Ontario Health

Exome Sequencing in Neurodevelopmental Disorders

Genetic testing, including exome sequencing (ES) for neurodevelopmental disorders (NDDs) can be offered by physician specialists who diagnose, care for, and/or treat individuals with NDDs (e.g., geneticists, developmental pediatricians, pediatric neurologists, child psychiatrists). Ordering physicians should have sufficient expertise in genetics to provide pre- and post-test counselling and to safely manage results.

Funded Indications for ES in NDDs

- Neurodevelopmental indications to be ordered by geneticists or physician specialists as per Provincial Genetic Program (PGP) guidance:
    - Global developmental delay **and** currently less than 5 years of age
    - Intellectual disability (moderate, severe, or profound)
    - Autism or mild intellectual disability, **and** one or more clinical features suggestive of a genetic syndrome (See list on page 2)

Limitations to ES

It is important to note that ES does not detect, or has limited detection of, certain DNA variant types (e.g., repeat expansion disorders, small structural variants, methylation status). If indicated based on the differential diagnosis or recommended by a genetics clinic, the following tests should be considered concurrently or sequentially with ES[1]:

1. **Chromosomal microarray analysis (CMA)** can be considered for patients if not previously completed or following an uninformative ES result. CMA and ES can be ordered concurrently in cases with time sensitivity, complicated specimen collection, or high suspicion of a genetic etiology.
2. **Fragile X testing** (repeat expansion testing of *FMR1* gene) can be ordered for patients with features of Fragile X syndrome or family history consistent with X-linked intellectual disability.
3. **Methylation testing** for individuals with suspected Prader-Willi syndrome and/or Angelman syndrome.
4. **Biochemical testing** for selected inherited metabolic diseases, if indicated.

Patient Clinical Features that may be Suggestive of a Genetic Syndrome

- **Abnormal head size:** Occipitofrontal circumference 2 standard deviations above or below the mean for age, sex, and ethnicity (e.g., microcephaly, macrocephaly).
- **Additional medical comorbidities:** Presence of additional medical conditions suggestive of a genetic basis (e.g., sensorineural hearing loss, vision impairment, renal disease, epilepsy, ataxia).

[1] Carter MT, et al. Genetic and metabolic investigations for neurodevelopmental disorders: position statement of the Canadian College of Medical Geneticists (CCMG). J Med Genet. 2023;60:523-532.

- **Congenital anomalies:** A non-progressive morphological anomaly of a single organ or body part which is present at birth (e.g., cleft palate, polydactyly, congenital heart defect).
- **Distinctive physical features:** Visible morphologic findings that differ from those commonly seen in the general population or within the same ethnic background (e.g., hypertelorism, syndactyly).
- **Unexplained growth abnormalities:** Growth parameters 2 standard deviations above or below the mean for age, sex, and ethnicity (e.g., prenatal growth restriction, postnatal failure to thrive, short stature, overgrowth).

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.