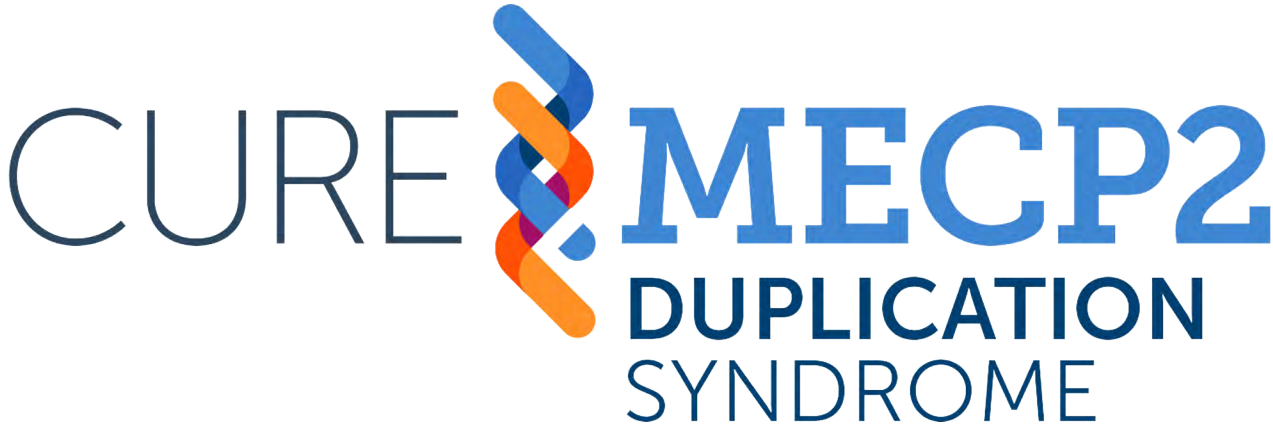

rev 1.2 04.03.2022

ABOUT US

The 401 Project started in January 2012 by Peter Anderson, USA and Collene Wright, Australia, parents to MECP2 duplication syndrome affected children. The 401 Project was a campaign launched to mobilize the global MECP2 duplication syndrome community of families to fund research projects into a cure for MECP2 duplication syndrome. The beneficiary of the 401 Project's efforts is Rett Syndrome Research Trust (RSRT,)USA. 100% of donations from the 401 Project are committed to research projects, deemed viable, by RSRT.

The Project's first funding project was Dr Zoghbi's research proposal aimed to test if MECP2 duplication syndrome was reversible . The results of this study were published in Nature journal in November 2015 and found that MECP2 duplication syndrome IS reversible . This was a significant and extremely positive research breakthrough.

The 401 Project has now generated more than US$4M toward research and has evolved to be called Cure MECP2 Duplication Syndrome: The 401 Project, or simply Cure MDS, with the continued focus on funding further research leading to a treatment in humans. RSRT continues to be the beneficiary of Cure MDS.

Our Board has grown, and we now have several parent facilitators:

Peter Anderson, Collene Wright, Jenny McMillan, Kim Spangler, Fiona Walton, Amy Morrison Baker, Daleth Scaramuzzi, Suzi Centrone, Beatrice Palma, Kate DaCosta, Misty Tallo, Kelli Collat, and Oliver (Oly) Freeman. All parents to MECP2 duplication syndrome affected children, all work on a volunteer basis.

We would like to thank all of the families who have supported our effort and encourage more families to join the fight and find a cure for MECP2 duplication syndrome.

Contact Tim Freeman at tim@rsrt.org to get a fundraiser or campaign started.

QUICK LINKS

RSRT
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MECP2 DUPLICATION SYNDROME IS REVERSIBLE

In November 2015, Nature journal published an article called "Reversal of phenotypes in MECP2 duplication mice using genetic rescue or antisense oligonucleotides" The research was conducted in the laboratory of Dr Huda Zoghbi, Houston, Texas. This is a significant scientific breakthrough and paves the way for a treatment in humans.

