Untangling the Helix 2017: Genomics for primary care providers

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Date and time: Friday, November 10th, 2017 from 13:30 to 14:30
Presenters: June C Carroll MD CCFP and Shawna Morrison MS CGC

Enclosed:

- Genetics of autism spectrum disorder GEC-KO *on the run*
- Genetics of autism spectrum disorder *point of care tool*
- Direct-to-consumer genetic testing GEC-KO *on the run*

All handouts, presentation slide sets and additional resources are available at www.geneticseducation.ca.

GENETICS OF AUTISM SPECTRUM DISORDER

Bottom line: Autism spectrum disorder (ASD) is a complex, genetically influenced disorder, affecting about 1 in 68 children. ASD is highly variable both in presentation and in etiology. In families where one child has ASD, the risk to subsequent siblings is about 10-19%. About 15-40% of individuals with ASD will have an identifiable contributing genetic cause. First tier genetic investigations for ASD are chromosomal microarray and fragile X syndrome testing. If an individual is determined to have ASD *plus* (signifying additional co-morbidities such as congenital anomalies, dysmorphic features, neurological symptoms e.g. seizures), additional investigations may be considered. A genetic diagnosis can potentially lead to guideline-based surveillance and management, tailored treatment options, opportunities to participate in clinical trials, information regarding natural history and prognosis, familial testing and more accurate recurrence risk counselling. Primary care providers who feel confident providing pre- and post –test counselling may be able to arrange first tier genetic investigations prior to or concurrent with referral for genetic consultation. Local laboratories may limit which providers can order these tests.

WHAT IS AUTISM SPECTRUM DISORDER?

Autism spectrum disorder (ASD) is a complex heterogeneous group of neurodevelopmental disorders affecting brain function and behaviour. The core features of ASD include pervasive impairments in communication and social interaction, repetitive behaviours and/or restricted interests[1].

HOW COMMON IS ASD?

Recent surveillance data suggest that about 1 in 68 children is affected by ASD with males diagnosed about four times more often than females[1,2].

HOW IS ASD DIAGNOSED?

Diagnosis of ASD is based on clinical criteria, the most recent of which are found in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-5]. A child may first be brought to attention following routine screening using a tool such as the validated Modified Checklist for Autism in Toddlers-Revised (M-CHAT-R™).

WHAT CAUSES AUTISM SPECTRUM DISORDER?

ASD is a genetically influenced disorder caused by genetic, epigenetic (*factors that affect gene expression and activity*) and non-genetic (*environmental*) factors[1,3,4]. For couples who have a child with ASD, the chance for each of their subsequent children to be diagnosed with ASD is about 10-19%[3,5,6]. Recurrence risks can sometimes be more accurately predicted if a genetic etiology is known.

About 15-40% of individuals with ASD will have an identifiable contributing genetic cause, depending on the study population and the type of genetic technology used[3,7].

About 25% of individuals with ASD will have complex ASD or ASD *plus*, meaning that autistic features are accompanied by congenital anomalies, dysmorphic features and/or neurological findings (see Figure 1).

WHAT ARE THE RED FLAGS THAT SUGGEST GENETIC CONSULTATION AND/OR GENETIC TESTING?

Once an ASD diagnosis is confirmed, a provider can consider the red flags below to determine if the individual has isolated ASD or ASD *plus.* A genetics referral could be made at that time. Alternatively, a provider who is comfortable providing pre-test counselling and post-test follow-up could begin the first tier genetic testing and refer upon receipt of results. Local laboratories may limit which providers can order these tests. Contact your local genetics centre for more.

