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.

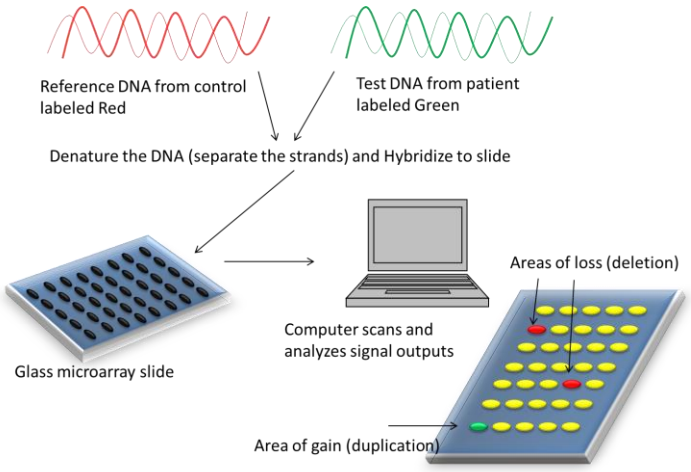

Figure 1. CMA.

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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