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Uniparental disomies 7 and 14

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precocious puberty
diagnostic scoring system
(epi-)genotype–phenotype correlation
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assisted reproductive technology
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Normally, one inherits one chromosome of each pair from one parent and the second chromosome from the other parent. Uniparental disomy (UPD) describes the inheritance of both homologues of a chromosome pair from the same parent. The biological basis of UPD syndromes is disturbed genomic imprinting. The consequences of UPD depend on the specific chromosome/segment involved and its parental origin. Phenotypes range from unapparent to unmasking of an autosomal-recessive disease to presentation as a syndromic imprinting disorder. Whilst paternal UPD(7) is clinically unapparent, maternal UPD(7) is one of several causes of Silver-Russell syndrome. Presentation of paternal UPD(14) ("Kagami syndrome") is a thoracic dysplasia syndrome with mental retardation and limited survival. Findings in maternal UPD(14) ("Temple") syndrome show an age-dependent overlap with the well-known maternal UPD(15) (Prader-Willi) syndrome and are dominated by initial failure to thrive followed by obesity, learning difficulties and precocious puberty. Diagnostic strategies to tackle the genetic heterogeneity of UPD(7) and UPD(14) syndromes will be explained. Management issues in UPD(7) and UPD(14) patients will be discussed, and finally areas requiring further research will be outlined.

Definitions

The regular chromosome make up of any human fertilised zygote and subsequent somatic cell comprises two haploid sets of chromosomes, one from each parent. On a karyotype level, this is called **diploidy**. When referring to an individual chromosome pair this status is called **biparental disomy**. If

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the two homologues of a chromosome pair originate from the same parent with no homologue from the other parent, this is called **uniparental disomy (UPD)**.[1] UPD may comprise an entire chromosome or part of a chromosome (segmental UPD).[2] UPD may be present as **isodisomy**, i.e. two copies of the same parental chromosome, or as **heterodisomy**, i.e. one copy each of the two homologues from the same parent (Fig. 1). **Nullisomy** describes the lack of a single chromosome, i.e. a haploid germ cell that contains 22 instead of 23 chromosomes is nullisomic for the lacking chromosome. **Mosaicism** describes the presence within an organism of at least two genetically different cell lines that are derived from a common precursor cell such as the fertilised zygote. Examples are mosaic trisomies with the trisomic cell lineage present in the extraembryonic tissues but not in the embryo proper.

Epigenetics is the regulation of gene expression through mechanisms other than DNA sequence changes. Well-known epigenetic mechanisms are de-/methylation of DNA residues such as of CpG dinucleotides and histone protein modifications. These epigenetics marks entail local changes of chromatin conformation and silencing of genes in the respective region.[3] Epigenetic marks such as

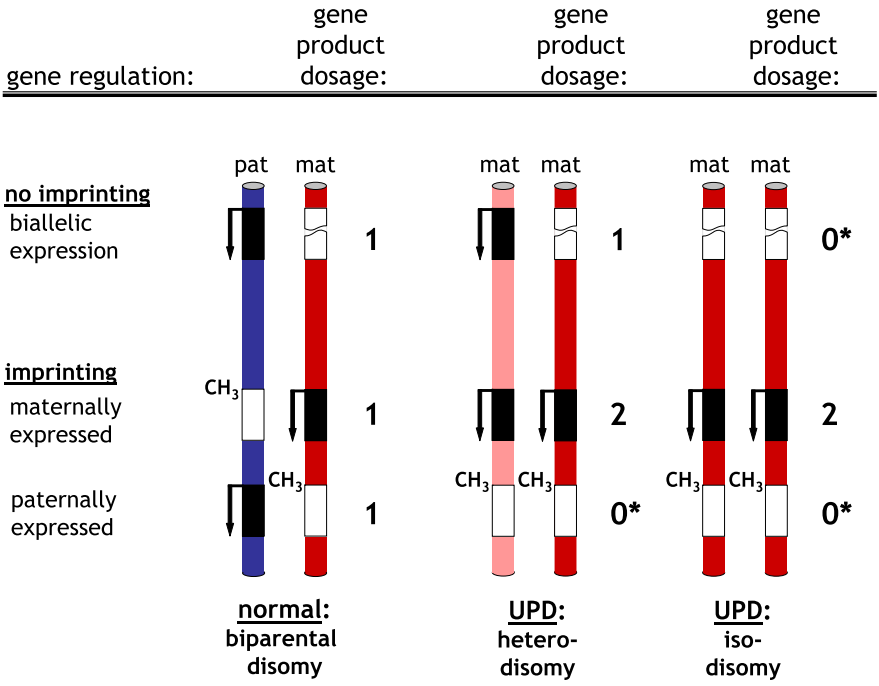

Fig. 1. Consequences of isodisomy and heterodisomy: imprinting disorder with or without unmasking of a mutant recessive allele. A pair of homologue chromosomes is symbolized by rods; blue indicates paternal, red maternal origin. Genes are drawn as rectangles, a mutated gene as an interrupted rectangle, an expressed gene as a blackened rectangle with an arrow alongside, and an imprinted gene as an empty rectangle with CH_3 symbolizing methylation. An asterisk indicates a contribution to the clinical phenotype. Let us assume, that in each case the mother is a heterozygous carrier for a gene mutation at an autosomal-recessive gene locus (top), whilst the father has two wildtype copies of this gene. The physiological state for an autosomal chromosome (biparental disomy) is shown on the left hand side and illustrates that differential gene regulation by imprinting may be of opposite parent-specific orientation in two adjacent genes. The heterodisomic proband in the middle has received both maternal homologues originating from the two maternal grandparents. This is the result of trisomic rescue after maternal meiosis I error. An imprinting disorder is caused by the lack of the paternally expressed copy of the gene that is physiologically imprinted (silenced by methylation) on the maternal chromosomes. The recessive mutation on one of the maternal chromosomes does not produce a clinical phenotype because the second maternal homologue carries a functioning wildtype copy of the same gene. In isodisomy on the right hand side two copies of the maternal chromosome with the recessive gene mutation have been passed on (e.g. trisomic rescue after meiosis II error). If the inherited maternal chromosome contains a recessive mutation, the proband will be homozygous for the recessive mutation thus having simultaneously an autosomal-recessive disease ("unmasking of a recessive allele") and an imprinting disorder. The two phenotypes may clinically be difficult to disentangle. The imprinting phenotype by itself is the same whether due to heterodisomy or isodisomy. Physiological recombination between homologue chromosomes in the germline prior to meiotic segregration errors means that there may be a combination of heterodisomy and isodisomy for different regions of the involved chromosome.