Outline

• Brief History of OMIM
• Production Process
• OMIM Goals and Priorities
• Clinical Synopses
• Human Phenotyping
• Inherent Limitations in Correlation of Human and Model Organism Phenotypes
Using OMIM

Number of Entries in *Mendelian Inheritance in Man*

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Entries in MIM</th>
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<tbody>
<tr>
<td>1965</td>
<td>MIM1</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>MIM4</td>
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<tr>
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<td>MIM5</td>
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<td>MIM6</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>MIM9</td>
</tr>
<tr>
<td></td>
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</tr>
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<td>MIM12</td>
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OMIM 19,852 15 January 2010

Hamosh    July 19, 2004
### SCORECARD
**Mapping of Clinical Disorders**
January 15, 2010

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Loci with 1 or more disorder</td>
<td>3,668</td>
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<tr>
<td>Disorders that have been mapped</td>
<td>5,396</td>
</tr>
<tr>
<td>1. Disorders mapped by wildtype gene</td>
<td>144</td>
</tr>
<tr>
<td>2. Disorders mapped by clinical phenotype</td>
<td>1,167</td>
</tr>
<tr>
<td>3. Disease-causing mutation(s) identified</td>
<td>4049</td>
</tr>
<tr>
<td>4. Deletion/Duplication syndrome</td>
<td>36</td>
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</table>

### Molecular Defects in Mendelian Disorders
(and somatic mutations in neoplasms)
January 15, 2010

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Total # of loci in OMIM with at least 1 known point mutation causing a disorder or neoplasm</td>
<td>2391</td>
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<tr>
<td>Total # of mapped disorders for which a causative Mutation has been identified</td>
<td>4049</td>
</tr>
<tr>
<td>Total # of mutations catalogued in OMIM</td>
<td>17,749</td>
</tr>
</tbody>
</table>
Using OMIM

Current Staff and Structure

Scientific Director: Ada Hamosh, MD
Deputy Scientific Director for Phenotypes: Open
Deputy Scientific Director for Genes: Alan Scott, PhD
Project Manager: Joanna Amberger
Editorial Director: Carol A. Bocchini, MS

Science Writers (PhD/MD):
- Paul Converse
- Patricia Hartz
- Cassandra Kniffin
- Marla O’Neill

Subject Author Editors (MDs):
- John A. Phillips III*
- George E. Tiller*
- Slobhan Dolan*
- John L. Black*
- Jane Kelly*
- Garry Bellus*
- Paul Brennan*

Editorial Staff:
- Anne Stumpf
- Matthew B. Gross
- Terry Hentges
- William Wang

Clinical Synopses
- Kelly Przylepa, MD*

*free-lance/consultants

Journals

- American Journal Human Genetics
- American Journal Medical Genetics/Part A
- American Journal Medical Genetics/Part B
- American Journal Medical Genetics/Part C
- Annals of Human Genetics
- Annals of Neurology
- Archives of Neurology
- Blood
- British Journal Cancer
- British Journal Haematology
- British Journal Med Genetics
- Cancer
- Cancer Gene Cytogenetics
- Cancer Research
- Circulation
- Circulation Research
- Clinical Dysmorphology
- Clinical Genetics
- European Journal Dermatology
- European Journal Human Genetics
- European Journal Med Genetics
- Genes and Development
- Genetic Counseling
- Genetics in Medicine
- Human Molecular Genetics
- Human Mutation
- Journal of Human Genetics
- Journal of Medical Genetics
- Genes Chromosomes and Cancer
- Genes to Cells
- Hemoglobin
- Human Heredity
- Immunology
- Immunogenetics
- JAMA
- Journal of Clinical Endocrinology and Metabolism
- Journal of Experimental Medicine
- Journal of Immunology
- Journal of Pediatrics
- Lancet
- Journal of Clinical Investigation
- Mammalian Genetics
- Molecular Cell
- Nature
- Nature Cell Biology
- Nature Genetics
- Nature Medicine
- Nature Reviews Genetics
- NEJM
- Neurogenetics
- Neurology
- Neuron
- Oncogene
- Pediatrics
- Pediatric Research
- Pharmacogenomics
- PNAS
- Science
- Trends in Genetics
- ... and more
OMIM Funding Source

