**Fragile X**

Fragile X syndrome is the most common form of inherited mentalretardation affecting 1 in 4000 males. The main characteristicsof the syndrome are mental retardation and macro-orchidism inmales. This disorder is a result of an expanded CGG trinucleotiderepeat in the 5'-untranslated region (5'-UTR) of the FMR1 gene([4](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C4)–[6](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C6)). This X-linked disorder is caused by the absenceof the fragile X mental retardation 1 protein (FMRP). Sincethe cloning of *FMR1* in 1991 much effort has been put into unravelingthe function of FMRP ([5](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C5),[7](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487%22%20%5Cl%20%22DDF051C7)–[9](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C9)). Although the precise functionof FMRP has not been elucidated several characteristics of theprotein have been described. Two homologs of *FMR1*, *FXR1* and*FXR2*, have been identified ([10](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C10)–[12](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C12)). Together, the threeproteins form a small family of fragile X related (FXR) proteins.Since these proteins show a high sequence homology, and overlapin tissue distribution, analogous functions are suggested ([13](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487#DDF051C13),[14](http://hmg.oxfordjournals.org/cgi/content/full/11/5/487%22%20%5Cl%20%22DDF051C14)).It has been suggested that these proteins might partly complementone another.

**Gene associated with the syndrome**:

FMR1

**Mouse model**:

#### *Fmr1tm1Cgr*/*Fmr1tm1Cgr* (cryopreserved at Jax)

Current work at Columbia…possibility of obtaining live mice. <http://www.fraxa.org/ra_Bauchwitz.aspx>

**Timothy Syndrome**

Timothy syndrome (TS) is a multiorgan dysfunction caused by a Gly to Arg substitution at

position 406 (G406R) of the human CaV1.2 (L-type) channel. The TS phenotype includes

severe arrhythmias that are thought to be triggered by impaired open-state voltage-dependent

inactivation (OS*vd*I). The most striking sign of Timothy syndrome is the co-occurrence of both [syndactyly](http://en.wikipedia.org/wiki/Syndactyly) (~0.03% of births) and [long QT syndrome](http://en.wikipedia.org/wiki/Long_QT_syndrome) (1% per year) in a single patient. Other common symptoms of Timothy syndrome are cardiac [arrhythmia](http://en.wikipedia.org/wiki/Arrhythmia) (94%), heart malformations (59%), [autism](http://en.wikipedia.org/wiki/Autism) or an autism spectrum disorder (80% who survive long enough for evaluation). Facial dysmorphologies such as flattened noses also occur in approximately half of patients. Children with this disorder have small teeth which, due to poor [enamel](http://en.wikipedia.org/wiki/Tooth_enamel) coating, are prone to [dental cavities](http://en.wikipedia.org/wiki/Dental_cavities) and often require removal. The average age of death due to complications of these symptoms is 2.5 years.[[1]](http://en.wikipedia.org/wiki/Timothy_syndrome#cite_note-Marks_1995a-0)[[2]](http://en.wikipedia.org/wiki/Timothy_syndrome#cite_note-Marks_1995b-1)[[3]](http://en.wikipedia.org/wiki/Timothy_syndrome#cite_note-Splawski_2004-2)

**Gene associated with the syndrome:**

[CACNA1C](http://en.wikipedia.org/wiki/Cav1.2) missense mutation (G406R)

**Mouse model:**

Possible live source: **http://www.ipt.med.tu-muenchen.de/forschung/Moosmang/Seiten/contact.html**

**Smith-Magenis syndrome**

Mental retardation syndrome characterised by behavioural abnormalities, including self injurious behaviours, sleep disturbance, and distinct craniofacial and skeletal anomalies. It is usually associated with deletion involving 17p11.2 and is estimated to occur in 1/25,000 births. Heterozygous frameshift mutations leading to protein truncation in retinoic acid induced 1 gene (RAI1) have been identified in individuals with phenotypic features consistent with SMS. RAI1 lies within the 17p11.2 locus, but these patients did not have 17p11.2 deletions.

**Gene associated with syndrome:**

RAI1

**Mouse model:**

## B6.129S7-*Rai1tm1Jrl*/J (cryopreserved)

<http://jaxmice.jax.org/strain/005981.html>

Histology: Expression analysis of RAI1

http://hmg.oxfordjournals.org/cgi/reprint/16/15/1802

**Angelman syndrome**

Disruption of the predominately maternally expressed *UBE3A* locus. AS is characterized by severe mental retardation, ataxic gait, lack of speech, and happy affect [[*2*](http://www.springerlink.com/content/vt740kr084370875/fulltext.html#CR2)]. Seizures, obesity, microcephaly, and hypopigmentation are also found in some AS patients.

Although mutations in *UBE3A* are sufficient to cause AS, differences in phenotype between the AS patients with uniparental disomy and deletions suggest other genes may contribute to the diversity of traits [[*5*](http://www.springerlink.com/content/vt740kr084370875/fulltext.html#CR5)].

