Genetics Education Canada - Knowledge Organization
Centre d'éducation en génétique canadien - Connaissances organisées

Untangling the helix: Genomics for primary care providers

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Enclosed:

- **Factor V Leiden** (FVL) Point of Care Tool with when to offer genetic testing for FVL and management for asymptomatic carriers of FVL
- **Hypertrophic cardiomyopathy** (HCM) Point of Care tool with evaluation and management of HCM

- Three GEC-KO *on the run*. These are concise summaries for healthcare providers on a genetic disorder, technology or topic written by an expert with input from a genetic counsellor, geneticist and family physician. They are evidence-based and referenced, and feature a 'Bottom line' with recommendations.

    a) **Alzheimer disease**

    b) **Chromosomal microarray**

    c) **Multiple Sclerosis**

All handouts, and more, are available on www.geneticseducation.ca

When to offer genetic testing for factor V Leiden (FVL)

Testing **is appropriate** in the following circumstances: [1,2]	Other clinical circumstances in which testing **may be appropriate** include the following: [1,2]	FVL testing is **not** routinely recommended: [1,2]
A first unprovoked VTE at any age (especially age <50 years)	Female smokers < 50 years with a myocardial infarction or stroke	• For the general population
A history of recurrent VTE	Women with recurrent unexplained first-trimester pregnancy losses, or an unexplained fetal loss after 10 weeks gestation, or stillbirth	• During routine pregnancy screening
Venous thrombosis at unusual sites (e.g., cerebral, mesenteric, hepatic, or portal veins)	Selected women with unexplained severe preeclampsia, placental abruption, or a fetus with severe intrauterine growth restriction	• Before the use of estrogen contraception hormone replacement or SERMs
VTE and a strong family history of thrombotic disease	A first VTE related to the use of tamoxifen or other selective estrogen receptor modulators (SERMs)	• For prenatal testing and screening of asymptomatic newborns, neonates, and children
VTE during pregnancy or the puerperium	Neonates and children with non-catheter-related idiopathic VTE or stroke	
VTE associated with the use of estrogen contraception or hormone replacement therapy (HRT)	Asymptomatic adult family members of individuals with a known FVL mutation, especially those with a strong family history of VTE at a young age (<50y), when that knowledge may influence pregnancy management, consideration of estrogen contraception use or pregnancy*	• For patients with a personal or family history of arterial thrombosis (acute coronary syndrome or stroke), unless unexplained in an individual under age 50
A first VTE and a first-degree family member with VTE < 50 years		

*Because thrombosis rarely occurs before young adulthood, asymptomatic relatives younger than 18 years are not usually tested, even relatives of homozygotes.[2]

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Management recommendations for asymptomatic FVL carriers

Education	Additional testing	During high risk situations
Carriers should be educated about: ✓ Circumstances that might increase the likelihood of VTE (obesity, age, surgery, reduced mobility due to injury or travel, use of oral contraceptives, HRT, or SERMs, and pregnancy) ✓ The signs and symptoms of VTE that require immediate medical attention ✓ The potential need for prophylactic anticoagulation in high-risk circumstances (e.g. postpartum)[4]	FVL is often seen with other inherited and/or acquired disorders. An individual with FVL should be tested for other thrombophilia disorders to better assess the absolute risk of thrombosis[1,2]. Consider:[1] ✓ Genetic testing for prothrombin 20210G>A variant ✓ Serologic assays for anticardiolipin antibodies and antibeta2glycoprotein 1 antibodies ✓ Multiple phospholipid-dependent coagulation assays for a lupus inhibitor	During high-risk clinical situations (e.g. surgery, pregnancy) prophylactic anticoagulation may prevent some VTE episodes. However, there is no evidence confirming the benefit of primary prophylaxis for asymptomatic FVL heterozygotes. Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment in each individual case. [1,3] Consultation with a specialist may be considered.

For more information on FVL see the GEC-KO *on the run* or the more comprehensive GEC-KO Messenger at www.geneticseducation.ca in Educational Resources.