- A contract from National Library of Medicine (NCBI), funding in large part by NHGRI
- No funding for database programming (all through NCBI)
- We create only the content as flat files
OMIM Goals and Priorities

- Mendelian Disorders
- Genes that cause mendelian disorders
- Other genes of known function
- Deletion/Duplication Syndromes
- Reorganize entries to include headings
- Complex traits with genetic component
  - Phenotypic series (e.g. IBD or BPQTL)
OMIM Numbering System

1----- (100000- ) Autosomal dominant
   (entries created before May 15, 1994)
2----- (200000- ) Autosomal recessive
   (entries created before May 15, 1994)
3----- (300000- ) X-linked loci or phenotypes
4----- (400000- ) Y-linked loci or phenotypes
5----- (500000- ) Mitochondrial loci or phenotypes
6----- (600000- ) Autosomal loci or phenotypes
   (entries created after May 15, 1994)
OMIM Statistics for January 17, 2010

Number of Entries

<table>
<thead>
<tr>
<th>SYMBOLS</th>
<th>Autosomal</th>
<th>X-Linked</th>
<th>Y-Linked</th>
<th>Mitochondrial</th>
<th>Total</th>
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<tr>
<td>* Gene with known sequence</td>
<td>12330</td>
<td>609</td>
<td>48</td>
<td>35</td>
<td>13022</td>
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<td>+ Gene with known sequence and phenotype</td>
<td>327</td>
<td>19</td>
<td>0</td>
<td>2</td>
<td>348</td>
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<tr>
<td># Phenotype description, molecular basis known</td>
<td>2443</td>
<td>216</td>
<td>4</td>
<td>26</td>
<td>2689</td>
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<td>$ Mendelian phenotype or locus, molecular basis unknown</td>
<td>1641</td>
<td>142</td>
<td>3</td>
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<td>Other, mainly phenotypes with suspected mendelian basis</td>
<td>1865</td>
<td>137</td>
<td>2</td>
<td>0</td>
<td>2004</td>
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<td>Total</td>
<td>18606</td>
<td>1123</td>
<td>59</td>
<td>63</td>
<td>19851</td>
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OMIM® - Online Mendelian Inheritance in Man®

Welcome to OMIM®, Online Mendelian Inheritance in Man®. OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overview in OMIM contains information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 in collaboration with the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers in personal questions.
### OMIM Update List

The following is a list of all Updates to NCBI OMIM since the creation of the database.

<table>
<thead>
<tr>
<th>Year</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
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</tbody>
</table>

**New:**

- 2010: 18
- 2009: 52
- 2008: 63
- 2007: 70
- 2006: 65

**Changed:**

- 2010: 489
- 2009: 914
- 2008: 633
- 2007: 653

### Allelic Variants

**Selected examples**

Allelic variants are given a 10-digit number: the 6-digit number of the parent locus followed by a decimal point and a unique 4-digit variant number.

Note that for most genes, only selected mutations are included in specific subentries. Criteria for inclusion include: the first mutation to be discovered, high population frequency, distinctive phenotype, historic significance, unusual mechanisms of mutation, unusual pathogenetic mechanisms, and distinctive inheritance (e.g., dominant with some mutations, recessive with other mutations in the same gene).

Most of the allelic variants represent disease-producing mutations. A few polymorphisms are included, many of which show a positive statistical correlation with particular common disorders.
OMIM is NOT

- The repository for all genes
- The repository for all mutations
- The best resource for data-mining
  - But we can help you

OMIM Is

- Naming new genetic diseases
- Deciding when to split diseases
  - Often based upon molecular diagnosis which can lead to specific therapy
- Working with the community to organize complex and overlapping diseases into defined categories
Clinical Synopsis History

- Initially, an index of MIM clinical terms
- Then extracted from MIM text by John Jackson (ends with Inheritance)
- Since 1998, based upon standard references or the original reports or reviews, standard structure, (starts with Inheritance)
- Each feature is reference based

Clinical Synopses Statistics

- 5019 clinical synopses
- 2231 new or revised
- Not (yet) indexed by NCBI
- Revised or new by 3 writers
Unrevised Clinical Synopsis

