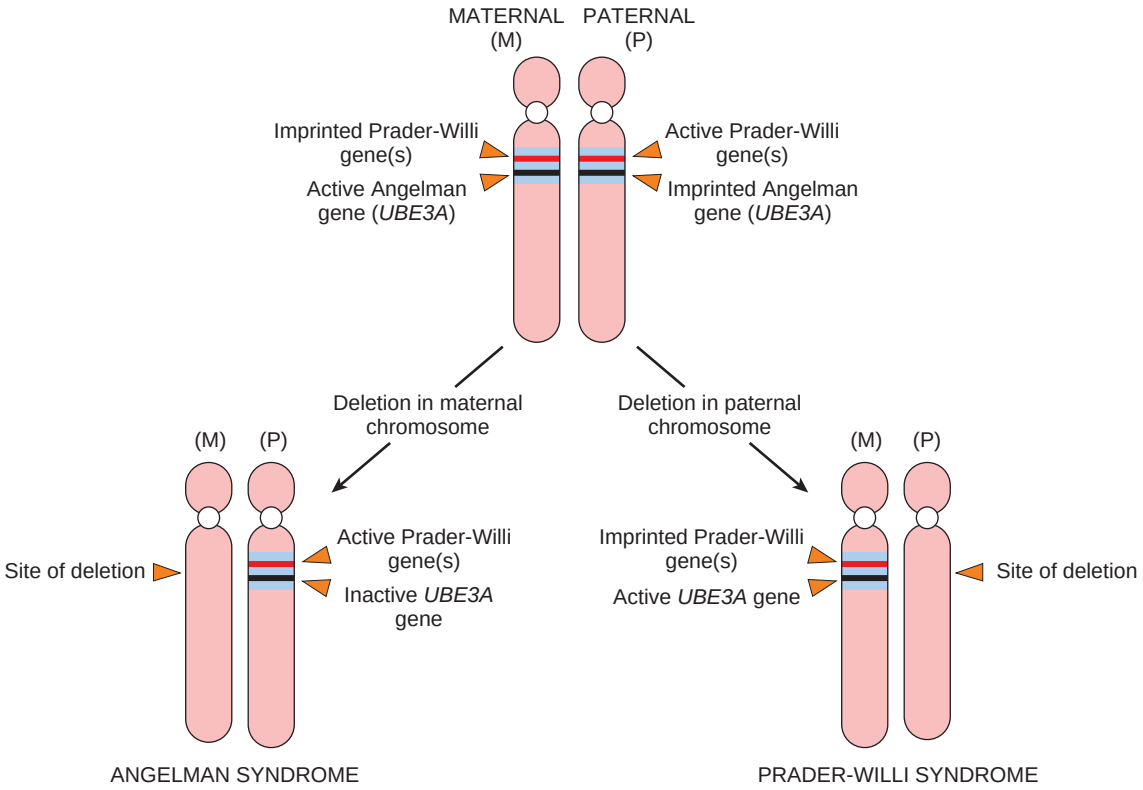

Figure 5-28 Diagrammatic representation of Prader-Willi and Angelman syndromes.

Prader-Willi syndrome. Conversely, a distinct gene that also maps to the same region of chromosome 15 is imprinted on the paternal chromosome. Only the maternally derived allele of this gene is normally active. Deletion of this maternal gene on chromosome 15 gives rise to the Angelman syndrome. Deletions account for about 70% cases.

- *Uniparental disomy.* Molecular studies of cytogenetically normal patients with the Prader-Willi syndrome (i.e., those without the deletion) have revealed that they have two maternal copies of chromosome 15. Inheritance of both chromosomes of a pair from one parent is called *uniparental disomy.* The net effect is the same (i.e., the person does not have a functional set of genes from the [nonimprinted] paternal chromosomes 15). Angelman syndrome, as might be expected, can also result from uniparental disomy of paternal chromosome 15. This is the second most common mechanism responsible for 20% to 25% cases.
- *Defective imprinting.* In a small minority of patients (1% to 4%), there is an imprinting defect. In some patients with Prader-Willi syndrome, the paternal chromosome carries the maternal imprint and conversely in Angelman syndrome the maternal chromosome carries the paternal imprint (hence there are no functional alleles).

The genetic basis of these two imprinting disorders is now being unraveled.

- In the Angelman syndrome, the affected gene is a ubiquitin ligase that is involved in catalyzing the transfer of activated ubiquitin to target protein substrates. The gene, called *UBE3A,* maps within the 15q12 region, is imprinted on the paternal chromosome, and is expressed from the maternal allele primarily in specific regions of the brain. The imprinting is tissue-specific in that *UBE3A* is expressed from both alleles in most tissues.
- In contrast to Angelman syndrome, no single gene has been implicated in Prader-Willi syndrome. Instead, a series of genes located in the 15q11.2-q13 interval (which are imprinted on the maternal chromosome and expressed from the paternal chromosome) are believed to be involved. These include the SNORP family of genes that encode small nucleolar RNAs which are involved in modifications of ribosomal RNAs. Loss of SNORP functions is believed to contribute to Prader-Willi syndrome.

Molecular diagnosis of these syndromes is based on assessment of methylation status of marker genes and FISH. The importance of imprinting is not restricted to rare chromosomal disorders. Parent-of-origin effects have been identified in a variety of inherited diseases, such as Huntington disease and myotonic dystrophy and in tumorigenesis.

KEY CONCEPTS

Genomic Imprinting

- Imprinting involves transcriptional silencing of the paternal or maternal copies of certain genes during gametogenesis. For such genes, only one functional copy exists in the individual. Loss of the functional (not imprinted) allele by deletion gives rise to diseases.