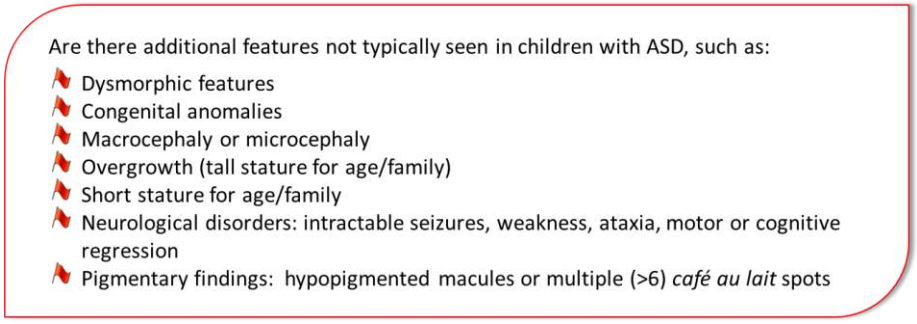

Figure 1. Red flags to alert a health care provider that their patient's ASD is complex, also known as ASD *plus*, and could benefit from a genetic consultation.

WHAT CAN MY PATIENT EXPECT AT A GENETIC CONSULTATION FOR AUTISM SPECTRUM DISORDER?

The role of a clinical geneticist is to identify the etiology of the ASD where possible, with the hope of improving management of the individual and providing genetic counselling for the family[9]. A clinical genetics consultation includes a review of the patient's prenatal, perinatal, medical and family histories, and a physical examination to document growth parameters (such as head circumference) and look for evidence of dysmorphic features[1].

The Canadian College of Medical Geneticists (CCMG) recommends that chromosomal microarray and fragile X syndrome testing be the first tier laboratory investigation for any male or female whose ASD and/or other developmental disability is unexplained after a thorough history and physical examination[10]. Second tier investigations may be guided by presentation. Clinical geneticists may ofter genetic testing for a single gene syndrome (e.g. Rett syndrome, Cowden syndrome) or a next-generation sequencing panel which could include tens to thousands of genes.

WHAT ARE THE BENEFITS OF GENETIC CONSULTATION [WITH OR WITHOUT GENETIC TESTING]?

Advances in genomic technology have provided the opportunity for many families to receive an answer to the question 'why does my child have ASD'. A genetic diagnosis can potentially lead to guideline-based surveillance and management, tailored treatment options, opportunities to participate in clinical trials, information regarding natural history and prognosis, familial testing and more accurate recurrence risk counselling. In the absence of an identifiable genetic etiology, a recurrence risk (RR) range can be quoted based on empirical studies. For families where one child has ASD, the RR is about 10-19%[5,6]. Males are at higher risk than females. Couples with two children with ASD have a higher RR, around 30%[3]. The more distant an affected relative is, the lower the RR.

WHAT ARE THE LIMITATIONS AND COMPLEXITIES OF GENETIC TESTING FOR AUTISM SPECTRUM DISORDER?

There are several complexities to genetic testing such as **uncertain results**. Not every genomic variation has been classified as either benign or pathogenic. This sort of result can neither confirm nor rule out a specific genetic etiology and can be frustrating for families and providers. Another complex result is an **ASD 'risk variant' with incomplete penetrance.** This is one of the most difficult scenarios for genetic counseling[3]. In this circumstance it is difficult to determine the chance of familial recurrence. This genetic change may have been inherited from an affected, mildly affected or even unaffected parent.

Not all individuals will have an identifiable genetic diagnosis. While the genetic contribution to ASD has been well established, today's technology and knowledge will identify a genetic etiology in about 15-40% of individuals with ASD. Individuals and families who attend a genetic consultation with the expectation of receiving a diagnosis may feel disappointed.

Find the contact information for your local genetics centre here.

For community support and research opportunities for your patient and his/her family, see Autism Speaks Canada.

For a complete **REFERENCE** list please see the GEC-KO Messenger. A point of care tool can be found here.

For an excellent review on ASD diagnosis in the primary care setting, please see Anagnoustou and colleagues[1].

