



About us

The Van Wright Foundation is a non-profit charity established in March 2012, by Collene and Phil Wright, the parents of Van Wright, who at 20 months of age was diagnosed with *MECP2* duplication syndrome. There was so little information about this disorder that even the medical team who made the diagnosis had not heard of it. From that point Collene and Phil vowed to raise awareness so that one day a cure may be found.

Our focus is to unite affected families, to increase awareness and most importantly to fund research projects designed to provide a better understanding of and treatments for *MECP2* duplication syndrome.

Globally, we have connected with those in the medical community who are interested in *MECP2* duplication syndrome, including Dr Ellaway, Professor Christodoulou, Dr Leonard and Dr Amor in Australia, Dr Ramocki, Dr Foust, Dr Zoghbi, Professor Kipnis in the USA, Professor Bird in the UK, Dr Van Esch in Belgium, Professor Michael Bauer in Germany.

We have established a working relationship with the Rett Syndrome Research Trust in the USA www.rsrt.org, an organization that is the main beneficiary of our fundraising efforts. One hundred percent of funds raised to study *MECP2* duplication syndrome are directed to research. We have also connected with other affected families around the world who are committed to finding a cure for *MECP2* duplication syndrome.

MECP2 duplication syndrome

First attributed directly to increased levels of the MeCP2 protein in 2005, *MECP2* duplication syndrome is a neurodevelopmental disorder mainly affecting males. Common features of *MECP2* duplication syndrome include infantile hypotonia (low muscle tone), global developmental delay, intellectual impairment, autistic traits, poor or absent speech development, seizures (epilepsy) and recurrent respiratory infections. *MECP2* duplication syndrome is a clinically recognizable syndrome.

MECP2 duplication syndrome is caused by a genetic abnormality, whereby there is a duplication (double dose) of a gene called *MECP2* (Methyl CpG binding protein 2). The *MECP2* gene is located on the X-chromosome in the Xq28 region. Chromosomes are structures, which contain our DNA and are found in almost every cell of the body. Every chromosome contains hundreds to thousands of genes, which may be thought of as individual instruction booklets that tell the body how to develop, grow and function.

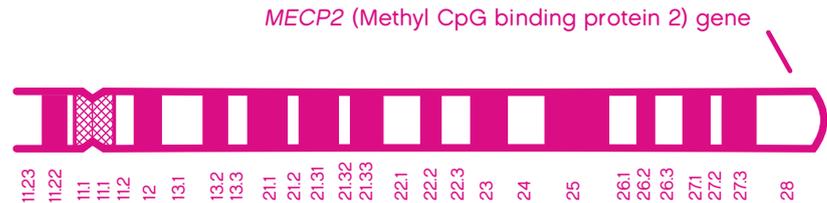
Mutations in the *MECP2* gene are most commonly associated with Rett

syndrome in females. The protein made by the *MECP2* gene, called MeCP2, plays a pivotal role in regulating brain function. Too little or too much of the MeCP2 protein results in abnormal brain function and physical impairment.

The genetic material involved in *MECP2* duplication syndrome is so miniscule that it may often be impossible to detect on a routine chromosome test. More cases are now being diagnosed with the widespread use of a test called Array CGH (Comparative Genomic Hybridization), which allows for sub-microscopic detection of missing or additional copies of genetic material. Currently, the prevalence (number of cases) in Australia and around the world is unknown. However, it is possible that *MECP2* duplication syndrome may account for 1-2% of unexplained intellectual disability and/or autism.

Duplication of the *MECP2* gene occurs in males and females. In boys the phenotype (symptoms) of *MECP2* duplication syndrome are severe, but in girls it is highly variable ranging from symptoms similar to those observed in affected boys, to mild

developmental problems, to psychiatric problems such as depression or anxiety to females who are completely asymptomatic. The variability in the clinical picture for girls is due in part to X chromosome inactivation (i.e. what percentage of the cells express the X chromosome with duplication vs. the X chromosome with a normal dosage of the *MECP2* gene). Girls have two X chromosomes, whereas boys only have one X chromosome, and therefore boys who carry a duplication always develop the more severe syndrome. Sometimes, the duplicated material from the X chromosome has been moved (translocated) to another chromosome. In these instances, X chromosome inactivation of the duplicated material does not occur and females develop the more severe syndrome similar to affected boys.



The cause of *MECP2* duplication syndrome is a double dose or duplication of the *MECP2* (Methyl CpG binding protein 2) gene.

What's next?

Why did this happen?

MECP2 duplication is an X-linked disorder. Most children inherit the duplication from their mothers. However in some cases the duplication occurs when both parents have normal chromosomes. The term that geneticists use for this is de novo (dn), which means 'new'.

MECP2 duplication syndrome is a genetic condition and there is nothing that either parent did or did not do to cause the disorder. Although there is limited information currently available and the number of cases is unknown, diagnosis is increasing.

