Clinical summary of breakthrough in Angelman syndrome research
by Professor Bernard Dan. 7th February 2012

Genetic Mechanisms which can cause Angelman Syndrome

Angelman syndrome is caused by the lack of expression of a small portion of DNA, i.e. the UBE3A gene, in brain cells. This gene is located on chromosome 15. We normally have two intact copies of it in each of our cells, as we inherit two full sets of chromosomes, one from our mother and one from our father.
However, the UBE3A gene is expressed (almost) exclusively from the chromosome 15 we received from our mother and the copy that is present on the chromosome 15 we got from our father is (virtually) not expressed at all.

- **Deletion** - Many people with Angelman syndrome have this condition because here the region containing the UBE3A gene on the chromosome 15 they inherited from their mother is missing; this is referred to as a deletion or del 15q11-q13.
- **Uniparental disomy** - Another genetic accident which may cause Angelman syndrome results when both chromosomes come from the father and none from the mother: this is paternal (=from the father) uniparental (=from one parent) disomy (=both chromosomes).
- **Imprinting defect** – another abnormality is not being able to identify the chromosome 15 which is inherited from the mother;

this is known as an imprinting defect.

- **UBE3A mutation** - Finally, there may be an abnormality within the sequence of the UBE3A gene; this is a UBE3A mutation.

All these mechanisms give rise to Angelman syndrome, but there may be statistical differences in the severity of the condition according to the underlying genetic mechanism. Some features like intellectual disability, speech impairment and epilepsy tend to be somewhat less severe in individuals who have uniparental disomy or imprinting defect than in those who have a deletion or a UBE3A mutation.

This variability may point to the possibility of residual (if minimal) expression of the gene which is intact, i.e. the copy of UBE3A which doesn't carry the typical 'READ ME' signal that normally marks it as coming from the mother: patients with a deletion or a mutation have one intact (but virtually non-functional) copy of the UBE3A gene, and those with uniparental disomy or imprinting defect have two intact (but virtually non-functional) copies.

For a number of years, several teams have tried to find ways to promote the expression of the intact but non-functional copy of the UBE3A gene. There have been great improvements in the understanding of mechanisms that naturally promote expression of the gene on the chromosome 15 inherited from the mother: This 'READ ME' signal is related to DNA methylation. This has led to various treatment attempts which have all failed to show clearly positive results up until now.

Recent Research breakthrough

Very recently, a team led by **Benjamin Philpot and Mark Zylka** in North Carolina used a different approach. They tested more than 2,000 known drugs on a mouse model of Angelman syndrome to see if some of them could activate the non-functional copy of UBE3A. And indeed, among these drugs, a small family of anti-cancer drugs, which are known to affect a specific process related to DNA, has been shown to activate the normally silenced paternal copy of the gene. The most potent drug in this group was topotecan, alias Topo.

When used to treat cancer, it is hoped that this drug alters the DNA in such a way that it can't undergo replication, eventually leading to the death of cancer cells. The property on which Topo treatment is based in that context is thus clearly cytotoxicity, or cell poisoning. The fact that this drug can activate UBE3A may have great implications for developing new strategies of chemical management of Angelman syndrome.

A lot of questions need to be answered before we know if and how these early results in animal experiments can impact individuals with Angelman syndrome; for example: Would the effect of such drugs on UBE3A expression be stable over time? What would be the effect on the manifestations of the syndrome in animal models? What doses would be useful and how should they be given? Which side-effects might there be? When should they be administered? And then how safe, useful and feasible would it be to give them in humans? Only then would we start exploring whether (and to what extent) drugs such as Topo might alleviate symptoms in individuals with Angelman syndrome. These are all new questions and the teams, technology, methodology and enthusiasm are already working on them, while keeping in mind that medical science must follow a sound, stepwise road and it is obvious that human trials cannot start before we have firm answers to the preliminary questions.

Editors note: Professor Dan has advised that one could expect a change in all genetic forms including deletion. *We thank Professor Dan for the summary in easy to read and understand format.*