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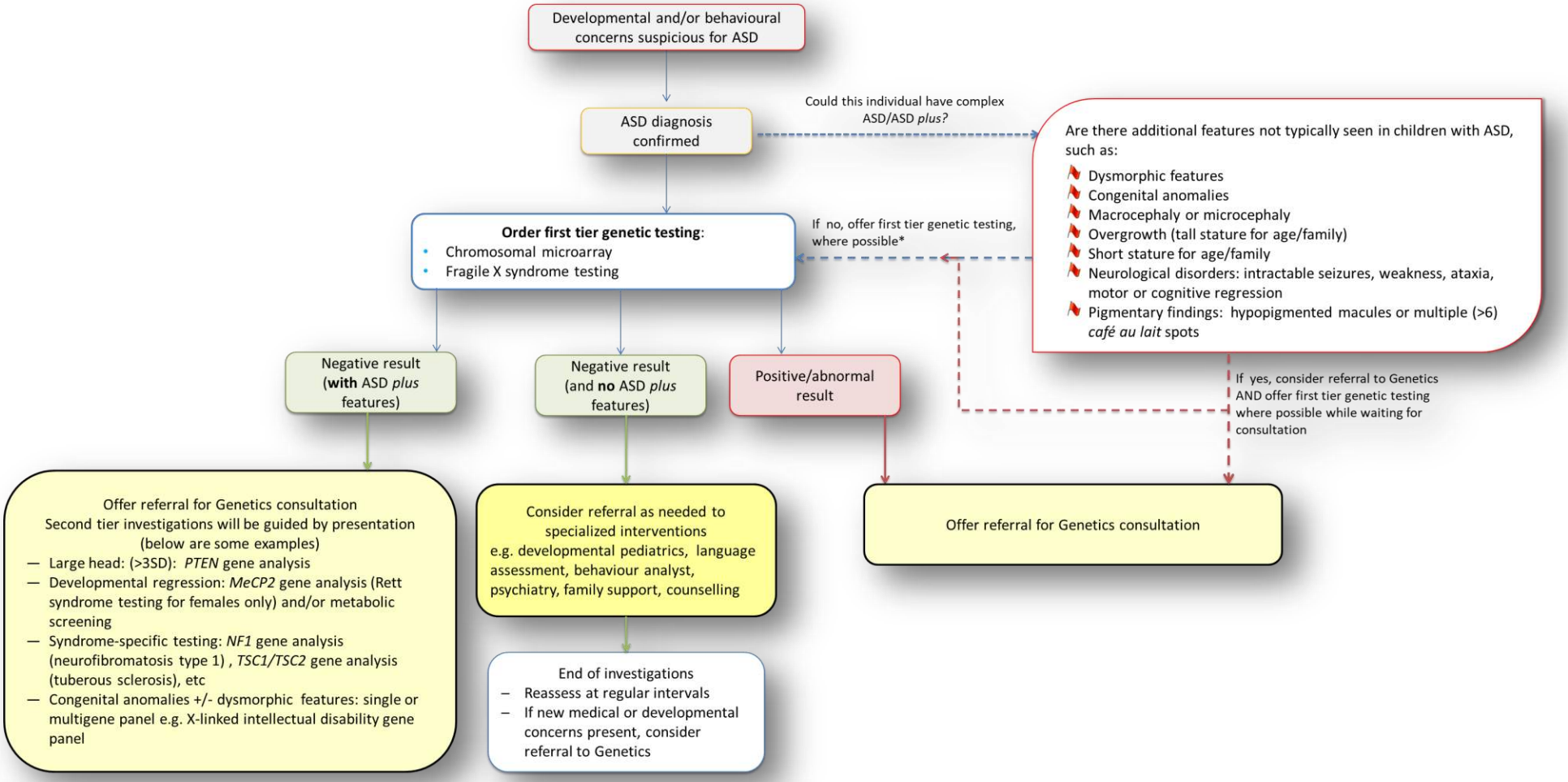
GENETICS OF AUTISM SPECTRUM DISORDER

A road map of possible genetic tests and consultations for the individual with autism spectrum disorder (ASD).



Autism spectrum disorder (ASD) is a complex, genetically influenced disorder, affecting about 1 in 68 children. ASD is highly variable both in presentation and in etiology. In families where one child has ASD, the risk to subsequent siblings is about 10-19%. About 15-40% of individuals with ASD will have an identifiable contributing genetic cause.

Once an ASD diagnosis is confirmed, a provider can consider the red flags above to determine if the individual has isolated ASD or ASD *plus.* A genetics referral could be made at that time. Alternatively, a provider who is comfortable providing pre-test counselling and post-test follow-up could begin the first tier genetic testing and refer upon receipt of results.

