiquiatr 2007;65:402-5.
7. Ashizawa T, Wong LJ, Richards CS, Caskey CT, Jankovic J. CAG repeat size and clinical presentation in Huntington's disease. Neurology 1994;44:1137-43.
8. Dong Y, Sun YM, Liu ZJ, Ni W, Shi SS, Wu ZY. Chinese patients with Huntington's disease initially presenting with spinocerebellar ataxia. Clin Genet 2013;83:380-3.
9. Kageyama Y, Yamamoto S, Ueno M, Ichikawa K. A case of adult-onset Huntington disease presenting with spasticity and cerebellar ataxia, mimicking spinocerebellar degeneration. Rinsho Shinkeigaku 2003;43:16-9.
10. Liu ZJ, Sun YM, Ni W, Dong Y, Shi SS, Wu ZY. Clinical features of Chinese patients with Huntington's disease carrying CAG repeats beyond 60 within HTT gene. Clin Genet 2014;85:189-93.
11. Chuo YP, Hou PH, Chan CH, Lin CC, Liao YC. Juvenile Huntington's disease presenting as difficult-to-treat seizure and the first episode of psychosis. Gen Hosp Psychiatry 2012;34:436.e9-11.
12. Gonzalez-Alegre P, Afifi AK. Clinical characteristics of childhood-onset (juvenile) Huntington disease: Report of 12 patients and review of the literature. J Child Neurol 2006;21:223-9.
13. Nance MA. Genetic testing of children at risk for Huntington's disease. US Huntington Disease Genetic Testing Group. Neurology 1997;49:1048-53.
14. Hao Y, Chen YY, Gu WH, Wang GX, Ma HZ, Li LL, *et al.* Clinical and genetic study of a juvenile-onset Huntington disease. Chin J Contemp Neurol Neurosurg 2012;12:288-93.
15. Dürr A, Dodé C, Hahn V, Pêcheux C, Pillon B, Feingold J, *et al.* Diagnosis of "sporadic" Huntington's disease. J Neurol Sci 1995;129:51-5.
16. Davis MB, Bateman D, Quinn NP, Marsden CD, Harding AE. Mutation analysis in patients with possible but apparently sporadic Huntington's disease. Lancet 1994;344:714-7.

