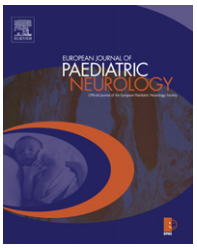
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2012) 1–2

Official Journal of the European Paediatric Neurology Society



Editorial

Maternal *UBE3A* in Angelman syndrome: "*The rest is silence*"?

Many a parent of a child with a neurogenetic condition often wonders whether *'tis nobler in the mind to suffer* the slings *and arrows of outrageous* fortune or to contemplate hope for effective treatment. With regard to Angelman syndrome, recent results from molecular biology have opened unsuspected avenues for circumventing the molecular defect. Hopefully, this will eventually lead to scientifically and ethically justifiable clinical trials.

Angelman syndrome is a neurodevelopmental disorder characterized by severe intellectual disability, absent speech, exuberant, joyful behaviour, motor impairment and epilepsy. It is caused by the lack of expression of the *UBE3A* gene, which is subject to genomic imprinting with virtually exclusive transcription of the maternal allele in brain neurons, while the paternal copy of this gene is normal. Various genetic mechanisms can result in Angelman syndrome: deletion or mutation of the *UBE3A* gene, which is located on chromosome 15, paternal uniparental disomy, i.e. inheritance of two paternal copies of chromosome 15 and no copy from the mother, and imprinting defect resulting in lack of the typical maternal pattern of DNA methylation required for *UBE3A* expression (Fig. 1). Though all these mechanisms give rise to Angelman syndrome, there are 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 less severe in individuals who have uniparental disomy or imprinting defect than in those who have a *UBE3A* deletion or mutation. This variability may point to the possibility of residual (if minimal) expression of the allele which is intact but is not activated by 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.

In this issue of the *Journal*, Daily et al. from Edwin Weeber's lab provide new evidence in support of silencing of the intact paternal *UBE3A* gene in the brain regions they studied (prefrontal cortex, motor cortex, hippocampus, striatum and cerebellum) in a mouse model with inactivation of the maternal *UBE3A* gene. They found similar results in the brain (prefrontal cortex, motor cortex, striatum and cerebellum) of human patients, whether child or adult, and therefore suggested that silencing is not age-dependent. Considering how (surprisingly) little pathological material has been available from patients with Angelman syndrome since the original clinical description in 1965, this effort is very remarkable indeed. Another important finding is very slight production of Ube3a protein in mice with knockout maternal allele but intact paternal allele, contrasting with the absence of detectable Ube3a protein in mice with deletion of both the maternal and paternal alleles. This molecular challenge to Hamlet's famous last line (*The rest is silence*) suggests that paternal expression of the intact *Ube3a* is not completely silenced.

For a number of years, several teams have tried to find ways to promote the expression of this intact but non-functional copy of the *UBE3A* gene. There have been great improvements in the understanding of mechanisms that promote gene expression, leading to various treatment attempts which have all failed to show clearly positive results up until now. Very recently, however, a team led by Benjamin Philpot and Mark Zylka used a different approach (published in *Nature*). They tested more than 2000 known drugs on mice with paternal allele expression reporter 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 known to affect a specific process related to DNA topology, has been shown to activate the normally silenced paternal copy of the gene. The most potent drug in this group was topotecan. This may have great implications for developing new strategies of pharmacological management of Angelman syndrome.

Now, 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. 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? Which doses would be effective (if at all) 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 to humans? We need firm answers to these preliminary questions before we can start exploring whether (and to what extent) such drugs might alleviate symptoms in individuals with Angelman syndrome, with due respect for the ethics of medical science, which must follow a sound, stepwise road. Although some might be tempted to take short-cuts, our commitment towards the patient's best interest compels us to

Please cite this article in press as: Dan B, Maternal *UBE3A* in Angelman syndrome: "*The rest is silence*"?, (2012), doi:10.1016/j.ejpn.2012.03.010

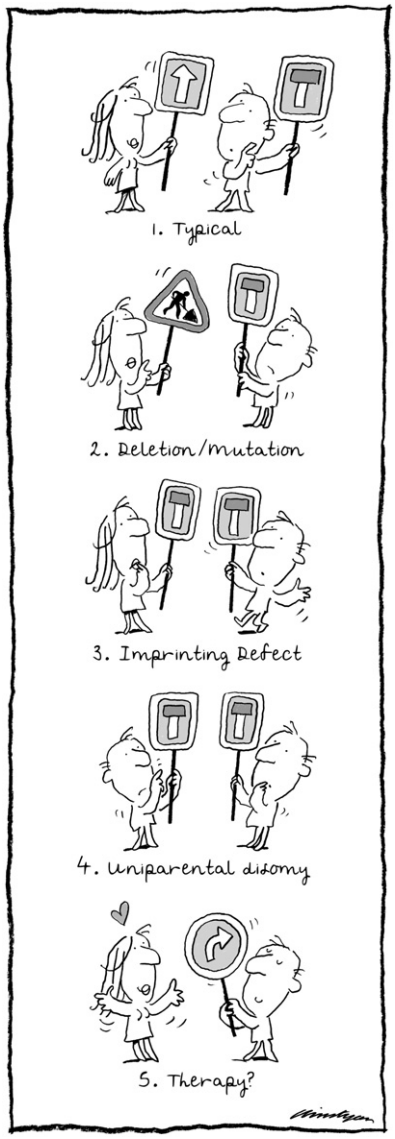


Fig. 1 – Cartoon illustrating the molecular classes that underlie Angelman syndrome. (© Christyan Fox 2012). Chromosome 15 inherited from the mother is represented by a woman, the one inherited from the father by a man. One Way sign indicates expression of UBE3A allele. Dead End sign indicates allele inactivation. Roadworks sign indicates gene deletion or mutation. Right turn sign indicates activation of silent allele. (1) In the typical situation, the chromosome 15 inherited from the mother carries an epigenetic signal enabling UBE3A gene expression whereas the paternal allele is inactive. (2) In case of deletion or mutation of the maternal copy, this cannot be expressed while the paternal allele is inactive as in the typical situation. (3) In case of imprinting defect, both alleles are inactive. (5) Promoting the expression of the paternal allele might be a promising therapeutic avenue.

critically appraise the scientific and ethical content of any clinical trials we might propose.

B. Dan*
Hôpital Universitaire des Enfants Reine Fabiola, Université libre de Bruxelles (ULB), Av. J.J. Crocq, 15, 1020 Bruxelles, Belgium

*Tel.: +32 2 477 3174; fax: +32 2 477 2350.
E-mail address: bernard.dan@ulb.ac.be

29 March 2012

1090-3798/$ – see front matter

doi:10.1016/j.ejpn.2012.03.010