First tier genetic investigations for all individuals with ASD are chromosomal microarray and fragile X syndrome testing. If an individual is determined to have ASD *plus* (signifying additional co-morbidities such as congenital anomalies, dysmorphic features, neurological symptoms (e.g. seizures)) additional investigations may be considered. A genetic diagnosis can potentially lead to guideline-based surveillance and management, tailored treatment options, opportunities to participate in clinical trials, information regarding natural history and prognosis, familial testing and accurate recurrence risk counselling. Primary care providers who feel confident providing pre- and post –test counselling may be able to arrange first tier genetic investigations prior to or concurrent with referral for genetic consultation.

*Local laboratories may limit which providers can order first tier investigations. Contact your local genetics centre for more information and advice.

For community support and research opportunities for your patient and his/her family, see Autism Speaks Canada.

For a concise, evidence-based resource on ASD and genetics including benefits and limitations of genetic testing for ASD, please see the GEC-KO on the run. For a more comprehensive review and complete reference list please see the GEC-KO Messenger.

For an excellent review on ASD diagnosis in the primary care setting, please see Anagnoustou and colleagues.

DIRECT TO CONSUMER GENETIC TESTING

Bottom line: Direct-to-consumer genetic testing (DTC-GT) is over-the-counter genetic testing available online to consumers through private companies. Generally, results report an individual's risk to develop a medical condition as being below average/low, average/general population, and above average/high based on genome wide association studies (GWAS). Results may provide medically useful information for consumers and potentially provide support and motivation for lifestyle changes (e.g. weight loss, smoking cessation) or even more vigilant surveillance (e.g. breast cancer screening), reveal carrier status of single gene conditions (e.g. cystic fibrosis), effectiveness and side-effect risk of certain medications, in addition to medically irrelevant information (e.g. curly hair). Currently, DTC-GT is not regulated or accountable to an appropriate governing body. Numerous professional societies express concern about how DTC-GT is marketed to consumers, what and how information is provided and the lack of genetic counselling. **Family health history-based risk assessment is still the gold standard in initial assessment for heritable conditions.**

WHAT IS DIRECT –TO-CONSUMER GENETIC TESTING?[1,2]

Direct-to-consumer genetic testing (DTC-GT), also referred to as personal genome testing, refers to genetic testing available for over-the-counter purchase without the requirement of health care provider involvement. Generally, DTC-GT is marketed with the promise of providing predictive genetic risk assessment for a variety of complex health conditions (e.g. diabetes, cancer, obesity) and information regarding response to and/or side-effect risk of certain medications (e.g. clopidogrel, statins). Additionally, DTC-GT is advertised as assistance in diet and exercise planning. Testing can uncover medically irrelevant information such as bitter taste perception or curly hair.

Generally, DTC-GT is available online to anyone for a cost and is usually performed on a saliva sample.

WHAT DO THE GENETIC TEST RESULTS MEAN?

Test results for DTC-GT depend on what condition is being tested and what technology is being used.

Appropriate pre- and post-test counselling are rarely offered directly by the DTC-GT company and are inconsistently accessed by consumers when available[3-6]. Ideally, testing should be carried out so that the consumer knows what the results might reveal (e.g. risk of multifactorial conditions that arise due to the combined contribution of genetic and environmental factors, carrier status of single gene conditions, including cancer predisposition syndromes) and understands the potential for results requiring additional medical follow-up, not limited to behavioural modifications (e.g. vigilant breast screening and discussion of risk reducing surgery as a result of a *BRCA* gene mutation). The implications for extended family members should be addressed.

Multifactorial disorders and genome-wide association studies (GWAS): GWAS are case-control studies which examine many common variations in our genetic code (single nucleotide polymorphisms [SNPs]). They compare large groups of individuals (unaffected controls versus individuals with symptoms of a specific disease or those experiencing a particular medication response) in an attempt to distinguish between non-harmful changes in the DNA code and pathogenic, disease causing/predisposing changes. SNPs (pronounced 'snips') are the most common type of genetic variation. Each SNP represents a difference in a single DNA building block, a nucleotide. SNPs occur normally in an individual's genome about once in every 300 nucleotides, thus there are about 10 million SNPs in the human genome.