Funding for the project was a fund-raising initiative generated by a global MECP2 duplication syndrome community of families called the 401 Project

The article reports that MECP2 duplication syndrome is reversible . "MECP2 Duplication syndrome is a childhood disorder caused by duplication of the MECP2 gene and, consequently, increased MECP2 protein levels. Huda Zoghbi and colleagues report that genetic correction of MECP2 levels largely reverses the behavioral, molecular and physiological deficits in a transgenic mouse model. Reducing MECP2 levels using an antisense oligonucleotide (ASO) strategy - which has greater potential for therapeutic application - similarly resulted in phenotypic rescue in adult transgenic mice and dose-dependently corrected MECP2 levels in cells from patients with MECP2 duplication .

These findings suggest that a disorder caused by copy number variation can be reversed after symptoms have emerged. " *

QUICK LINKS
NATURE JOURNAL
HUDA ZOGHBI LAB
CUREMDS

*Nature journal, 25 November 2015, article summary

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, autistic traits, poor or absent speech, 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). In very rare instances, there is a triple dose, or triplication of the MeCP2 gene resulting in more severe symptoms.

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 minuscule that it may often be impossible to detect on a routine chromosome test. More cases are now being diagnosed with the widespread use of at test called Array CGH (Comparative Genomic Hybridization), which allows for sub- microscopic detection of missing or additional copies of genetic material.

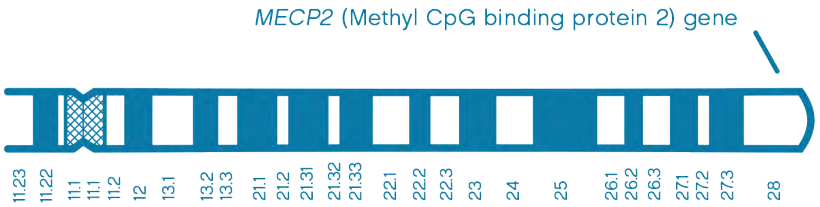
Currently, the prevalence (number of cases) around the world is unknown . However, it is possible that MECP2 duplication syndrome may account for 1-2% of unexplained intellectual disability and/or autism. Early findings suggest prevalence could be 1.8 in 10,000 live births.

QUICK LINKS
GARD
CUREMDS

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 (trans-located) to another chromosome in females. 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 nova (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 nova), 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 those affected 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.

QUICK LINKS

GARD

CUREMDS

MEDICAL PROFESSIONALS AND CARE

The relationship between MECP2 duplication syndrome and Rett Syndrome (same gene), means that pediatricians specializing 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 Pediatrician, Gastroenterologist Neurologist, Epileptologist, Cardiologist, Respiratory and Sleep Physician, Immunologist Ear Nose and Throat Specialist, Clinical Geneticist,

Genetic Counselor 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 .

QUICK LINKS

US CLINICS (PDF)

INTERNATIONAL CLINICS (PDF)

CUREMDS

MECP2 DUPLICATION SYNDROME IS REVERSIBLE

QUICK LINKS
US CLINICS (PDF)
INTERNATIONAL CLINICS (PDF)
CUREMDS

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.
Scientists involved in longitudinal research of MECP2 duplication syndrome:

Dr Suter
Baylor College of Medicine, Texas, USA

Dr Pehlivan
Baylor College of Medicine, Texas, USA

Dr Peters, Vanderbilt University
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

Dr Anastasia (Anna) Khvorova,
UMass Medical Center, Boston, Massachusetts, USA

Dr Ronald Cohn,
The Hospital for Sick Children (Sick Kids), Toronto, Canada

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

Professor Jonathan Kipnis , University of Virginia , Virginia , USA

RESEARCH PROJECTS AND FUNDING

QUICK LINKS
CURATIVE PROJECTS
CURATIVE PROJECTS (PDF)
MDS RESEARCH PUBLICATIONS

In 2022, we are continuing to raise funds to expedite current projects, proactively seek further projects and fund clinical research, if required . The current projects and funding required are detailed below:

MDS Clinical Studies for Drug Treatment

MDS is still relatively poorly characterized with newly identified features continuing to be identified. The accurate frequency of each symptom also varies significantly between each cohort and needs to be more reliably established. The Texas children's hospital (TCH) Rett Center in Houston currently has detailed genetic information on about 100 patients. Importantly, most of them have been clinically evaluated at tch. A team of experts who are familiar with mecp2 related disorders and severity scale development has been assembled. These experts will formulate and develop the first set of domains in the severity scale. Additional survey studies that cover core features of the syndrome will be added. These studies will provide crucial information for the scale development and help us to understand the natural progression of MDS better.