[1] Kujovich JL. Factor V Leiden thrombophilia. *Genet Med* 2011; 13(1): 1-13

[2] Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA, ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. *Genet Med* 2001; 3(2):139-48

[3] Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW; American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):381S-453S.

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The Role of Genetic Testing in Hypertrophic Cardiomyopathy[1]

Hypertrophic cardiomyopathy (HCM) is:

- characterized by cardiac hypertrophy in the absence of another cardiac or systemic disease
- said to affect 1 in 500 people
- the most common cause of sudden cardiac death in the young

The evaluation and management of HCM is outlined in the table on the right. The principal role of genetic testing is not to confirm a diagnosis but rather to identify the causative gene in the affected individual and to provide a clinical tool for screening family members at risk of developing the disease. In general, affected individuals and their first degree relatives should be referred to both cardiology and genetics specialists.

For more information on HCM see the GECKO *on the run* in Educational Resources at www.geneticseducation.ca .

Table: Evaluation and management of HCM

Evaluation	• Personal and family history • Physical examination • ECG • 2-dimensional echocardiography
Diagnosis	• Generally established by echocardiography • ECG abnormalities may occasionally precede the onset of left ventricular hypertrophy on the echocardiogram • Distinguish patients with HCM from patients with physiological causes of hypertrophy (e.g., athlete's heart) or infiltrative disorders

Management	• Risk stratification of patients is recommended to determine the risk for Sudden Cardiac Death (SCD)
	• Major risk factors are:
	  • family history of premature SCD
	  • unexplained syncope
	  • non-sustained ventricular tachycardia (VT)
	  • abnormal blood pressure response to exercise
	  • massive left ventricular hypertrophy (maximum left ventricular wall thickness >30 mm)
	• *In patients considered high risk for SCD, an implantable cardioverter-defibrillator (ICD) is indicated*
	• *Exercise restriction is recommended to minimize arrhythmia provocation in high-risk individuals*

Surveillance	• Regular echocardiographic and ECG monitoring • All first-degree relatives (including children) of an affected person should have regular cardiac exams, echocardiograms and ECGs, unless they test negative for a known disease-causing familial mutation

[1] This GECKO POC Tool was adapted from Gollob *et al.*, Recommendations for the Use of Genetic Testing in the Clinical Evaluation of Inherited Cardiac Arrhythmias Associated with Sudden Cardiac Death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society Joint Position Paper. *Canadian Journal of Cardiology* 2011; 27: 232–245.

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ALZHEIMER DISEASE

Informative genetic testing is currently available to only a small number of families with a history of early-onset (younger than 60-65 years of age) Alzheimer disease (AD). For these families, the benefits of genetic testing are limited and are mainly related to the individual's perception of the psychological advantages of knowing whether or not he or she is predisposed to develop AD. There remains no cure or effective preventive therapy for AD.

Genetic testing is not feasible for most cases of AD at this time. Apolipoprotein E gene variations alone cannot be used to predict future disease occurrence. Rare families with a history of early-onset AD might be eligible for genetic testing, while families with multiple relatives affected with late-onset AD (60-65 years of age and older) might be eligible to participate in AD research studies.

WHAT IS ALZHEIMER DISEASE? [1]

Alzheimer disease (AD) is an adult-onset progressive dementia. It is relatively common and the overall lifetime risk of developing dementia is 10-12%. Seventy-five percent of AD cases are sporadic, of unknown cause and usually have late onset of symptoms. Twenty-five percent of AD cases are familial (i.e. ≥ 2 persons in family have AD) and are composed of two types:

- Early-onset familial AD (EOAD) with a mean age of onset < 60-65 years (<2%)
- Late-onset familial AD (LOAD) with a mean age of onset of >60-65 years (15-25%)

Three genes have been associated with early-onset familial AD (EOAD) – amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*). Each of the identified genes is involved in production of the amyloid ß (Aß) peptide, a major component of amyloid plaques. EOAD follows an autosomal dominant inheritance pattern. [1]