Odds ratios and relative risks are used to categorize an individual as at increased risk (higher than average), average (general population risk), or decreased risk (lower than average). Results from GWAS may be used to report an individual's risk for cancer, heart disease or diabetes. Test laboratories use variable literature sources, data set and technologies for testing and variant classification which adds complexity to interpretation.

Mendelian disorders and ethnicity-specific testing or next generation sequencing: Single gene disorders (e.g. cystic fibrosis, *HFE*-associated hemochromatosis, *BRCA*-associated hereditary breast and ovarian cancer syndrome) are often screened for by targeting only ethnicity-based gene variations. For example, screening for mutations in the *BRCA1* and *BRCA2* genes is limited to the three commonly found in individuals of Ashkenazi Jewish ethnicity, regardless of the consumer's reported ethnicity. This means that not all clinically relevant mutations or even

genes are necessarily included in analysis; possibly resulting in false reassurance with negative results[7].This is of particular importance where there is a known family history.

Additionally next generation sequencing (NGS) may be employed, where the entire coding region of a gene is sequenced (read) looking for significant variation as compared to a reference sequence. While some variations are well known to be either pathogenic or benign, some require expert analysis by a genomic specialist. Genetic changes that are only weakly associated with disease may be reported, possibly leading to anxiety or inappropriate additional testing[7]. Additionally, due to variability in interpretation, there is the possibility of conflicting risk interpretations between companies.

Pharmacogenomics: The goal of pharmacogenomics is to identify gene-drug interactions to improve the safety and efficacy of medications[8]. Currently, few DTC-GT companies offer pharmacogenomics as part of their testing menu. Like genetic testing for Mendelian disorders, pharmacogenomics testing is highly dependent upon ethnicity-based gene variations[8]. Most often companies are analysing for specific SNPs in genes that code for enzymes key to specific drug/drug class metabolism e.g.CYP2D6 and codeine metabolism[9]. Drug and/or dosage response are then predicted. International guidelines have been published and are often referred to on reports[10].

WHAT ARE THE BENEFITS OF DIRECT-TO-CONSUMER GENETIC TESTING?

While there are limited data to support the clinical validity (ability to predict clinical outcome) and utility (the likelihood of improving patient outcome), some consumers might benefit from DTC-GT as results may:

- Encourage positive behaviour modifications (e.g. increase exercise, smoking cessation), although study results are conflicting [11,12]
- Provide useful information for medication choice or management
- Provide information to individuals who have no or limited information about their family history (e.g. an individual who was adopted)
- Reveal carrier status of a genetic condition that could have implications for family planning e.g. cystic fibrosis, sickle cell anemia
- Reveal increased risk of an adult-onset disorder with published screening and surveillance guidelines e.g. alpha-1 antitrypsin deficiency, *BRCA*-associated hereditary breast and ovarian cancer

WHAT ARE THE LIMITATIONS AND RISKS OF DIRECT-TO-CONSUMER GENETIC TESTING?

Caution when interpreting DTC-GT should be exercised as:

- DTC-GT does not take into account numerous factors important when interpreting genetic test results such as age, family history, lifestyle (e.g. smoking, obesity) and other environmental factors that are a significant contribution to common complex disease development[13,14]
- **Family health history-based risk assessment is still the gold standard in the initial assessment for heritable conditions**[15]

RELEVANT RESOURCES YOU MAY BE INTERESTED IN:

Ethnicity-based screening in Canada point of care tool

Expanded carrier screening point of care tool

Alzheimer disease GEC-KO *on the run*

Multiple sclerosis GEC-KO *on the run*

Hereditary breast and ovarian cancer syndrome GEC-KO *on the run*

Lynch syndrome (formerly hereditary non-polyposis colorectal cancer syndrome) GEC-KO *on the run*

More information about DTC-GT in Canada, references and additional resources can be found at www.geneticseducation.ca > GEC-KO Messenger > Direct to consumer genetic testing.

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