3.2 Challenges in the interpretation of genetic variations

High-throughput sequencing technology can help identify genetic variations related to diseases such as intellectual disability and epilepsy. Among the identified genetic variations, approximately one-third are harmful, one-fourth may be harmful, and the effects of the remaining genetic variations are still unclear. This indicates that the interpretation process is very complex (Bedja-Iacona et al., 2025). To make the judgment more accurate, it is necessary to classify the grades according to international standards, combine the patient's onset manifestations, family medical history, and conduct multidisciplinary discussions (Çapan, 2025). How to clarify the meaning of those unexplainable genetic variations is a common problem, especially when many functionally unknown genetic variations are discovered after sequencing. In neonatal screening, the effects of many missense variations are still unclear, and no definite diagnosis can be given. Therefore, it is necessary to continuously update the database and combine metabolic indicators to improve the accuracy of the judgment.

3.3 The role of genetic testing in early screening, diagnosis, and genetic counseling

For patients with rare neurological disorders, genetic testing is very important for early detection and diagnosis. Many children with complex developmental problems have found the cause through exon sequencing, and some treatable diseases have been discovered in time, providing a basis for formulating targeted treatment plans (Gaouzi et al., 2025). Early clarification of genetic diagnosis can also guide the selection of antiepileptic drugs, monitor possible complications, and provide reference for precise treatment (May et al., 2025). For some late-onset neurodegenerative diseases and ataxias, genetic testing also helps to assess the development trend of the disease (Figure 1) (Srinivasan et al., 2025).

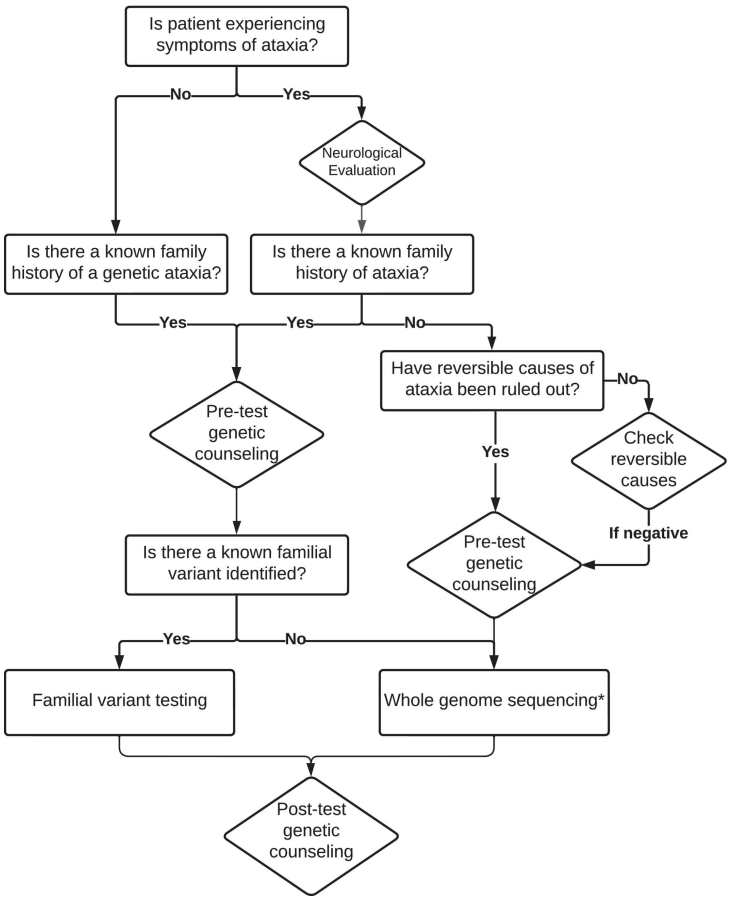

Figure 1 Proposed workflow for evaluation of hereditary ataxia (Adopted from Srinivasan et al., 2025)

Image caption: Genetic counseling may be conducted by a genetic counselor, neurologist with dedicated neurogenetics training, or geneticist based on suspected indication and level of comfort in test selection/interpretation. *Whole genome sequencing (WGS) must include technology capable of reliably detecting repeat expansions. See Recommendation #18 for more details, including alternative testing options such as a dedicated repeat expansion panel (Adopted from Srinivasan et al., 2025)