Epilepsy

1 in 160 Canadians has Epilepsy

- Causes of epilepsy can be classified by three groups: genetic, structural-metabolic and unknown.
- Several factors can influence the risk of epilepsy in family members including:
  - Young age of onset (<20 years)
  - Number and relationship of affected relatives
  - Affected parent gender (maternal effect)
  - Specific seizures types
  - Certain types of electroencephalogram (EEG) abnormalities
- Canadians over 65 are almost as likely to develop epilepsy as children ten and under
  - Many cases of early-onset epilepsy have an underlying genetic predisposition
  - Many seizures occurring later in life are related to health problems like stroke and heart disease

Genetics Play an Important Role

- Over 50% of all epilepsies have some genetic basis
  - Genetic forms of epilepsy occur in isolation or as part of a genetic syndrome
  - More than 20 genes are currently known to be associated with idiopathic epilepsy
  - Genetic forms of epilepsy may be inherited or the result of a new genetic mutation
    - 10% of individuals with epilepsy have a family history
- Genetic forms of epilepsy may occur in a variety of ways
  - Single gene (and metabolic) disorders
    - Can demonstrate autosomal dominant, autosomal recessive or X-linked inheritance
  - Chromosomal disorders
  - Mitochondrial disorders
  - Multifactorial disorders
  - Epigenetic disorders
- The chance of developing epilepsy and the response to treatment may depend on genetic factors

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  - 60-70% of individuals respond to treatment, such as medication, surgery and/or diet
- Overlapping clinical presentations, reduced penetrance and variable expression of genetic forms of epilepsy can make diagnosis difficult without a genetic test.

Genetic testing can Help

- The results of genetic testing can provide individuals and their families with important information by:
  - Confirming a diagnosis, particularly when clinical findings are unclear
  - Guiding treatment decisions, thereby increasing the chance of controlling seizures
  - Providing important information about prognosis and future health concerns
  - Clarifying risks to family members
  - Empowering individuals to make family planning decisions
- Genetic testing can seem complicated. Our team of certified genetic counsellors and client-care specialists are available to support you along the way

We offer a variety of genetic tests for nonsyndromic and syndromic epilepsy

Selected Nonsyndromic Epilepsies with a Known Genetic Cause		
Seizure Type	Testing offered through LifeLabs Genetics	Detection Rate
Presenting in the first year of life		
Benign familial neonatal-infantile seizures	SCN2A	Unknown/Rare
Benign familial neonatal seizures	KCNQ2, KCNQ3	50-60%
Early infantile epileptic encephalopathy	ARHGEF9, ARX, CDKL5, KCNQ2, SCN1A, SCN2A, SCN8A, SLC25A22, SPTAN1, STXBP1, PCDH19, PLCB1,PNKP	• 5-10% of affected males have a mutation in the ARX gene. • 10-17% of patients with infantile spasms have a mutation in the CDKL5 gene. • ~35% of those affected with Ohtahara syndrome have a mutation in the STXBP1 gene. • >10% of girls with onset of seizures before the of age of 5 have PCDH19 mutations. • ~85% of patients with Dravet syndrome have a mutation in SCN1A

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Familial infantile myoclonic epilepsy	TBC1D24	Unknown/Rare
Generalized epilepsies		
Childhood absence epilepsy	GABRG2, GABRA1, GABRB3, CACNA1H, JRK, SLC2A1	~8%
Juvenile absence epilepsy	EFHC1	Unknown
Focal epilepsies		
Amish infantile epilepsy	ST3GAL5	Unknown
Familial focal epilepsy with variable foci	DEPDC5	12-37%
Familial temporal lobe epilepsy	CPA6	Unknown
Nocturnal frontal lobe epilepsy	CHRNA2, CHRNA4, CHRNB2, KCNT1	~15%
Partial epilepsy hereditary panel	CACNA1H, CACNB4, CHRNA2, CHRNA4, CHRNB2, CLCN2, CPA6, DEPDC5, EFHC1, GABRA1, GABRB3, GABRD, GABRG2, JRK, KCNMA1, KCNQ2, KCNQ3, LGI1, MTATP6 , SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SLC2A1, SRPX2	Unknown/Rare - ~50% dependent on subtype and/or additional features
Febrile seizures		
Dravet syndrome	SCN1A, SCN2A, SCN9A, GABRG2	~85%
Generalized epilepsy with febrile seizures plus	SCN1A, SCN1B, SCN2A, GABRG2, GABRD, SCN9A	73-92%
Other		
Epileptic encephalopathy panel	ACY1, ADSL, ALDH7A1, AMT, ARHGEF9, ARX, CDKL5, CNTNAP2, CPT2, FOLR1, FOXG1, GABRG2, GAMT, GCSH, GLDC, GRIN2A, GRIN2B, KCNJ10, KCNQ2, MAGI2, MAPK10, MECP2, MTHFR, NRXN1, PCDH19, PLCB1, PNKP, PNPO, POLG, PRRT2, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SLC19A3, SLC25A22, SLC2A1, SLC9A6, SPTAN1, SRGAP2, STXBP1, TBCE, TCF4, TREX1, UBE3A, ZEB2	5%-70% dependent on subtype and/or additional features