Late-onset familial AD (LOAD) has been associated with apolipoprotein E (APOE) gene variations. These are considered a risk modifier, especially APOE ε4. Approximately 1% of the general population are APOE ε4 homozygotes (carry two copies of ε4). Approximately 42% of persons with AD do NOT have an APOE ε4 allele.[1]

Inheritance of AD is a complex interaction between genetic and environmental factors. With one affected first-degree relative, the risk of AD is approximately 20-25%.[1]

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

Genetic testing for AD is only available for a small number of families with EOAD, with testing likely to be initiated in a living affected relative. If a gene mutation is found, other family members are eligible for testing for the identified family mutation. Clinical testing is currently not available for LOAD or sporadic cases. When there are multiple related affected individuals, research testing may be available. APOE ε4 testing is not recommended for risk assessment because of low sensitivity and specificity; APOE ε4 is neither necessary nor sufficient for the disease[2].

Consider a genetics consult for patients with:

- AD with age of onset <60-65 years
- Late-onset AD and multiple affected close relatives
- Close relatives of the above two types of patients
- A family member who has an identified mutation in the *APP, PSEN1* or *PSEN2* genes

See www.geneticseducation.ca for how to connect to your local genetics centre.

WHAT DOES THE GENETIC TEST RESULT MEAN?[1]

Inheriting a mutation in *APP*, *PSEN1* or *PSEN2* gene causes EOAD. Information about the genetic factors involved in LOAD is limited; for example, data suggest that a young asymptomatic person with two copies of the APOE ε4 allele may have an increased lifetime risk of developing AD and a lower age of onset of AD compared to persons who have only one or no copies of the APOE ε4 allele.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

In the case of genetic testing for EOAD, a positive test result for a known family gene mutation can result in:

- Relief from uncertainty
- An increased feeling of control
- Opportunity to plan life decisions given this additional information

A negative test result for a known family gene mutation for EOAD can result in:

- Relief from fear of developing early-onset AD
- Knowledge that children are not at risk for early-onset AD

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Currently no cure or effective preventive therapy is available if a gene mutation is found. A positive test result for a known EOAD family gene mutation can result in:

- Adverse psychological reaction, family issues/distress
- Insurance/job discrimination, confidentiality issues

A negative test result for a known family EOAD gene mutation can result in survivor guilt.

When an individual with no known familial gene mutation has genetic testing, a negative result is not a definitive answer.

For recent review articles on AD see Alonso Vilatela ME *et al.,* Genetics of Alzheimer's disease. *Arch Med Res.* 2012; 43(8): 622-31 and Goldman JS *et al.,* Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med* 2011; 13(6): 597-605

References

[1] Bird TD. Alzheimer Disease Overview. 1998 Oct 23 [Updated 2014 Jan 30]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1161/

[2] American College of Medical Genetics/American Society of Human Genetics Working Group on *APOE* and Alzheimer's disease (1995) Statement on use of apolipoprotein E testing for Alzheimer's disease. *JAMA* 1995; 274(20): 1627-1629

Other AD resources: http://www.alzheimer.ca/en (Alzheimer Society)

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Updated from the original Gene Messenger developed for the GenetiKit research project.
GenetiKit team: Principal Investigators: Carroll JC, Allanson J, Wilson BJ, Co-Investigators: Blaine S, Cremin C, Dorman H, Gibbons C, Graham GE, Graham I, Grimshaw J, Honeywell C, Meschino WS, Permaul J, Wilson BJ.

CHROMOSOMAL MICROARRAY

Chromosomal microarray (CMA) is a high resolution genetic test to assess very small gains and losses (copy number variants) of genomic information in an individual.
CMA should be considered for clinical presentation of:

- ✓ isolated autism spectrum disorder (ASD) or ASD **plus** other findings
- ✓ isolated global developmental delay or intellectual disability
- ✓ multiple congenital anomalies in the absence of a syndrome diagnosis
- ✓ unusual physical features (dysmorphisms)

CMA is not appropriate if a single gene condition (e.g. Duchenne muscular dystrophy) or an aneuploidy (e.g. Down syndrome, trisomy 18) is suspected. It is not appropriate for couples experiencing multiple miscarriages or infertility.