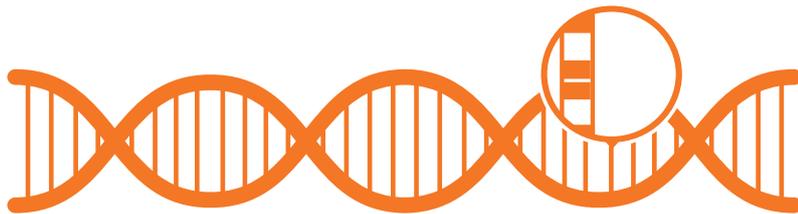
Can it happen again?

If the mother is a carrier, then the risk of passing on the duplication to a child is 50% for every pregnancy. A son who inherits the duplication will be affected, but a daughter who inherits the duplication could be asymptomatic or could be more mildly affected as discussed above. If the duplication occurred as a new event (de novo), then there is less than a 5% chance for recurrence.

It is important for families who receive this diagnosis to obtain genetic counseling to identify other at risk relatives and to discuss recurrence risk as well as options for screening for *MECP2* duplication syndrome in subsequent pregnancies. Options for screening include polar body biopsy for egg selection or preimplantation genetic diagnosis of embryos using in vitro fertilization techniques and prenatal diagnosis for pregnancies that have already been conceived.

What is the outlook?

Because *MECP2* duplication syndrome was only described in recent years, and because the technology that allows for efficient diagnosis has only recently become available and affordable for widespread use there is limited information currently available to provide a clear outlook. The most recent literature (Ramocki 2010) reports that 38% of affected boys/men have died before the age of 25 years. With increasing diagnosis and interest in *MECP2* duplication syndrome from the scientific community, greater understanding of this disorder will unfold.



Advances in genetic testing and more widespread use of Array CGH (Comparative Genomic Hybridization) has lead to increased diagnosis of *MECP2* duplication syndrome.

Medical professionals and care

The relationship between *MECP2* duplication syndrome and Rett Syndrome (same gene), means that paediatricians specialising in Rett syndrome are well placed to oversee the care of those with *MECP2* duplication syndrome. Many major children's hospitals around the world run Rett Syndrome Clinics and this is a relatively easy way to find a relevant specialist.

Medical management requires a multidisciplinary approach and other medical sub-specialists are frequently necessary to optimize health and quality of life for affected individuals. This care team may include: a Paediatrician, Gastroenterologist, Neurologist, Cardiologist, Respiratory and Sleep Physician, Immunologist, Ear Nose and Throat Specialist, Clinical Geneticist, Genetic Counsellor and Palliative care specialist. Neuropsychological evaluation and support can be very helpful to optimize and support the educational environment. Year-

round physical, occupational, and speech/communication therapies are essential to promote skills and to prevent regression.

We can change this.

The exciting news is that there are many people around the world interested in finding a cure for *MECP2* duplication syndrome. Already, ties with the leading scientists specializing in the *MECP2* gene have been forged. Thanks to the fundraising efforts of affected families worldwide, research has commenced into finding a cure for *MECP2* duplication syndrome.

If every family who is faced with this diagnosis unites to find a cure, then we will change this.

www.vanwrightfoundation.org

Scientists involved in longitudinal research of *MECP2* duplication syndrome:

Dr Melissa Ramocki,
Baylor College of Medicine, Texas, USA

Dr Hilde van Esch,
Ku Leuven, Belgium

Dr Carolyn Ellaway,
The Children's Hospital at
Westmead, Sydney, Australia

Dr Helen Leonard,
Telethon Institute for Child Health
Research, Perth, Western Australia

Scientists involved in research for a
cure of *MECP2* duplication syndrome:

Dr Huda Zoghbi,
Baylor College of Medicine, Texas, USA

Professor Adrian Bird,
University of Edinburgh, Edinburgh, UK

Dr Kevin Foust,
The Ohio State University, Ohio, USA

Professor Jonathan Kipnis,
University of Virginia, Virginia, USA

Links:

www.vanwrightfoundation.org

www.401project.com

www.mecp2duplication.com

www.mecp2wordpress.com

www.duplication-mecp2.fr

www.mecp2.nl

Clinical features of boys/men with *MECP2* duplication syndrome

Currently the clinical spectrum of *MECP2* duplication syndrome is unknown. However a number of common features have emerged.

Common features:

- Infantile hypotonia (low muscle-tone, floppy)
- Global developmental delay with or without developmental regression
- Intellectual impairment
- Recurrent respiratory infections (progressive lung problems are common)
- Epilepsy (in approximately 50% of cases)
- Autistic features include limited or absent speech development, repetitive behaviours such as stereotypic hand movements (hand wringing, flapping, mouthing etc.) and abnormal social development.
- Progressive lower limb spasticity (stiffness observed with movement).
- Other less common features:
 - Ataxia (wobbly movements)
 - Gastroesophageal reflux, that is often severe in infancy
 - Severe constipation (may present as intestinal pseudo-obstruction)
 - Feeding difficulties (e.g difficulty chewing and swallowing)
 - Failure to thrive
 - Increased tolerance to pain
 - Common facial features include a flat nasal bridge, slightly upturned nose, hypotonic face with tented upper lip, open mouth and excessive drooling. Some affected boys have deep-set eyes, a narrow nose, prominent chin, and large ears
 - Undescended testes
 - Mild heart problems, including structural abnormalities and abnormal heart rhythms
 - Obstructive sleep apnoea and other sleep disorders