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Selected Genetic Syndromes Involving Epilepsy			
Syndrome	**Additional Features**	**Risk of Epilepsy**	**Inheritance***
Angelman/Angelman-like Syndrome	"Happy" appearance, intellectual disability, severe speech impairment, microcephaly, and ataxia.	>80%	AD
Creatine Deficiency Syndromes:			
Arginine-glycine Amidinotransferase (AGAT) Deficiency	Intellectual disability, delayed speech and autism. Seizures are more common with fever.	20%	AR
Creatine Transporter (SLC6A8) Deficiency	Intellectual disability, delayed speech and autism	50%	XLD
Guanidinoacetate Methyltransferase (GAMT) Deficiency	Intellectual disability, speech impairment, autism, hypotonia and movement disorders.	>92%	AR
Familial Cerebral Cavernous Malformations	Individuals may experience headaches, paralysis, vision loss or hearing loss. May be asymptomatic.	55%	AD
Fragile X Syndrome	Intellectual disability, delayed speech, anxiety, hyperactivity, and autism. Males are more severely affected than females.	20-40%	XLD
Glucose Transporter Deficiency Syndrome Type 1	Intellectual disability, acquired microcephaly difficulty speaking, and movement disorders including ataxia, dystonia, and chorea	90%	AD, AR
Mitochondrial encephalopathy, lactic acidosis, and Stroke-like episodes (MELAS)	Normal early development, stroke-like episodes before age 40 years, dementia, recurrent headaches and/or vomiting.	>95%	Mt
Mowat-Wilson Syndrome (Hirschsprung Disease-Mental Retardation)	Distinctive facial features, intellectual disability, delayed development, genitourinary and eye abnormalities, congenital heart defects, agenesis of the corpus callosum, and Hirschsprung disease.	70-75%	AD
Myoclonus epilepsy with ragged-red fibers (MERRF)	Myoclonus, ataxia, hearing loss, short stature, dementia, cardiomyopathy and/or optic atrophy.	>99%	Mt
Rett/Atypical-Rett Syndrome	Normal early growth and development followed by rapid regression and stagnation beginning ~18months of age. Intellectual disability, acquired microcephaly, gait ataxia, and characteristic hand movements.	70-80%	XLD, AD
Tuberous Sclerosis	Development of benign tumors in the brain, kidneys, and other organs, intellectual disability, kidney disease and particular skin findings.	80%	AD

*AD= autosomal dominant, AR = autosomal recessive, XLD = X-linked, Mt = mitochondrial

Technical Sensitivity: The technical sensitivity of a Next Generation Sequencing panel test is estimated to be 98.5%. The technical sensitivity of Sanger sequencing is >99.8%. The deletion/duplication testing via qfPCR or MLPA can detect deletions or duplications encompassing one or more exons, including mutations as small as 250 base pairs (bp). The field of genetics is always evolving and so are we. Please visit our website for a current test list

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References

Hani 2015 Genetics of Pediatric Epilepsy (in RefWorks)

Myers,C.T.; Mefford,H.C. Advancing epilepsy genetics in the genomic era

Idiopathic generalized epilepsy phenotypes associated with different EFHC1 mutations.

Stogmann E[1], Lichtner P, Baumgartner C, Bonelli S, Assem-Hilger E, Leutmezer F, Schmied M, Hotzy C, Strom TM, Meitinger T, Zimprich F, Zimprich A.

Mutations of DEPDC5 cause autosomal dominant focal epilepsies.

Ishida S[1], Picard F, Rudolf G, Noé E, Achaz G, Thomas P, Genton P, Mundwiller E, Wolff M, Marescaux C, Miles R, Baulac M, Hirsch E, Leguern E, Baulac S.

Familial focal epilepsy with variable foci mapped to chromosome 22q12: expansion of the phenotypic spectrum.

Klein KM[1], O'Brien TJ, Praveen K, Heron SE, Mulley JC, Foote S, Berkovic SF, Scheffer IE.

Carboxypeptidase A6 gene (CPA6) mutations in a recessive familial form of febrile seizures and temporal lobe epilepsy and in sporadic temporal lobe epilepsy.

Salzmann A[1], Guipponi M, Lyons PJ, Fricker LD, Sapio M, Lambercy C, Buresi C, Ouled Amar Bencheikh B, Lahjouji F, Ouazzani R, Crespel A, Chaigne D,Malafosse A.

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.

Ottman R[1], Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.