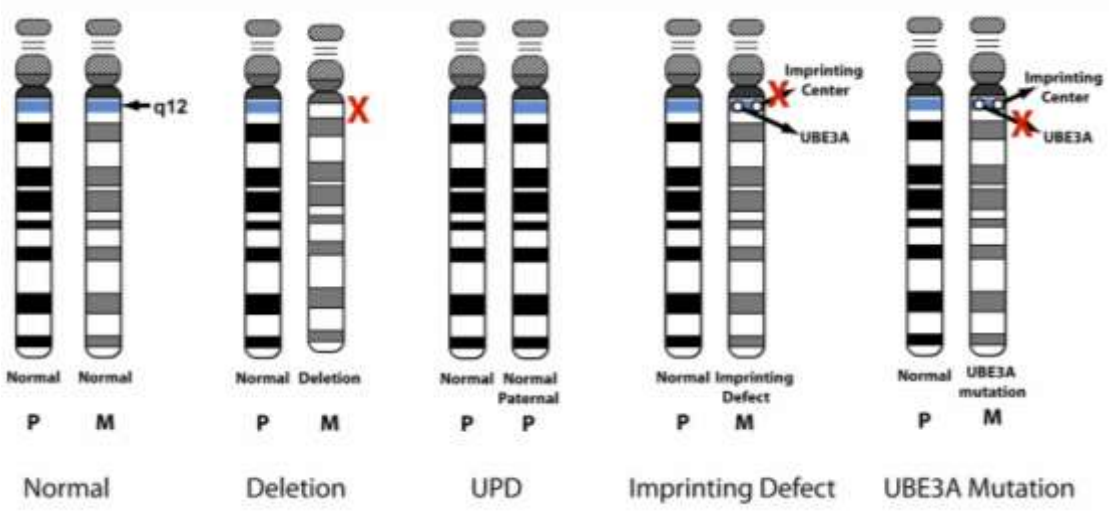
Facts About AS

Genetic Mechanisms that Cause AS

In 1997, mutations in the gene, UBE3A located on chromosome 15, were identified as the cause of AS. All mechanisms known to cause AS either disrupt, inactivate or lead to absence of this gene on the maternally derived chromosome 15. There are several genetic "classes" or mechanisms that can disrupt UBE3A and thus cause AS. These mechanisms are depicted in this illustration.



A chromosome 15 pair is illustrated for each mechanism and a normal chromosome pair is depicted on the left with a normal q12 chromosome region. P = paternally-derived chromosome and M = maternal derivation. AS can be caused by a large deletion of the maternal chromosome 15q12 region (where the active UBE3A gene resides). AS can also be caused by inheritance from the father of 2 paternal chromosomes; a phenomenon termed paternal uniparental disomy (UPD). Another cause, referred to as an imprinting defect (ID), occurs when the chromosome 15 inherited from the mother has the paternal pattern of gene functioning so that UBE3A expression is actually turned off. The IC is located some distance from the UBE3A gene but it is still able to regulate UBE3A by a complex mechanism that is the subject of intense research. Finally, AS can be caused by a mutation in the UBE3A gene on the maternally derived chromosome 15.

Mechanism	Frequency (%)
Deletion	~70
UPD	2 - 3
Imprinting defect	3 - 5
UBE3A mutation or deletion	5 - 10
Other chromosome Rearrangements	1 - 2
Unknown	10 - 15

Source: 7th edition Facts about Angelman Syndrome by Charles A. Williams, M.D., Sarika U. Peters, Ph.D., Stephen N. Calculator, Ph.D. in 2009