Once developed the scale will be shared with all interested stakeholders, affected families and care providers, therapists, physicians, researchers, and industry.

Understand how and to what extent genomic structural differences contribute to patients' severity.

Cutting-edge technologies such as high-resolution array comparative genomic hybridization, optical mapping, and whole-genome sequencing will be used to identify the various genomic duplications. Protein levels will also be analyzed and compared to the genetic structure and clinical severity. Develop biomarker(s) to use as a guide for dosing of ASO to ensure safety. Biospecimens including blood, skin, and cerebrospinal fluid have been collected to identify biomarkers from 10 MDS patients and 10 male Rett patients. Plans are to continue the enrollment of additional patients. Various analyses will be done to identify biomarkers that track with disease severity.

Dr. Pehlivan is funded through 2022 for this research with the support of Ionis.

RESEARCH PROJECTS AND FUNDING

Antisense Oligonucleotide Therapy

Dr. Zoghbi's Nature journal paper published in November of 2015 provided solid evidence that the MECP2 Duplication Syndrome is reversible , at least in mice. Furthermore, it offered a potential therapeutic strategy to reducing levels of the MeCP2 protein which is causing the horrific array of symptoms. That strategy is called antisense oligonucleotide therapy, or ASO. It lowers the level of MeCP2 by interfering with protein production.

Dr. Zoghbi and her lab are funded through 2022 for this research with the support of Ionis.

Drug Screen

There are multiple strategies that can be employed to lower production of the MeCP2 protein . Having multiple strategies gives us more opportunity to reach our goal but also provides the chance for combining strategies. One approach is using the ASO strategy described above. Dr. Zoghbi and her lab are employing a second strategy as well. She is undertaking a screen in search of compounds that can safely reduce levels of the protein. Any positive "hits" could form the foundation for drug discovery efforts.

Dr. Zoghbi has been fully funded ($1,485,949) for this project by RSRT through the efforts of the global MECP2 family community

QUICK LINKS
CURATIVE PROJECTS
CURATIVE PROJECTS (PDF)
MDS RESEARCH PUBLICATIONS

RESEARCH PROJECTS AND FUNDING

QUICK LINKS
CURATIVE PROJECTS
CURATIVE PROJECTS (PDF)
MDS RESEARCH PUBLICATIONS

Gene Therapy: siRNA and CRSPR

A third approach to reducing the MeCP2 protein is to deliver RNA interference to disrupt protein production. RNA interference is a biological process in which RNA molecules inhibit gene expression, typically by causing the destruction of specific mRNA molecules. Dr. Foust is currently attempting to deliver RNA interference via adeno- associated virus (AAV.). If successful, the project will provide proof-of-concept data showing that MeCP2 reduction is a therapeutic option for patients.

siRNA

The lab of Dr. Khvorova is developing siRNA-based compounds to reduce levels of MeCP2 and potentially silence gene expression. Dr. Khvorova has developed a new RNA interference scaffold that shows robust siRNA distribution throughout the brain and spinal cord in animal models. Her approach suggest that the siRNA treatment would need to be dosed every 9 to 12 months in humans and may have a better safety profile than other forms of gene silencing. $799,445 has been awarded to this project through RSRT.

Gene Editing (CRSPR)

This project is a “one and done” type of approach to removing the duplicated region. It is being done in the lab of Dr. Cohn and has been fully funded. Dr. Cohn has already shown that this strategy works successfully in MDS patient fibroblasts and has shown symptom improvement in a mouse model of Duchenne Muscular Dystrophy using the same approach.