17. Wang YX, Zhang BS. Clinical phenotype and genetic analysis of sporadic Huntington's disease clinical phenotype and genetic analysis (in Chinese). Tianjin Med J 2010;38:1006-7.
18. Alonso ME, Yescas P, Rasmussen A, Ochoa A, Macías R, Ruiz I, *et al.* Homozygosity in Huntington's disease: New ethical dilemma caused by molecular diagnosis. Clin Genet 2002;61:437-42.
19. Kremer B, Goldberg P, Andrew SE, Theilmann J, Telenius H, Zeisler J, *et al.* A worldwide study of the Huntington's disease mutation. The sensitivity and specificity of measuring CAG repeats. N Engl J Med 1994;330:1401-6.
20. Shi SS, Lin Y, Zhao GX, Gan SR, Wu ZY. A Chinese pedigree with an individual homozygous for CAG repeats of Huntington's disease. Psychiatr Genet 2012;22:53-4.
21. Wang CK, Wu YR, Hwu WL, Chen CM, Ro LS, Chen ST, *et al.* DNA haplotype analysis of CAG repeat in Taiwanese Huntington's disease patients. Eur Neurol 2004;52:96-100.
22. Soong BW, Wang JT. A study on Huntington's disease associated trinucleotide repeat within the Chinese population. Proc Natl Sci Counc Repub China B 1995;19:137-42.
23. Pramanik S, Basu P, Gangopadhaya PK, Sinha KK, Jha DK, Sinha S, *et al.* Analysis of CAG and CCG repeats in Huntingtin gene among HD patients and normal populations of India. Eur J Hum Genet 2000;8:678-82.
24. Pulkes T, Papsing C, Wattanapokayakit S, Mahasirimongkol S. CAG-expansion haplotype analysis in a population with a low prevalence of Huntington's disease. J Clin Neurol 2014;10:32-6.
25. Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, *et al.* Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet 1993;4:387-92.
26. Langbehn DR, Hayden MR, Paulsen JS, PREDICT-HD Investigators of the Huntington Study Group. CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. Am J Med Genet B Neuropsychiatr Genet 2010;153B: 397-408.
27. Aziz NA, Jurgens CK, Landwehrmeyer GB, EHDN Registry Study Group, van Roon-Mom WM, van Ommen GJ, *et al.* Normal and mutant HTT interact to affect clinical severity and progression in Huntington disease. Neurology 2009;73:1280-5.
28. Jiang H, Sun YM, Hao Y, Yan YP, Chen K, Xin SH, *et al.* Huntingtin gene CAG repeat numbers in Chinese patients with Huntington's disease and controls. Eur J Neurol 2014;21:637-42.
29. Ravina B, Romer M, Constantinescu R, Biglan K, Brocht A, Kieburtz K, *et al.* The relationship between CAG repeat length and clinical progression in Huntington's disease. Mov Disord 2008;23:1223-7.
30. Warby SC, Montpetit A, Hayden AR, Carroll JB, Butland SL, Visscher H, *et al.* CAG expansion in the Huntington disease gene is associated with a specific and targetable predisposing haplogroup. Am J Hum Genet 2009;84:351-66.
31. Warby SC, Visscher H, Collins JA, Doty CN, Carter C, Butland SL, *et al.* HTT haplotypes contribute to differences in Huntington disease prevalence between Europe and East Asia. Eur J Hum Genet 2011;19:561-6.
32. Pêcheux C, Mouret JF, Dürr A, Agid Y, Feingold J, Brice A, *et al.* Sequence analysis of the CCG polymorphic region adjacent to the CAG triplet repeat of the HD gene in normal and HD chromosomes. J Med Genet 1995;32:399-400.
33. Ma M, Yang Y, Shang H, Su D, Zhang H, Ma Y, *et al.* Evidence for a predisposing background for CAG expansion leading to HTT mutation in a Chinese population. J Neurol Sci 2010;298:57-60.
34. Zhang BR, Tian J, Yan YP, Yin XZ, Zhao GH, Wu ZY, *et al.* CCG polymorphisms in the huntingtin gene have no effect on the pathogenesis of patients with Huntington's disease in mainland Chinese families. J Neurol Sci 2012;312:92-6.
35. Masuda N, Goto J, Murayama N, Watanabe M, Kondo I, Kanazawa I. Analysis of triplet repeats in the huntingtin gene in Japanese families affected with Huntington's disease. J Med Genet 1995;32:701-5.
36. Vonsattel JP, Keller C, Cortes Ramirez EP. Huntington's disease-neuropathology. Handb Clin Neurol 2011;100:83-100.
37. Wu AG, Wong VK, Xu SW, Chan WK, Ng CI, Liu L, *et al.* Onjisaponin B derived from radix polygalae enhances autophagy and accelerates the degradation of mutant a-synuclein and huntingtin in PC-12 cells. Int J Mol Sci 2013;14:22618-41.
38. Xiao G, Fan Q, Wang X, Zhou B. Huntington disease arises from a combinatory toxicity of polyglutamine and copper binding. Proc Natl Acad Sci U S A 2013;110:14995-5000.
39. Parkinson's disease and movement disorder group in Neurologic Branch of Chinese Medical Association. Guideline for diagnosis and treatment of Huntington's disease. Chin J Neurol 2011;44:638-41.
40. Agostinho LA, Dos Santos SR, Alvarenga RM, Paiva CL. A systematic review of the intergenerational aspects and the diverse genetic profiles of Huntington's disease. Genet Mol Res 2013;12:1974-81.
41. Biglan KM, Ross CA, Langbehn DR, Aylward EH, Stout JC, Queller S, *et al.* Motor abnormalities in premanifest persons with Huntington's disease: The PREDICT-HD study. Mov Disord 2009;24:1763-72.
42. Paulsen JS, Nopoulos PC, Aylward E, Ross CA, Johnson H, Magnotta VA, *et al.* Striatal and white matter predictors of estimated diagnosis for Huntington disease. Brain Res Bull 2010;82:201-7.
43. Tabrizi SJ, Reilmann R, Roos RA, Durr A, Leavitt B, Owen G, *et al.* Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24 month observational data. Lancet Neurol 2012;11:42-53.
44. Aylward EH, Nopoulos PC, Ross CA, Langbehn DR, Pierson RK, Mills JA, *et al.* Longitudinal change in regional brain volumes in prodromal Huntington disease. J Neurol Neurosurg Psychiatry 2011;82:405-10.
45. Stout JC, Paulsen JS, Queller S, Solomon AC, Whitlock KB, Campbell JC, *et al.* Neurocognitive signs in prodromal Huntington disease. Neuropsychology 2011;25:1-14.
46. Kincses ZT, Szabó N, Tóth E, Zádori D, Faragó P, Németh D, *et al.* Diffusion MRI measured white matter microstructure as a biomarker of neurodegeneration in preclinical Huntington's disease. Ideggyogy Sz 2013;66:399-405.
47. Georgiou-Karistianis N, Scahill R, Tabrizi SJ, Squitieri F, Aylward E. Structural MRI in Huntington's disease and recommendations for its potential use in clinical trials. Neurosci Biobehav Rev 2013;37:480-90.
48. Johnson CD, Davidson BL. Huntington's disease: Progress toward effective disease-modifying treatments and a cure. Hum Mol Genet 2010;19:R98-102.
49. Nance MA. Therapy in Huntington's disease: Where are we? Curr Neurol Neurosci Rep 2012;12:359-66.
50. Mestre T, Ferreira J, Coelho MM, Rosa M, Sampaio C. Therapeutic interventions for symptomatic treatment in Huntington's disease. Cochrane Database Syst Rev 2009;(3):CD006456.

Received: 18-01-2015 **Edited by:** Yuan-Yuan Ji
How to cite this article: Xu M, Wu ZY. Huntington Disease in Asia. Chin Med J 2015;128:1815-9.

Source of Support: This work was supported by a grant of the National Natural Science Foundation (No. 81125009). **Conflict of Interest:** None declared.