BRAIN DISEASE AND DEVELOPMENTAL DELAY

There are over 1,000 genetic disorders that affect the development and function of the brain. This large group of diseases includes leukodystrophies, peroxisomal biogenesis disorders, tuberous sclerosis, and various forms of intellectual impairment linked to the X chromosome. Many of these diseases are progressive and increasing knowledge of how they damage the nervous system has led to new treatments that are most effective when initiated before there are symptoms, or when symptoms are still mild. An accurate and early genetic diagnosis is essential as specific therapeutic strategies are increasingly being recognized.

MITOCHONDRIAL DISEASE

Mitochondria provide the energy for cell functions and are critical for the normal growth and development of most organs and tissues. Inherited disorders of mitochondrial function can present at any age and may affect a single organ or multiple systems. Symptoms include poor growth, loss of coordination, weakness, visual problems, hearing loss, learning disability, liver disease, kidney disease, gastrointestinal disorders, respiratory problems, neurological problems and dementia. These disorders are also associated with a high occurrence of pregnancy loss. Genetic Diagnosis is important to facilitate screening and early treatment for potential complications such as diabetes, cataracts, heart disease, and seizures.

REFERENCES

### Epilepsy
Epilepsy is a common neurological condition, affecting about 1 in 100 Canadians of all ages and ethnicities. In many patients, there is no family history of the disease. LifeLabs Genetics offers an epilepsy search test and seven genetic epilepsy panels for a wide range of neurological conditions including:

- Dravet syndrome
- Lennox-Gastaut syndrome (LGS)
- GLUT1 deficiency syndrome
- Sune syndrome
- LPR syndrome
- ALD (Culo Gerhich disease)
- Mitochondrial disease
- Myoclonic epilepsy
- Neurocutaneous syndromes

#### Dravet syndrome
- A severe form of epilepsy that can lead to developmental delays and sudden unexplained death
- More than 70% of cases have associated fever in the SCNA gene (most of these mutations are not inherited so there is no family history of epilepsy)
- Certain drugs are effective in seizure control while others are likely to increase seizures
- A correct diagnosis at any age can improve management of seizures and quality of life

#### Lennox-Gastaut syndrome (LGS)
- A severe disorder associated with intellectual and behavioral regression due to uncontrolled seizures in infancy and early childhood
- Accounts for 5-10% of childhood epilepsy and 1-2% of adult epilepsy
- Several drugs have been specifically approved for the treatment of LGS

#### GLUT1 deficiency syndrome
- Caused by mutations in the SLC2A1 gene
- Associated with frequent seizures usually beginning in infancy
- A high-fat, low-carb diet has been shown to control seizures in some patients

#### ALD (Culo Gerhich disease)
- Most common cause of neurologic death in Canada
- Many of the cases are associated with some lesions in the SCNA gene
- Nearly 1/3 of patients are misdiagnosed and may undergo unnecessary surgeries
- A genetic test is recommended in all cases (70-75% of cases of a family history)
- The CHRNA7 gene accounts for 40-50% of familial cases
- A specific SOD1 gene mutation is associated with rapid disease progression while another SOD1 mutation is associated with survival of more than 10 years
- A rare familial juvenile ALS form has onset between 3 and 10 years of age
- Genetic testing may predict progression and determine those at risk for dementia
- Genetic testing identifies individuals who are eligible for gene specific research and clinical trial participation

### NeuroMuscular Disease
Movement disorders are a group of conditions characterized by impairments or involuntary movements. Syringobulbia, opsoclonus, and familial hemiparetic migraine are three inherited movement disorders. Parkinson disease, dystonia, and corticobasal degeneration can also be genetic.

**Parkinson disease (PD)**
- Second most common neurodegenerative disease after Alzheimer disease
- Autosomal dominant and accounts for 1% of cases
- Associated with tremor, stiffness, slowness, impaired balance and muscle rigidity
- 50% of patients develop dementia
- Average age of onset is 60 (50% are diagnosed before 50, 5-10% before 40)
- Mutations account for 5% of cases and 50-60% of early onset cases
- More than 5 genes are known to cause PD
- Parkinson disease is associated with early onset slowly progressive disease and a good response to levodopa. Autosomal recessive PARK2 mutations are the most common cause of early onset familial PD
- LRRK2 is associated with moderate slowly progressive disease and dementia is uncommon
- Patients with LRRK2-linked PD also respond favorably to levodopa. Autosomal dominant LRRK2 mutations are the most common cause of late onset slowly progressive disease
- Genetic testing may predict disease severity, facilitate screening for dementia, and predict responsiveness to medications

### Peripheral Neuropathy
Peripheral neuropathies are nerve disorders associated with numbness, tingling, weakness, and pain that typically starts in the feet and later affects the hands.

**Charcot-Marie Tooth disease (CMT)**
- Most common inherited peripheral neuropathy, affecting 1 in 2,500 people
- Divides group of disorders associated with mutations in more than 50 genes
- Genetic mutation identified in 60-70% of cases (4 genes account for 90-95% of these)
- Disease onset is usually by age 20 although some mutations carriers never show signs
- 20-30% of patients have no family history
- Genetic testing may reduce the need for other invasive diagnostic tests such as ENG, nerve conduction, or nerve biopsy
- A number of drugs are toxic to CMT patients and should be avoided by both symptomatic and asymptomatic individuals with a genetic diagnosis

### Neuromuscular Disease
Muscle dystrophies are a group of diseases that affect skeletal muscles. Common symptoms include muscle weakness, rigidity, loss of coordination, breathing, speech, and pain. Genetic neuromuscular disorders are individually rare, but collectively they affect 1% of Canadians. A number of these disorders are associated with developmental delay, dysarthria, myoclonus and malignant hyperthermia. There are more than 50 known genetic causes of muscular dystrophy alone.

**Limb-girdle muscular dystrophy**
- Characterized by hip and shoulder weakness
- Autosomal dominant and accounts for more than 90% of cases
- Mutations in 9 genes account for 90-95% of cases
- Four forms are limited to skeletal muscle involvement
- A precise genetic diagnosis is important for determining which patients require close monitoring and/or early intervention for potential pulmonary and heart complications

### Dementia
What You Need To Know
Collectively affect almost 1% of the population.

- Alzheimer disease
  - Most common cause of dementia
  - Most cases present after age 65 and are not strongly genetic
  - Up to 5% of patients have dementia onset before age 65 and a positive family history (FADAD)
  - A genetic mutation is identified in 40-80% of families with FADAD and in a small number of patients with early-onset disease without a family history
  - A prompt genetic diagnosis is important so that patients and their families can plan for the future before dementia becomes severe
  - Early genetic diagnosis also facilitates access to medications that may help alleviate symptoms and improve quality of life

#### Frontotemporal degeneration
- Second most common cause of dementia in individuals under age 65
- 60% of cases are inherited
- Some genes and mutations are associated with severe disease, Parkinsonism and tremor, and responsiveness to certain drugs
- Genetic diagnosis may eliminate the need for other potentially invasive diagnostic tests such as lumbar puncture for conformational diagnosis
- Genetic test results may predict disease severity and age of onset, facilitate screening for potential complications, and in some cases, predict responsiveness to medications

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An estimated 3.6 million Canadians of all ages and ethnicities are affected by neurological conditions. This number is expected to increase significantly in the coming years due to ageing of the population and longer life expectancy. Many common conditions, such as epilepsy, Alzheimer disease and Parkinson disease, can be genetic. There are over 200 inherited neurological disorders that collectively affect almost 1% of the population.