Identifying the underlying etiology of an individual's intellectual challenges and/or congenital anomalies is important for many reasons including counselling (e.g. family planning and prenatal testing, prognosis), providing access to appropriate resources, and alleviating psychological stress by ending the parental diagnostic odyssey.

WHAT IS CHROMOSOMAL MICROARRAY?

Chromosomal microarray (CMA) is a technology used to determine if there are small extra (micro-duplication) or missing (micro-deletion) pieces of genetic information. These gains and losses are called copy number variants (CNVs). A CNV can be: of no medical consequence; pathogenic resulting in physical and/or intellectual consequences; or protective against disease (e.g. HIV infection). The contribution of CNVs to common, complex diseases, such as diabetes, is less well understood.

Identifying the underlying etiology of an individual's intellectual disability and/or congenital anomalies ends the diagnostic odyssey and eliminates other unnecessary diagnostic tests. Additionally, diagnosis can: facilitate access to needed services; empower families by knowing the underlying cause of a relative's disorder; identify associated medical risks; facilitate more accurate recurrence-risk counselling; and allow for targeted testing of at-risk family members.

A microarray is a small glass slide on which thousands of genes are arrayed. Using conventional DNA hybridization process, DNA probes are attached (hybridized) with differentially-labelled DNA - patient (green) and control/reference (red) - to reveal CNV (gains and losses) at a much higher resolution than routine karyotype (chromosome analysis). In a normal situation, each probe on the array should hybridize equally to test (green) and control (red) DNA. This will produce a yellow signal. Extra pieces of DNA produce a green signal and missing pieces produce a red signal. The slide is scanned and images analyzed by computer.

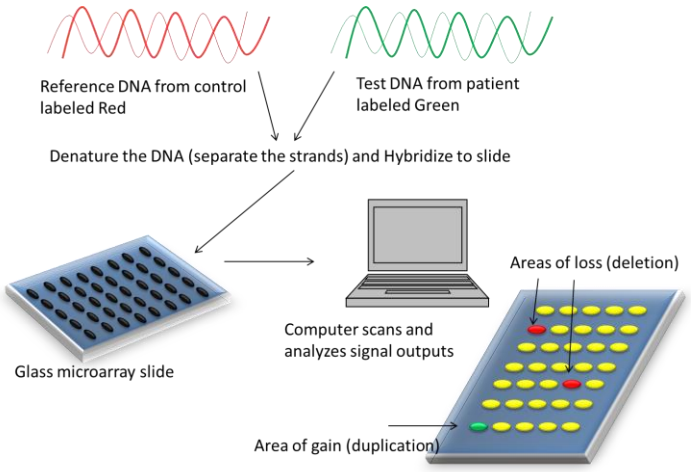

Figure 1. CMA.

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

- Isolated autism spectrum disorder* (ASD)
  - Any individual with autistic features **should first be assessed to make a definitive diagnosis,** usually using tools such as ADOS and ADI
    - Autism Diagnostic Observation Schedule (ADOS) is an instrument for diagnosis and standardized assessment of autism. Autism Diagnostic Interview (ADI) is a companion instrument.
  - If autism is confirmed, a genetics referral should be considered
  - The genetics assessment will look for physical features (see those below) that might point to a syndrome or specific single gene disorder.
- ASD- "Plus" is ASD accompanied by any of the findings below:
  - A. Microcephaly^{+} OR macrocephaly$^{\#}$
  - B. Failure to thrive OR obesity
  - C. Short stature OR overgrowth
  - D. Dysmorphic features
  - E. Congenital malformations
  - F. Seizures
  - G. Pigmentary changes suggestive of TSC on Wood's lamp examination
  - H. Family history of ASD, developmental delay or a known single gene condition
- Isolated global developmental delay or intellectual disability without ASD or any findings listed above

