The New Genetic Inheritance: Mechanisms of Inheritance That Mendel Would Not Have Predicted With Sweet Peas

R. Douglas Wilson, MD, MSc, FRCSC, FACOG, FCCMG (Hon)

Department of Obstetrics and Gynaecology, Cumming School of Medicine, University of Calgary, Alberta Health Services, Calgary Zone, Calgary AB

J Obstet Gynaecol Can 2016;38(8):727-730

INTRODUCTION

This brief and directed update is intended to provide readers with a better understanding of the "new genomics." My aim is to help readers better understand the results of prenatal/fetal testing and to simplify interpretation of these results for their patients—at least on a basic level. Most importantly this update is intended to help readers know when they need assistance from a reproductive geneticist for making decisions and providing choices.

TRADITIONAL CLASSIFICATION OF GENOMIC DISORDERS[1]

1. Chromosomal disorders (numerical or structural feature): these have major prenatal and neonatal effects
2. Mendelian or single gene disorders: these provide a health burden from the perinatal stages to adult life
3. Multifactorial/polygenic complex disorders: these tend to present later in life
4. Congenital anomalies and diseases associated with specific mitochondrial gene mutations

Key Words: Genetic inheritance, genetic recombination, copy number variance, chromosomal deletion, chromosomal duplication

Competing Interests: None declared.

Received on April 1, 2016

Accepted on April 5, 2016

http://dx.doi.org/10.1016/j.jogc.2016.04.091

NEW CLASSIFICATION OF GENOMIC DISORDERS

This classification applies to genomic disorders that do not follow the conventional principles of inheritance[1] but result in de novo or inherited reproductive and developmental consequences.

1. Genome architecture disorders (genomic rearrangements): these are very complex and variable
2. Tri-nucleotide repeats (genomic instability results in expansion)
3. Chromosome breakages (genomic instability due to abnormal DNA repair)
4. Non-disjunction disorders (genomic instability due to dysfunctional chromatid pairing)
5. Complex genomic diseases (genomic variation single nucleotide polymorphisms/copy number variant)

These disorders all have underlying mechanisms that involve certain genomic regions that directly or indirectly influence regulation and expression of one or more genes, manifesting in complex phenotypes.[1–3]

Genome architecture/genomic rearrangements include structural variants, such as deletions, duplications, triplications, added amplifications, and other large-scale CNVs (average exon with size 50 to 200 base pairs to mega-bases of DNA) and neutral CNVs (inversions/insertions/translocations). These structural variations are not usually able to be detected by a standard chromosomal karyotype.

Structural variants differ from SNPs (polymorphism) or single nucleotide variants, which only change a single base or a few bases. Structural variants result from different mutational mechanisms, including DNA recombination-associated, replication-associated, and repair-associated processes.

Repeat sequences are present in approximately 50% of the human genome and include mobile elements such

as pseudogenes, simple sequence repeats, tandemly repeated sequences (with specific locations such as centromeres, telomeres, short arm of acrocentric chromosomes, and ribosomal gene clusters), and low copy repeats.

Recurrent rearrangements share the same size and genomic content in unrelated individuals, whereas non-recurrent rearrangements have a unique size and genomic content at a given locus in unrelated individuals. Recurrent structural variants have mechanisms resulting from non-allelic homologous recombination between directly oriented LCRs (which creates a deletion and duplication) or from inverted oriented LCRs that are length-dependent (creating an inversion between the repeats) in areas that flank the unique sequence genomic regions.

Non-recurrent structural variants have been identified as causing at least 70 genomic disorders.

Six mechanisms of molecular disruption for the newly understood genomic disorders are summarized in the Figure.[2]

TNR disorders are due to genomic instability/expansion. The effects of the TNR expansion are varied with loss of gene expression, a gain of gene function, or abnormal RNA processing. TNR disorders include conditions such as fragile X syndrome, myotonic dystrophy, Huntington disease, spinal bulbar muscular atrophy, and Friedreich ataxia (as well as other inherited ataxias).[4]

Chromosome breakage disorders are due to genomic instability. The primary mechanism is a defect in DNA repair, with an "instability" that causes rearrangements or other abnormal cytogenetic behaviour. The three classic conditions in this category are Fanconi pancytopenia, ataxia-telangiectasia, and Bloom syndrome.[5]

Non-disjunction disorders in meiosis and mitosis are due to genomic instability. The causes of meiotic ND are a degradation of the adhesion of the homologous chromatids of the bivalent chromosome. This failure of "snug" apposition leads to the chromosome adopting unstable positions when meiosis resumes. Certain genetic and maternal age factors are involved in this increased ND outcome. Meiosis II oocytes show variable, non-equatorial locations of chromosomes and a degenerating spindle apparatus in older women. Mitotic, postzygotic, and somatic ND results have been well-described for chromosomes 21 and 8. For chromosome 21, postzygotic mosaicism can result from a normal 46, N embryo with a subsequent mosaic 46, N/47,+21 embryo; a normal 46,XX embryo with a subsequent mosaic 45,X/46,XX/47,XXX embryo; or postzygotic anaphase lag (trisomy rescue) from a 47,+21 embryo with a possible subsequent 46,N outcome. Trisomy rescue can also lead to uniparental disomy; this has been demonstrated for chromosome 15 in either Prader-Willi syndrome (loss of the paternal chromosome 15) or Angelman syndrome (loss of the maternal chromosome 15).[5]

Complex genomic disease mechanisms (genomic variation SNPs/CNVs) are beyond the scope of this short discussion, but these DNA abnormalities can be identified with prenatal microarray technology when used following the prenatal identification of fetal anomalies or with a request for a more in-depth fetal DNA analysis with a normal prenatal standard karyotype.

ABBREVIATIONS

CNV	copy number variant
LCR	low copy repeats
ND	non-disjunction
SNP	single nucleotide polymorphism
TNR	tri-nucleotide repeat

NEW GENOMIC GLOSSARY

Allele: one of two forms of a gene, or other portion of DNA, located at the same place on the chromosome

Deletion: loss of a portion of a chromosome leading to monosomy expression (single gene copy) on the undeleted chromosome pair; deletion types include interstitial (portion of the short or long chromosome arm) or terminal/subtelomeric (at the ends of the short or long chromosome arm)

Duplication: a portion of a short or long chromosome arm from the chromosome pair is duplicated, leading to a trisomy (three gene copy) expression of the duplication chromosome portion from the normal single copy and duplicated double copy; duplication types include interstitial (portion of short or long chromosome arm), direct (abab) or inverted (abba), and terminal/subtelomeric (at the ends of the short or long chromosome arm)

Complex trait/disease: a trait or disease that is determined by more than one gene and/or environmental factors (traits or diseases determined by one gene only are referred to as *single gene traits/diseases*)

Copy number variation: variation between individuals in the number of copies of a particular region of genomic DNA

DNA microarray: known DNA sequence fragments attached to a slide or membrane, allowing for the detection of specific sequences in an unknown DNA sample