**Gene associated with the syndrome:**

UBE3A (and others)

**Mouse Model:**

Ube3atm1Alb/Ube3a+

<http://jaxmice.jax.org/strain/004477.html> (cryopreserved)

**Rett Syndrome**

Mutations in the X-linked *MECP2* gene are the primary cause ofRett syndrome (RTT), a severe autism spectrum disorder withdelayed onset that affects 1 in 10,000 girls ([*1*](http://www.sciencemag.org/cgi/content/full/315/5815/1143#REF1)). *MECP2* mutationsare also found in patients with other neurological conditions,including learning disability, neonatal encephalopathy, autism,and X-linked mental retardation ([*2*](http://www.sciencemag.org/cgi/content/full/315/5815/1143#REF2)). RTT patients show abnormalneuronal morphology, but not neuronal death ([*3*](http://www.sciencemag.org/cgi/content/full/315/5815/1143#REF3)), which impliesthat it is a neurodevelopmental rather than a neurodegenerativedisorder. MeCP2 is expressed widely, but is most abundant inneurons of the mature nervous system ([*4*](http://www.sciencemag.org/cgi/content/full/315/5815/1143#REF4)).

**Gene associated with syndrome:**

MECP2 gene encodes a methyl-CpG-binding protein which is thought to bind specifically to methylated CpG dinucleotides ([11](http://www.pnas.org/content/99/24/15536.full#ref-11)) and to act as a transcriptional repressor by virtue of its interaction with a histone deacetylase/Sin3 complex ([12](http://www.pnas.org/content/99/24/15536.full#ref-12), [13](http://www.pnas.org/content/99/24/15536.full#ref-13)). The involvement of the Mecp2 gene product in methylation-specific transcriptional repression suggests that RTT may be a result of misregulated gene expression. Because the prevailing model (based on biochemical evidence) suggests that Mecp2 acts as a global transcriptional repressor, it would predict that Mecp2 deficiency should result in widespread gene derepression.

**Mouse Model:**

## B6.129P2(C)-*Mecp2tm1.1Bird*/J (available live)

<http://jaxmice.jax.org/strain/003890.html>

**Prader–Willi Syndrome (contiguous gene syndrome)**

Prader–Willi syndrome (PWS) is a neurodevelopmental disorder caused by deletion or inactivation of paternally expressed imprinted genes on human chromosome 15q11–q13 ([Nicholls & Knepper, 2001](http://www3.interscience.wiley.com/cgi-bin/fulltext/123224697/main.html%2Cftx_abs#b24)). This cluster of imprinted genes contains a number of paternally expressed genes and brain-specific small nucleolar RNA (snoRNA) species, and two maternally expressed genes ([Buiting et al., 2007](http://www3.interscience.wiley.com/cgi-bin/fulltext/123224697/main.html%2Cftx_abs%22%20%5Cl%20%22b2)). PWS is characterized clinically by a failure to thrive in infancy, and, on emergence from infancy, an abnormal satiety response to food intake and obsession with food, and mild learning disabilities ([Holm et al., 1993](http://www3.interscience.wiley.com/cgi-bin/fulltext/123224697/main.html%2Cftx_abs#b14)). In addition to these core phenotypic characteristics, individuals with PWS can also display a high incidence of problem behaviours and neuropsychiatric abnormalities, such as affective disorder, including mood instability, non-psychotic depression, and psychosis ([Soni et al., 2007](http://www3.interscience.wiley.com/cgi-bin/fulltext/123224697/main.html%2Cftx_abs%22%20%5Cl%20%22b34)).

**Genes or genetic subtypes:**

abnormal functioning of the snoRNA mbii-85

chromosome 15 maternal uniparental disomy (mUPD)

imprinting centre (IC) mutation

above are results of paternal 15q11–q13 deletion

**Mouse model:**

IC deletion mouse model of PWS (PWS-IC+/−)

**ATR-X syndrome**

Alpha-thalassemia [X-linked mental retardation syndrome](http://www.healthline.com/galecontent/sutherland-haan-syndrome) is also known as ATRX syndrome, X-linked mental retardation hypotonic facies syndrome, and alpha thalassemia/mental retardation, X-linked. This condition is characterized by mental retardation, severe [developmental delay](http://www.healthline.com/galecontent/developmental-delay-1), unique craniofacial features, skeletal abnormalities, hypotonia, and genital abnormalities. These patients often have a form of anemia, called alpha **thalassemia**, which results from a defect in the production of [hemoglobin](http://www.healthline.com/adamcontent/hemoglobin). The syndrome has been recognized fairly recently and, thus, information about it is still evolving.

**Gene:**

ATRX on X chromosome. Males only. Females are carriers.

**Mouse model:**

None but have an overexpressed phenotype

**Possible sources for live mice:**

Baylor College of Medicine

<http://mrrc.bcm.tmc.edu/researchareas.html>

[Arthur L. Beaudet, M.D.](http://mrrc.bcm.tmc.edu/investigators/beaudet.html) – Angleman mice

[David L. Nelson, Ph.D.](http://mrrc.bcm.tmc.edu/investigators/nelson.html) – Fragile X

[Richard E. Paylor, Ph.D.](http://mrrc.bcm.tmc.edu/investigators/paylor.html) - Smith-Magenis syndrome and Fragile X

[Daniel G. Glaze, M.D.](http://mrrc.bcm.tmc.edu/investigators/glaze.html) , [Paolo M. Moretti, M.D.](http://mrrc.bcm.tmc.edu/investigators/moretti.html), [Jeffrey L. Neul, M.D., Ph.D.](http://mrrc.bcm.tmc.edu/investigators/neul.html), [Huda Y. Zoghbi, M.D.](http://mrrc.bcm.tmc.edu/investigators/zoghbi.html) – Rett