ASD- Persistent deficits in communication and social interaction, and repetitive, restricted behaviours and/or interests; Microcephaly^{+} – head circumference below the 2nd centile; Macrocephaly$^{\#}$ – head circumference above the 98th centile; TSC - Tuberous Sclerosis complex

FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC TESTING

- A close relative with a known CNV related to a clinically significant physical and/or intellectual disability

When referring to Genetics for a positive family history include as much information about the affected family members as possible and encourage your patient to seek medical records and documentation.

WHAT DOES THE GENETIC TEST RESULT MEAN?

There are three possible results when ordering CMA. Patients should be counselled about all possible outcomes.

1. Normal
   - Excludes a micro-deletion/micro-duplication (CNV) within the limits of resolution of the test (typically very high)
     - This does not exclude a syndrome caused by a mutation within a single gene or detect a balanced translocation
   - A referral for genetic consultation should be considered so that additional genetic testing, depending on the patient's presentation, may be offered
2. Pathogenic micro-deletion or micro-duplication (CNV)
   - CNV previously described and associated with a known abnormal phenotype
   - Depending on the finding, parental testing and/or additional medical surveillance may be indicated
3. Variation of unclear clinical significance (VUS)
   - Not every CNV in the genome is pathogenic
   - A variant that has not been described in the literature is challenging to interpret. Knowledge of parental status will determine whether or not the CNV is familial, and less likely to be pathogenic, or *de novo* (new in the affected individual) and more likely pathogenic
   - Parental samples should be obtained and analysed, then refer to genetics, if not already initiated

See www.geneticseducation.ca connect to your local genetics centre.

For guidelines on the genetics evaluation of ASD see Schaefer et al., Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med* 2013; 15(5): 399-407 and Carter and Scherer. Autism spectrum disorder in the genetics clinic: a review. *Clin Genet 2013;* 83(5):399-407

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Multiple Sclerosis

There is a well-recognized genetic contribution to the development of multiple sclerosis (MS). The risk of MS to first-degree family members of an affected individual is between 3 and 5%. This recurrence risk increases with the number of affected relatives in the family and the degree of relationship between them. Despite this, no single gene mutation is known to cause MS. Recent genetic studies have identified dozens of genes which collectively contribute small effects to MS risk. The frequency of MS-variant genes in the general population limits the value of genetic testing which does not contribute to prognosis or management. Genetic testing for MS is not available in Canada. It is important to recognize that genetic testing may be available for certain conditions with overlapping symptoms to MS (MS mimics) and in these instances testing may aid accurate diagnosis. Disease-modifying treatments (DMT) are part of standard care for individuals with MS. They are not recommended during pregnancy or breastfeeding though evidence of teratogenicity has not been convincingly established to date.

What is Multiple Sclerosis?

Multiple sclerosis (MS) is a demyelinating condition of the central nervous system (CNS) that affects 1 in 500 Canadians[1]. It is characterized by inflammation and axonal degeneration within the CNS. Symptoms include numbness or tingling, visual disturbances, difficulty walking, and fatigue[1]. First symptoms typically present between age 20 and 40 years but can appear at any age. MS affects women 2-3 times more often than men. The most common course of disease is marked by relapse into symptoms followed by periods of remission[1].

The role of genetics in MS risk was established with the study of recurrence risks within families[2-6]. First degree relatives of individuals with MS have a 3-5% chance to develop MS in their lifetime. This is 15 to 25 times higher than the population prevalence. Chance for relatives to develop MS increases with the number of affected family members and the degree of relationship between them. The risk for the monozygotic twins of an individual with MS approaches 30%[2] and illustrates the effects of increased genetic sharing and common *in utero* environment[3]. Studies of adoptees, step-siblings and spousal controls show no increased MS risk over the population prevalence suggesting that the shared familial micro- environment (i.e. household) is not a significant risk factor[4-6].

