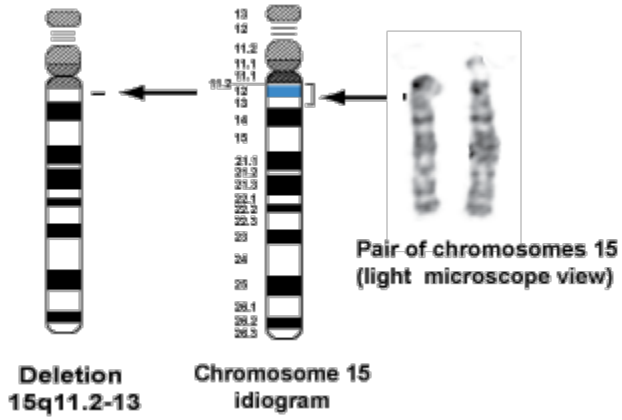
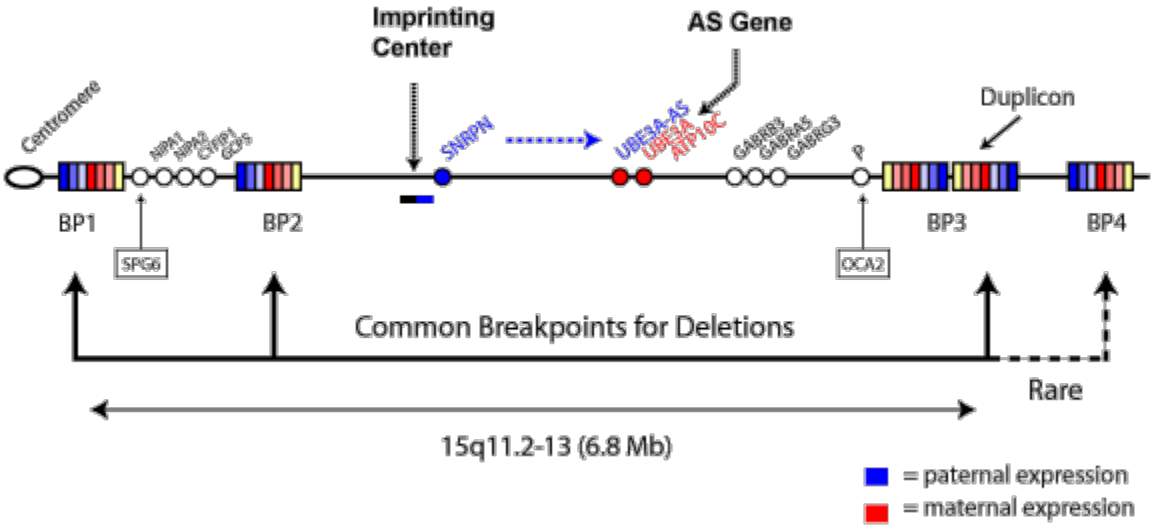
Illustrations Depicting chromosome 15 and the UBE3A Gene

The Angelman syndrome gene (UBE3A)is located on chromosome number 15 as illustrated below. An real image of this chromosome as viewed by light microscopy is seen on the right along with a diagram of this chromosome. The chromosome is numbered and region 15q11.2 through q13 is where the Angelman gene is located. The diagram illustrates one of this most common ways that the gene can be disrupted: by a large chromosome deletion that removes it from the one of the chromosomes. In Angelman syndrome, it is the maternally derived chromosome 15 that sustains this deletion event. Other mechanisms (see below) can also disrupt the Angelman gene.