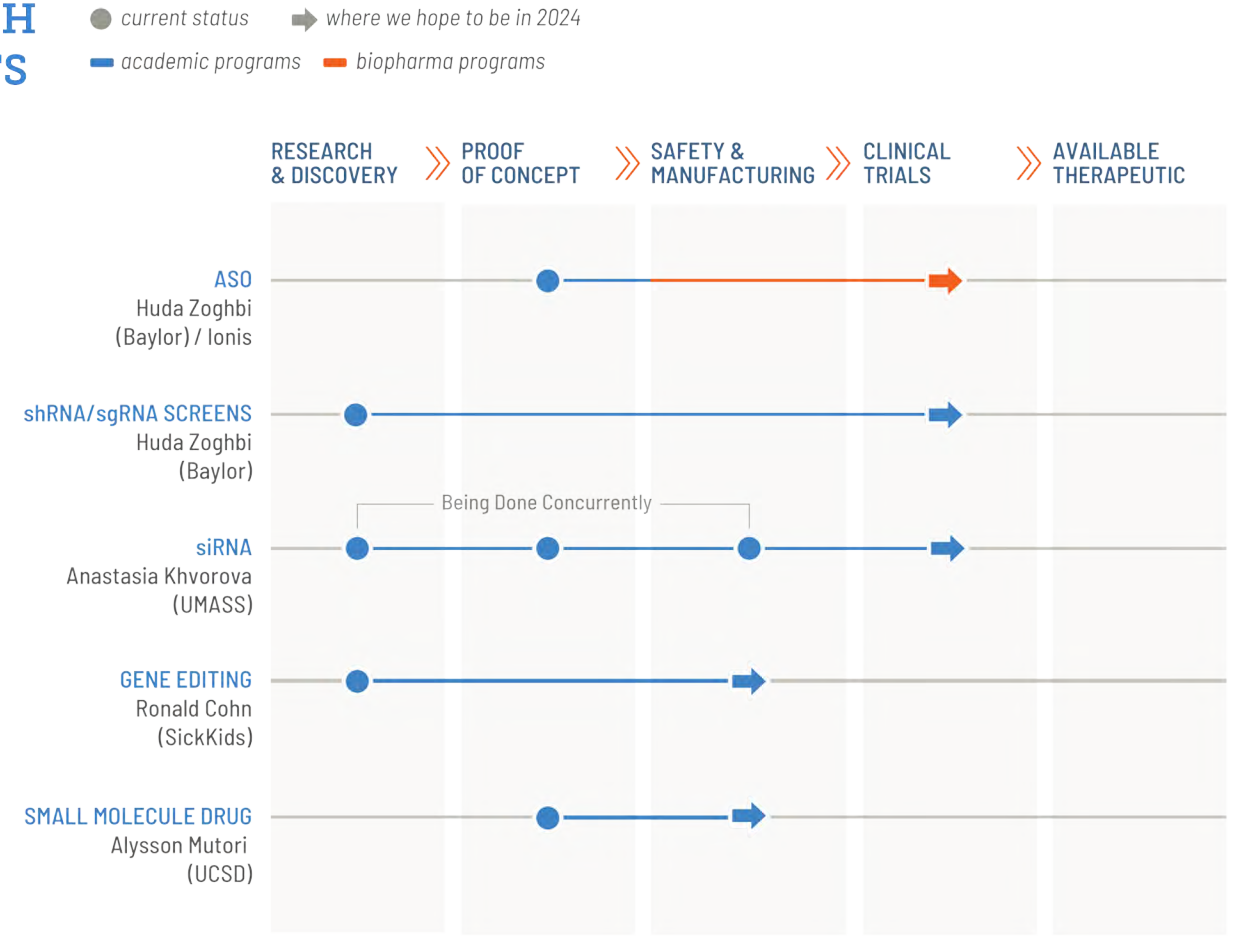
Recruiting new labs

To date our efforts have funded projects from scientists who have submitted their proposals.

We would like to move to a model where we have a pool of funds, enabling us to proactively seek proposals from scientists.