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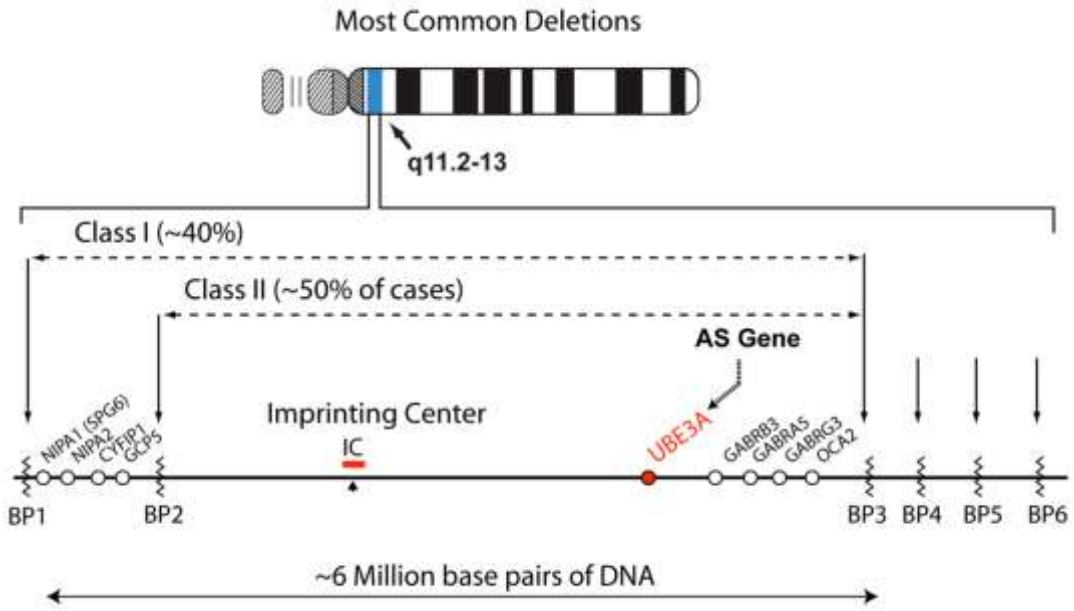
The table indicates the prevalence of each genetic mechanism and also notes that about 10-15% of individuals with the clinical features of AS actually will have normal genetic studies. At this time, it is unclear if these individuals have the correct diagnosis or if they have other yet-to-be-identified genetic defects that cause AS. The most common genetic mechanism causing AS is the large chromosome deletion. The diagram explains more information about this. The typical deletion region is indeed large and spans about 6 million molecules (base pairs) of DNA. Most deletions extend from break point one (BP1) to either BP2 or BP3 and are termed class I or class II deletions. About 10% of the deletions extend further beyond BP3, for example, at site BP4. New methods of clinical testing such as array----based comparative genomic hybridization can distinguish between class I and class II deletions. However, the FISH test will not be able to determine this.

All the large deletions remove UBE3A from the maternally derived chromosome. The deletions also remove additional genes as pictured (e.g., GABA receptor genes) but UBE3A deletion causes essentially all the problems associated with AS.



UBE3A and the Ubiquitin Pathway

The UBE3A gene makes the UBE3A protein (also called E6-AP) and this protein is an important component of the ubiquitin-proteasome pathway (pictured below). This pathway is extremely important to all cells, especially brain neurons. The pathway enables a small protein molecule, ubiquitin, to be attached to certain proteins, thereby causing them to be degraded. Ubiquitin is a small protein (76 amino acids in length) that can be tagged onto

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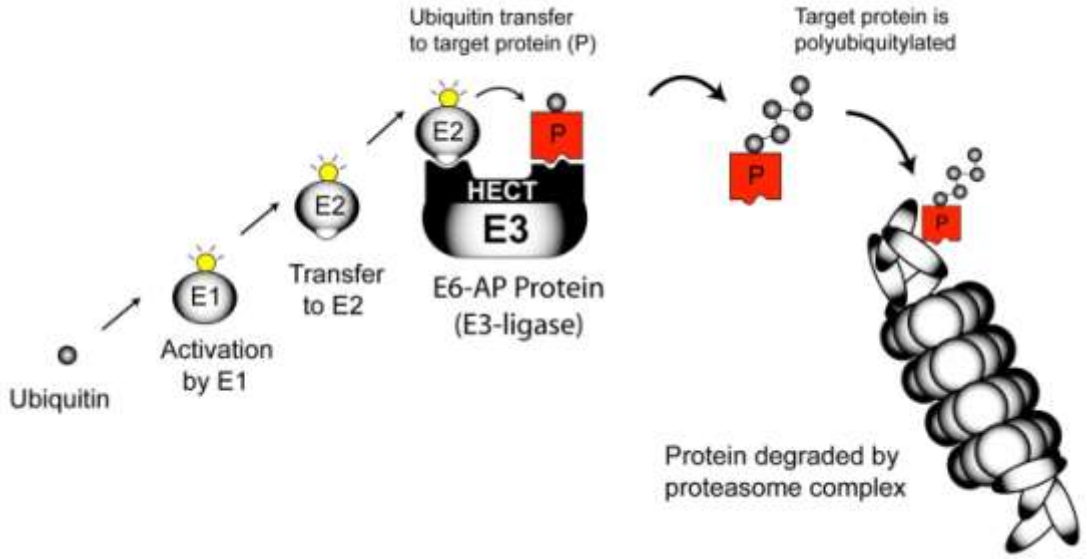
other proteins in order to initiate their destruction. As pictured, E1 and E2 proteins activate (yellow) and transfer ubiquitin to E3. There are many different types of E3 proteins and UBE3A is one of them. UBE3A is able to chemically attach ubiquitin onto target proteins (red). Important in UBE3A''s protein structure is the HECT domain, a molecular pocket that enables ubiquitin and the target protein to come into close proximity, allowing for attachment of the activated 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.



