GeneReviews **Educational Materials: Comprehensive Genome Sequencing and Multi-Gene Panels**

Supplementary Material: Table 1. Genetic Disorders Caused by Imprinting Errors and Uniparental Disomy Not Detectable by Sequence Analysis

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Imprinting

Imprinting is the process by which maternally and paternally derived chromosomes are uniquely chemically modified (usually by methylation), leading to different expression of a certain gene or genes on those chromosomes depending on their parental origin. Patterns of gene expression and repression of gene expression vary between imprinted regions.

Methylation, the attachment of methyl groups to DNA at cytosine bases, is correlated with reduced transcription of a gene and is thought to be the principal mechanism of imprinting. An assay designed to detect the methylation pattern at a specific chromosome locus (e.g., methylation-sensitive multiplex ligation probe analysis [MS-MLPA], methylation-sensitive quantitative PCR [MS-qPCR], Southern blotting) is necessary to identify epigenetic imprinting errors. Sequencing techniques including next-generation sequencing used in exome sequencing and genome sequencing do not identify methylation patterns.

Uniparental Disomy

Uniparental disomy (UPD) is the situation in which both members of a chromosome pair or segments of a chromosome pair are inherited from one parent and neither is inherited from the other parent; uniparental disomy can result in an abnormal phenotype if genes within the chromosome segment are imprinted.

The ability of sequence analysis to identify UPD by sequencing DNA from the proband alone depends on the type: uniparental isodisomy versus uniparental heterodisomy.

- **Uniparental isodisomy** (i.e., two copies of a single chromosome or chromosome segment are inherited from one parent and no copy is inherited from the other parent) may be identified by long stretches of homozygosity by sequencing techniques; however, further testing (e.g., chromosomal microarray analysis) may be required to distinguish a deletion from uniparental isodisomy.
- **Uniparental heterodisomy** (i.e., both chromosomes of a chromosome pair or chromosome segment are inherited from one parent and no copy is inherited from the other parent) cannot be identified by sequencing techniques unless recombination has reduced regions of the chromosome to homozygosity. Other test methods such as methylation studies or parental testing (e.g., short tandem repeat (STR) analysis or SNP array) are required to identify uniparental heterodisomy.

Table 1 provides a list of disorders caused by imprinting errors and UPD organized by chromosome locus.

Table 1. Genetic Disorders Caused by Imprinting Errors and Uniparental Disomy [1] Not Detectable by Sequence Analysis

Chromosome Locus	Disorder [2]	Proportion of Disorder Due to Imprinting Error Not Detectable by Sequence Analysis	Proportion of Disorder Due to Uniparental Disomy (Parental Origin of Disomic Chromosome)
6q24.2	Transient neonatal diabetes mellitus, 6q24 related	21%	41% (paternal)
chr 7	Russell-Silver syndrome		7%-10% (maternal)
11p15.5	Russell-Silver syndrome	35%-50%	
11p15.5	Beckwith-Wiedemann syndrome	55%	~20% (paternal)
11p15.5	Isolated hemihyperplasia (OMIM 235000)	6% [3]	16% [3]
11p15.5	Isolated Wilms tumor (see Wilms Tumor Predisposition)	<1% [4]	<1% [4]
14q32	Temple syndrome (OMIM 616222)		100% (maternal)
14q32	Kagami-Ogata syndrome (OMIM 608149)		100% (paternal)
15q11.2-q13	Prader-Willi syndrome	2%	20%-30% (maternal)
15q11.2-q13	Angelman syndrome	80%	~7% (paternal)
20q13	Pseudohypoparathyroidism 1B (OMIM 603233)	~10%-30%	~10% [5] (paternal)
20	UPD(20)mat [6]		12 individuals (maternal)

1. Long stretches of homozygosity caused by uniparental isodisomy may be detected by exome or genome sequence analysis; however, not all mechanisms by which uniparental disomy occurs result in stretches of homozygosity [Kearny et al 2011]. The ability of a laboratory to recognize stretches of homozygosity will vary.
2. For more information see hyperlinked GeneReview. An OMIM phenotype entry (if available) is provided if there is no GeneReview.
3. Shuman et al [2006], Soellner et al [2017]
4. Scott et al [2008]
5. Takatani et al [2015]
6. Mulchandani et al [2016]

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