Our target for this approach is to have a float of $1 million at all times.

RESEARCH PROJECTS PIPELINE



CLINICAL RESEARCH

In addition to funding projects into a cure or treatment for MECP2 duplication syndrome. Funding is also required for projects to better understand the disease and also work out objective outcome measures that can be used in clinical trials.

In 2022, our aim is to raise $500k toward the next phase of Dr. Khvorova's project.

How can you help fund this clinical research?

Easy – by having your child (children) participate in the following clinical studies:

Telethon Kids Institute MDS Database:

It is very important to have a registry in order to fund all of these projects and to move forward with clinical studies and pharmaceutical approval. The Telethon Kids Institute team is still looking for families to take part in their online questionnaire study. Your answers will go toward better characterizing MDS and contribute to the current literature that we need.

.

You don't have to finish the questionnaire in one sitting. For more information, please visit:

https://Rett.TelethonKids.org.au/About/MECP2-Duplication-Syndrome/

NRI MDS Database:

This registry is a participant-driven project, overseen by MDS research advocates, with the purpose of furthering our understanding of this disorder and developing novel therapies. By sharing contact information and genetic reports in a secure centralized database, families will enable researchers like Dr. Pehlivan to coordinate studies and treatment trials, greatly facilitating progress in MDS research.

Visit www.curemds.org/enroll for information on how to sign up.

Natural History Study:

The purpose of this study is to advance the understanding of the natural history of the disorder. This study will not include clinical trials, but should set the stage for such trials and other translational projects. Visit www.curemds.org for information on how to sign up based on where you live in the United States.

QUICK LINKS
DATABASE ENROLL
CUREMDS
MDS RESEARCH PUBLICATIONS

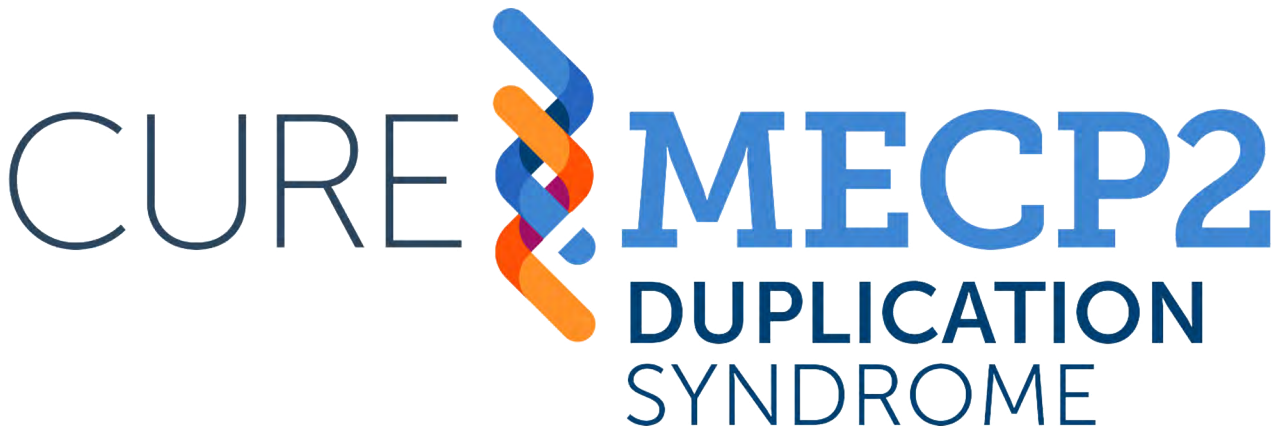
CLINICAL FEATURES OF MECP2 DUPLICATION SYNDROME

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
- Recurrent respiratory infections (progressive lung problems are common)
- Epilepsy (in approximately 50% of cases)
- Autistic features include limited or absent speech, repetitive behaviors 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 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 apnea and other sleep disorders

QUICK LINKS
CUREMDS
MDS RESEARCH PUBLICATIONS


CURE
MECP2
DUPLICATION
SYNDROME