Genotype-phenotype correlation in 1015 Chinese families with spinocerebellar ataxia type 3

Zhi-Ying Wu

Department of Medical Genetics and Center for Rare Diseases, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

**ABSTRACT**

**Introduction:** Given the diverse clinical manifestations and significant prevalence of spinocerebellar ataxia type 3 (SCA3) in China, we conducted an in-depth analysis in a large cohort of Chinese SCA3 patients.

**Methods:** Over the past 15 years, 1062 patients and 271 premanifest individuals from 1015 genetically confirmed SCA3 families were enrolled across three leading academic hospitals in China. The clinical profile and the genotype-phenotype correlation were explored.

**Results****:** Among the 1333 SCA3 individuals, 1326 (99.4%) were of Han Chinese ethnicity, while the remaining 7 belonged to four ethnic minorities. Family history was positive in 908 of the 974 families (93.2%), with 40.6% showing paternal inheritance, 35.8 % maternal inheritance, and the remaining 16.8% could not be definitively attributed to either parent. The mean age at onset (AAO) was 37.6 ± 11.7 years (range: 4–72 years), and the mean number of expanded CAG repeats (expCAG) was 74.0 ± 4.0 (range: 52–87 repeats). A quadratic model best described the relationship between AAO and expCAG (r² = 0.612, *p* < 0.001). The mean number of expanded CAG repeats (expCAG) was slightly higher in patients with paternal inheritance (74.4 ± 3.8) compared to those with maternal inheritance (73.8 ± 3.8, t-test, *p* = 0.0261). Clinical profiles were assessed in 1050 SCA3 patients. Gait ataxia was the most common initial symptom, affecting 91.1% of patients. Among those with non-gait ataxia onset, diplopia was the most frequent presenting symptom (18.8%), followed by dizziness (11.1%) and dysarthria (11.1%). The 1050 SCA3 patients were classified into five subtypes based on clinical presentation. Subtypes I, II, and III comprised 88 patients (8.4%), 710 patients (67.6%), and 235 patients (22.4%), respectively. The mean expCAG in subtypes I, II and III were 79.8, 74.5 and 70.3, respectively. The mean AAO was 18.5 years for Subtype I, 36.0 for Subtype II, and 51.8 for Subtype III. Subtype IV included only 5 patients (0.5%) who exhibited parkinsonism-like features, with a mean expCAG of 69.8 repeats and a mean AAO of 41.7 years. The remaining 12 patients (1.1%) were classified as Subtype V, characterized by a higher number of expanded CAG repeats (mean: 78.8 ± 4.8) and an earlier AAO (mean: 22.4 ± 9.6 years).

**Conclusion:** Our study provides the most comprehensive genotype-phenotype correlation analysis in the largest cohort of SCA3 individuals to date, highlighting the clinical heterogeneity of the disease.