UBE3A and Imprinting

UBE3A is known to be "imprinted" in brain neurons. This means that UBE3A gene from the paternally-derived chromosome 15 is almost completely inactive in many brain regions while the maternally-derived chromosome 15 gene is normally active. The brain neurons are normal even though they only have one active copy of the UBE3A gene. That chromosome deletions in AS occur only on the maternally-derived chromosome 15 indicate that UBE3A is active only on this chromosome, hence the deletion removes the only active copy of the gene. Disruptions of genes that are active on the paternally----derived chromosome 15 cause another developmental disorder, the Prader----Willi syndrome (PWS). PWS also involves imprinted gene(s) that are located close to but distinct from UBE3A. AS and PWS are quite unique because almost all other genetic disorders do not exhibit this type of imprinting effect.

The term "imprinting inheritance" can be difficult to understand. In order for an imprinted gene to be normally inherited and active on the correct parentally-derived chromosome

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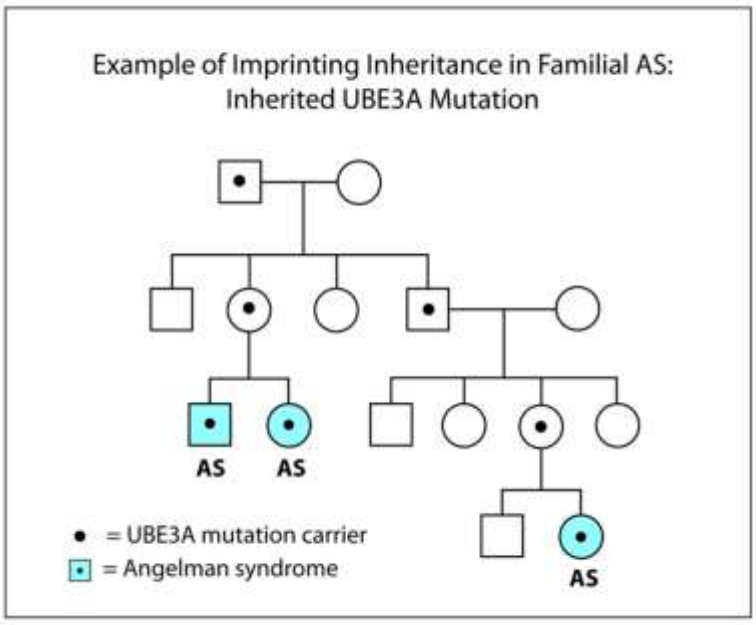
(e.g., as occurs in normal individuals), there must be a mechanism for reversing the expression of genes at certain times of egg and 10 embryo development. For example, when a normal father produces sperm, regardless of whether the sperm end up having the maternally or paternally derived 15, all must now be “stamped” or “imprinted” so that their UBE3A genes will be turned off. The opposite occurs in the normal mother, whose eggs must have all their UBE3A genes turned on. Imprinted genes are thus capable of having their activity instructions erased and re‑stamped.

The pedigree illustrates how imprinting inheritance can cause recurrence of AS in somewhat distantly related relatives. When a UBE3A mutation is inherited in a family, individuals who inherit the mutation may get AS but others can be normal! Inheritance of a UBE3A mutation from the father (top left of pedigree) has no detectable effect on his immediate children since he passed on an inactive UBE3A gene. It does not matter if this gene has a mutation since each of his immediate children also inherited a normal chromosome 15 (e.g., normal UBE3A gene) from their mother. However, should his carrier daughter transmit the UBE3A mutation to any child, it will have AS since that child would also get an inactivated UBE3A from her father so now there is essentially no UBE3A activity present. The same type of inheritance pattern can also be seen in some families with Imprinting Center defects. Refer to the Genetic Counseling page for more information.



Fortunately, most individuals with AS will have acquired their condition through a non‑inherited, spontaneous mutation. This is the situation in almost all cases of the large common deletion and thus imprinting inheritance in not observed.

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