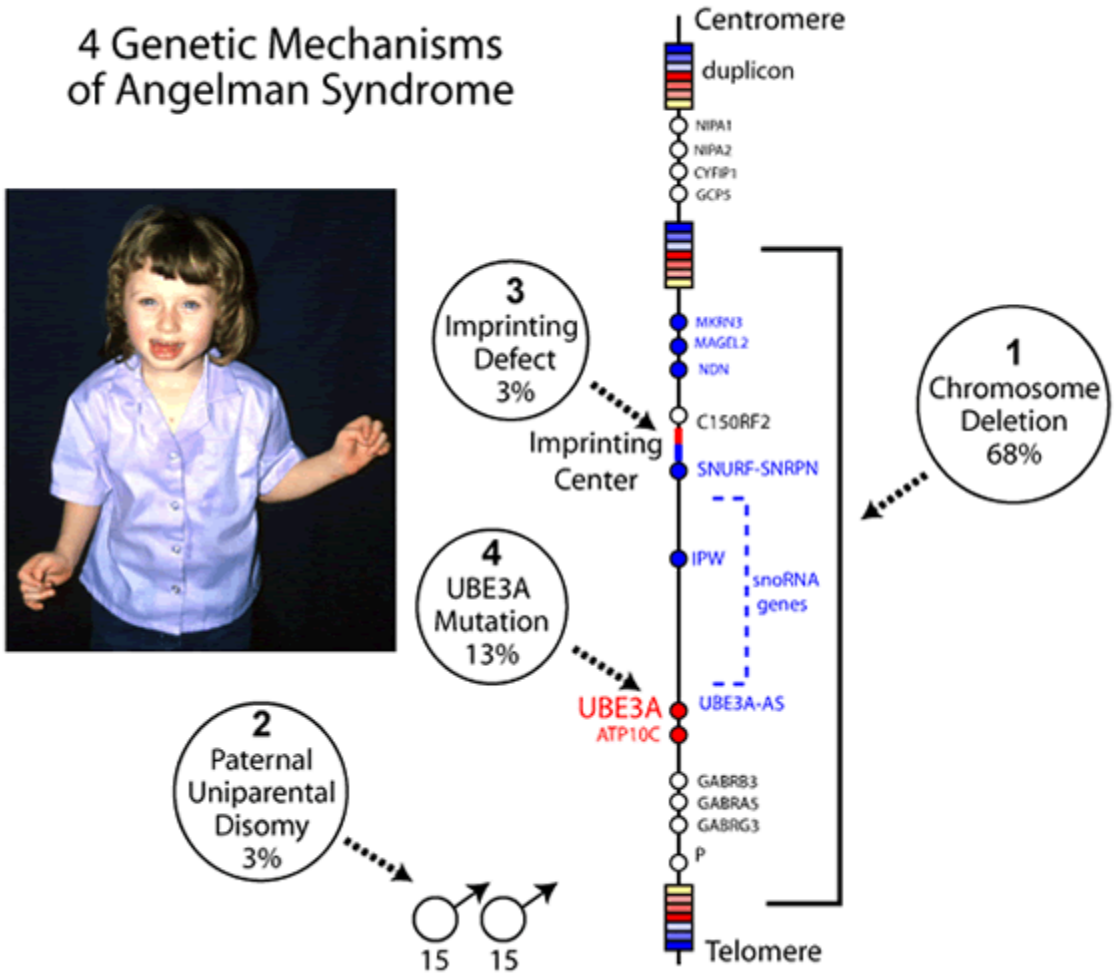
A more precise location of the UBE3A gene is illustrated in the next diagram and with other genetics aspects of this complex area.



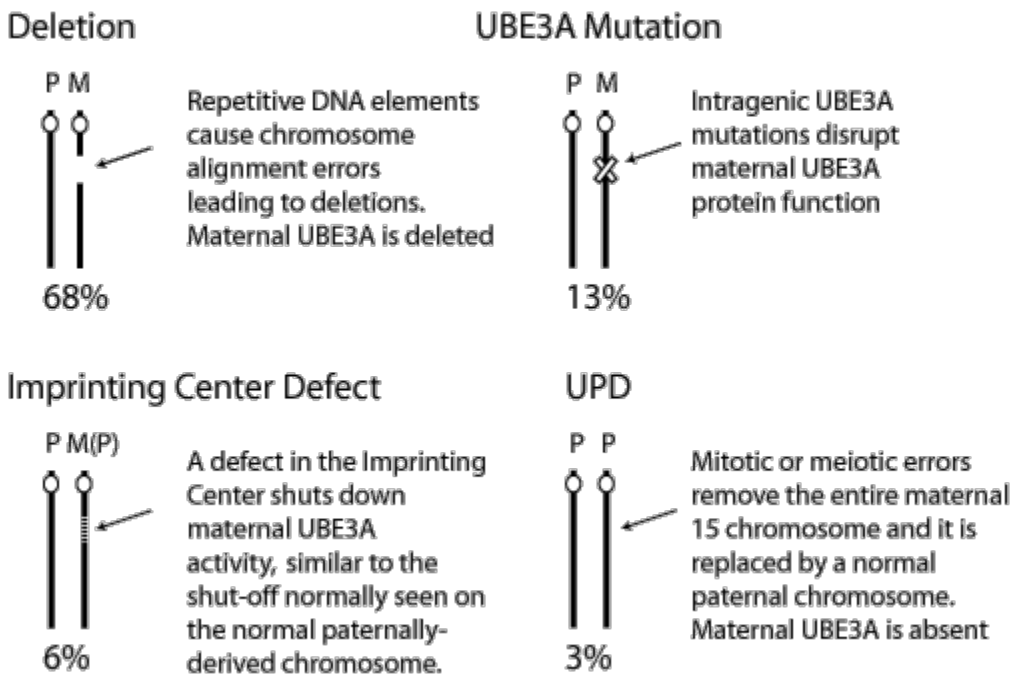
The blue color represents paternal and red represents maternally expressed genes, and the white circles represent bi-allelically expressed (e.g., on both parental chromosomes) ones. The Imprinting Center, an important region that controls transcription of UBE3A, is located at a distant site from the gene (about 1-2 millions base pairs of DNA away). Repetitive, duplicated elements (duplicons) are displayed as multicolored rectangles. These are fragile areas of the chromosome (about 100-300,000