The *HLA DRB1* gene, lying within the major histocompatibility complex, has consistently been associated with MS. This gene functions within the immune system to distinguish self from foreign antigen[7]. The HLA DRB1*1501 variant of this gene is found two to three times more often in those with MS than in unaffected controls[8]. Recently, dozens of genes with odds ratios of less than 1.2 have been identified which collectively contribute small effects to overall MS risk[9,10]. The vast majority of these susceptibility variants have an immune-related function[10]. It is important to note that these variants are commonly found in healthy controls.

Non-genetic risk factors for MS include living at higher latitude, vitamin D deficiency, a history of cigarette smoking and Epstein-Barr virus exposure[11].

Management/treatment

Medical management is usually performed by specialists in the field of MS. Disease-modifying treatments (e.g. interferonB-1b) have been shown to reduce the number of relapses and slow progression of the disease. Symptom-specific medications (e.g. for pain or bladder dysfunction) as well as relapse treatments (typically steroids) are often used for management. Vitamin D supplementation is also recommended.

Red flags to consider genetic testing or genetic consultation

Most of the time, a diagnosis of MS is not a strong indicator to refer for genetic assessment. Discussions of recurrence risks, psychosocial needs and medication safety during child-bearing years can be initiated with primary healthcare providers or neurologists.

Genetic testing is not available for diagnostic, predictive or prenatal purposes. However, referral to Genetic or Metabolic specialists should be considered for individuals who:

- Present at a very young age (i.e. less than 10 years)
- Display a strong family history in keeping with Mendelian inheritance (dominant, recessive or X-linked)
- Have MRI findings atypical for MS
- Do not experience typical progression in keeping with the natural history of MS
- Develop atypical symptoms such as migraine or dementia which may indicate the need to rule out other disease (e.g. inherited arteriopathy or leukoencephalopathy)

Any of the above may indicate a rare form of demyelinating disease[12], some of which are caused by a single gene mutation. Genetic testing may be available in these instances and genetic counselling should be provided to advise of screening for family members at risk and to discuss family planning options.

WHAT DOES THE GENETIC TEST RESULT MEAN?

Testing for the multiple sclerosis susceptibility gene variants is not currently offered, or recommended. The frequency of MS-variant genes in the general population limits the value of genetic testing which would not contribute to prediction of risk, prognosis or management. As more variants are studied, testing may be indicated to determine which persons respond to different treatment options but this is not the case at present.

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Genetic testing is not clinically available for multiple sclerosis. For people who present with results obtained through private-pay direct-to-consumer testing, interpretation is not straightforward as each risk variant confers such a small effect on genetic predisposition. Some people with MS have few or none of these susceptibility variants and conversely, most people found to carry these variants will never develop MS.

ARE THERE RISKS ASSOCIATED WITH MS TREATMENT AND PREGNANCY OR BREAST FEEDING?

Disease Modifying Therapies (DMT)
Limited studies on the safety of disease-modifying treatments for MS during pregnancy and breastfeeding have not demonstrated risk for congenital malformation. However, the current recommendation remains to stop the use of DMT during pregnancy and lactation. Relapse rates are naturally suppressed by pregnancy in many women but may increase post-partum.

Other Treatments
Some medications, such as chemotherapy used to treat aggressive forms of MS, are contraindicated during pregnancy and breastfeeding and may reduce chances of becoming pregnant in the future. Each symptom-specific treatment should be assessed for safety in women who may become pregnant. Your local genetics centre and the Motherisk program at The Hospital for Sick Children are good resources to determine the safety of medication during pregnancy and breastfeeding. Affected women and their partners are encouraged to discuss family planning with all prescribing physicians involved in their care.

See www.geneticseducation.ca for the full-length GEC-KO Messenger on MS and how to connect to your local genetics centre.

For a recent review article on MS see Sawcer *et al.,* Multiple sclerosis genetics. *Lancet Neurol* 2014; 13: 700–09.

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