Ontario Health

Exome Sequencing in Neurogenetics

Genetic testing for neurogenetic indications can be offered by physician specialists (e.g., geneticists, neurologists, physiatrists, and other specialists with expertise in neurogenetic conditions) who diagnose, manage, and/or treat individuals with neuromuscular disorders, ataxia, epilepsy, movement disorders, or other neurological conditions with a genetic basis.

When neurogenetic diagnostic certainty is high, especially with supporting ancillary test results, the recommended testing approach is to select the most appropriate single or multi-gene panel. However, exome sequencing (ES) is the recommended first-tier test for the following individuals:

Funded Neurology-related Indications for ES

- Suspected neuromuscular disease (NMD) in children under 24 months of age
    - Genetic NMDs are a common cause of severe neonatal and early infant disease and are part of the broad differential for neonatal hypotonia and developmental delay
    - ES can be done concurrently and/or following creatinine phosphokinase (CPK)
- Suspected ataxia in children under 5 years of age
    - Genetic ataxias can present in the first 5 years of life, but can be challenging to distinguish from other neurogenetic subtypes, particularly spastic paraplegias, in this age group
    - Acquired causes of ataxia should be appropriately ruled out or deemed not applicable (i.e., in children) prior to genetic testing. The likelihood of acquired causes (and the specific causes to consider) vary by age, but may include:
        - Cerebellar vascular lesions (hemorrhage, ischemia, vascular malformations)
        - Mass lesions (tumours)
        - Secondary effects of medication
        - Drugs or other intoxicants
        - Acquired vitamin deficiencies
        - Autoimmune or post-infectious encephalitis
    - If family history is suggestive of autosomal dominant ataxia, consider ataxia repeat expansion testing prior to ES
- Two or more unrelated neurological conditions diagnosed at any age (e.g., movement disorders, ataxia, seizures, spasticity)
- Suspected neurogenetic condition in the context of additional non-neurologic feature(s) suggestive of a genetic syndrome (e.g., congenital anomaly, dysmorphic features, and/or other organ system involvement)

If a patient is eligible for ES as outlined above, it is important to note that ES does not detect all DNA variant types. If indicated based on the differential diagnosis, the following tests should be considered and may be ordered sequentially or concurrently to ES:

1. Chromosomal microarray analysis (CMA)
2. *DMPK* repeat expansion testing for myotonic dystrophy type 1 (DM1)
3. Methylation status assessment for Prader-Willi syndrome (PWS)/Angelman syndrome (AS)
4. Deletion/duplication analysis of *SMN1* and *SMN2* for spinal muscular atrophy (SMA)
5. Deletion/duplication analysis of *DMD* for Duchenne muscular dystrophy (DMD)
6. Ataxia repeat expansion testing in individuals with family history consistent with an autosomal dominant ataxia

Additional Support

For further assistance in test selection, test ordering, result interpretation, and management recommendations, please consider the following options as needed:

- Access lab requisitions and additional details at Genome-wide Sequencing Ontario
- Send a referral to your local genetics clinic (Genetics Clinics in Ontario)
- Submit an eConsult request to connect with a genetics specialist through OTNhub