base pairs in size)and are prone to breaks and rearrangements, and the common breakpoints associated with AS deletions are labeled BP1-BP4. About 90% of chromosome deletions in AS are due to BP1-BP3 or BP2-BP3 deletions. Non-imprinted disorders that map within the AS deletion region include oculocutaneous albinisim type 2 (OCA2) and spastic paraparesis type 6 (SPG6) but these problems are ususally not present in individuals with AS.

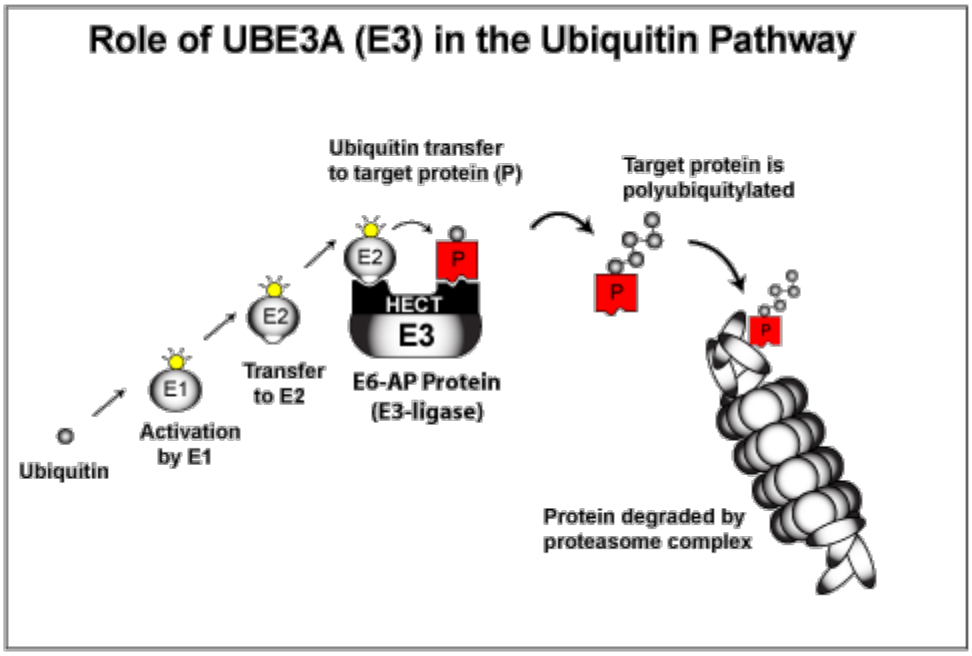
This next illustration depicts the four genetic mechanisms that are known to disrupt UBE3A function. The approximate percentage of each mechanism is indicated, and this number slightly varies depending on which group of AS individuals are studied. The chromosome deletion (number 1) mechanism usually involves chromosome breaking in a region of repetitive elements (labeled as duplicons). The brackets indicate the extent of one of the more common large deletions.



The diagram below recapitulates the information illustrated in the above diagram and provides more discussion about how UBE3A is disrupted in each mechanism. Maternal (M) and paternal (P) chromosomes are labeled.



This final diagram shows how the UBE3A protein (labeled E3)is part of the ubiquitin protein degradation pathway. The pathway is extremely important in all cells including those of the CNS. Ubiquitin is a small protein that can be tagged onto other proteins in order to initiate degradation of the protein through the proteasome complex (lower part of diagram). Ubiquitin must first be activated then transferred to UBE3A where it is then chemicallly attached onto the target protein (red). Important in UBE3A's protein structure is the HECT domain that enables ubiquitn and the target protein to come into close proximity and allow for the attachment of the ubiquitin molecule. Some protein targets for UBE3A are known but it is currently unknown which protein targets are linked to the precise brain dysfunction in AS. UBE3A is closely associated with neuronal synaptic function.


Role of UBE3A (E3) in the Ubiquitin Pathway
Ubiquitin transfer to target protein (P)
Target protein is polyubiquitylated
E2
P
HECT
E3
E2
E1
Transfer to E2
E6-AP Protein (E3-ligase)
Activation by E1
Ubiquitin
P
P
Protein degraded by proteasome complex