

RETT SYNDROME: HOPE OF CURE DRIVES FUNDRAISING AND UNDERPINS NEW TRIALS



Rett syndrome affects one in 10,000 girls.

Rett syndrome is a severe autistic-spectrum disorder with delayed onset that affects 1 in 10,000 girls. Some 16,000 individuals have Rett syndrome in the US, and an estimated 2,400 in the UK. It is a regressive disease that causes loss of speech and hand movement, coupled with autistic behaviour, an undersized brain (microencephaly), and growth retardation. Affected girls develop normally for around 18 months then regress, losing abilities they once had and requiring increasing levels of care as they age.

Rett syndrome was previously believed to be a developmental or neurodegenerative disease because of its early appearance and the gradual deterioration of those affected. A cure or therapy was thought to be most unlikely.

In most cases the disease is due to mutations in the gene coding for MeCP2, which negatively regulates gene expression. In 2001, researchers led by Professor Sir Adrian Bird developed a mouse model for Rett syndrome by introducing a mutation into the mouse MeCP2 gene. Heterozygous female mice carrying this mutation had behavioural characteristics similar to those of girls with Rett syndrome, including poor motor coordination, behavioural deficits and breathing arrhythmia. This mouse model is currently used in hundreds of labs across the world.

SYMPTOMS SHOWN TO BE REVERSIBLE IN MICE

In 2007, Dr Jacky Guy and other scientists in Professor Sir Adrian Bird's group introduced a modified MeCP2 gene into Rett model mice that allowed controlled expression of normal MeCP2 protein. Mutant female mice carrying this modified gene exhibited the characteristics of Rett syndrome until normal MeCP2 expression was activated, after which they rapidly regained normal behaviour.

This striking result indicated that the developmental or degenerative changes seen in Rett patients are reversible, and overturned previous understanding of the disease.



A scientist in Professor Sir Adrian Bird's research group at work.

CHARITY FORMATION AND INCREASED AWARENESS



The RSRT public information campaign in Times Square, New York.

RESEARCH FINDINGS UNDERPIN CLINICAL TRIALS

Multiple clinical trials are under way in both Europe and the US to test a variety of drugs in the hope of achieving symptom improvement. For example, a trial of Insulin-like Growth Factor-1 (IGF-1) is in progress. IGF-1 is indirectly regulated by MeCP2 and has been shown to ameliorate several features of Rett-like disease in mice. The Edinburgh research underpins the rationale of the trial.

Concurrently, research targeted at the underlying cause of Rett Syndrome, for example gene therapy with MeCP2, is being pursued. It is expected that attacking the root of the problem in this debilitating disease may profoundly impact symptoms.

As a direct result of the 2007 results, a small group of US parents of children with Rett syndrome, led by Monica Coenraads, formed the Rett Syndrome Research Trust (RSRT), a highly efficient non-profit charity devoted to finding a cure for the condition. The RSRT was established purely because these parents believed there was now a real prospect of a cure for Rett syndrome. The RSRT was launched in September 2008 and has so far raised more than \$25 million in donations. A remarkable 96 per cent of funding raised is committed to research seeking to cure Rett Syndrome.

The RSRT launched a powerful campaign in November 2011 to boost awareness of Rett syndrome. It is estimated that 1.5 million people per day for three months viewed the campaign's public service announcement in Times Square, New York. In addition, the documentary film *RETT: there is hope*, was honoured in 2012 with a Rising Star Award (Canada International Film Festival) and won the USA Awareness Film Festival. Filmmaker Jason Rem was inspired to make the documentary, which features the Edinburgh research, after attending an RSRT charity event.

The UK charity ReverseRett was formed in July 2010 by families across the UK who wanted to contribute to RSRT's efforts to accelerate treatments for Rett Syndrome. The UK charity has raised £2 million since 2010.

Rachael Bloom, Executive Director of ReverseRett, says: 'This is a global issue not a national issue. In every country, children with Rett syndrome are suffering tremendously. This relentless disorder impacts children and the families who love them across all cultures and races. We believe Rett syndrome is reversible. Everything we do stems from this belief.'



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