**OMIM:**

**110569**  
**BLEPHAROCHEILODONTIC SYNDROME**

**Clinical Synopsis**

- **Mouth:** Cleft lip and/or palate
- **Eyes:**
  - Ectropion of lower eyelids
  - Ocular hypertelorism
- **Teeth:** Conical teeth
- **Inheritance:** Autosomal dominant

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Revised or New Clinical Synopsis

**OMIM:**

**600864**  
**OROFACIAL CLEFT & SUSCEPTIBILITY TO**

**Clinical Synopsis**

- **Inheritance:** Isolated cases
- **Head and Neck:**
  - Mouth: Cleft lip, isolated
  - Cleft palate, isolated
  - Cleft lip and alveolar palate

**Molecular Basis:**

- Genomic heterogeneity (see OTC, 119550)
- Atrophic change in the craniofacial regulatory factor 5 gene (SRS, 607100.0013)

**Creation Date**

Cassandra L. Kniffin: 12/21/2004

**Edit History**

- Updated: 12/21/2004

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### Clinical Synopsis Structure

- **INHERITANCE**
- **GROWTH:**
  - [Height];
  - [Weight];
  - [Other];
- **HEAD AND NECK:**
  - [Head];
  - [Face];
  - [Ears];
  - [Eyes];
  - [Nose];
  - [Mouth];
  - [Teeth];
  - [Neck];
- **CARDIOVASCULAR:**
  - [Heart];
  - [Vascular];
- **RESPIRATORY:**
  - [Nasopharynx];
  - [Larynx];
  - [Airways];
  - [Lung];
- **CHEST:**
  - [External features];
  - [Ribs, sternum, clavicles, and scapulae];
  - [Breasts];
  - [Diaphragm];
- **ABDOMEN:**
  - [External features];
  - [Liver];
  - [Pancreas];
  - [Biliary tract];
  - [Spleen];
  - [Gastrointestinal];
- **GENITOURINARY:**
  - [External genitalia, male];
  - [External genitalia, female];
  - [Internal genitalia, male];
  - [Internal genitalia, female];
  - [Kidneys];
  - [Ureters];
  - [Bladder];
- **SKELETAL:**
  - [Skull];
  - [Spine];
  - [Pelvis];
  - [Limbs];
  - [Hands];
  - [Feet];
- **SKIN, NAILS, HAIR:**
  - [Skin];
  - [Nails];
  - [Hair];
- **MUSCLE, SOFT TISSUE:**
- **NEUROLOGIC:**
  - [Central nervous system];
  - [Peripheral nervous system];
  - [Behavioral/psychiatric manifestations];
Clinical Synopsis Structure

- VOICE:
- METABOLIC FEATURES:
- ENDOCRINE FEATURES:
- HEMATOLOGY:
- IMMUNOLOGY:
- NEOPLASIA:
- PRENATAL MANIFESTATIONS:
  - [Movement];
  - [Amniotic fluid];
  - [Placenta and umbilical cord];
  - [Maternal];
  - [Delivery];
- LABORATORY ABNORMALITIES:
- MISCELLANEOUS:
- MOLECULAR BASIS:
- CREATION DATE

Inheritance

- Autosomal dominant
- Autosomal recessive
- X-linked dominant
- X-linked recessive
- Y-linked
- Pseudoautosomal dominant
- Pseudoautosomal recessive
- Mitochondrial
- Somatic mosaicism
- Somatic mutation
- Isolated cases
- Digenic, recessive
- Digenic, dominant
- Multifactorial
Why Not A Rigid Ontology or Controlled Vocabulary

- Time in Clinic
- Literature-based so defer to word used by author if ambiguous
- Evolution of language over time
- Terms used are established medical terms: definitions in common medical dictionaries
- OMIM has been incorporated into UMLS

Human Phenotyping

- Evolving diagnostic testing
  - imaging
  - blood and urine chemical analysis
  - DNA testing
- Evolving Treatment Modalities
  - uncovers new manifestations
  - changes natural history
Loeys-Dietz Syndrome

• Initially described by Loeys et al, 2005
• Recognition based upon new imaging technique: CT or MR angiography
  – Distinguishes diffuse arterial tortuosity + connective tissue abnormalities

Loeys et al, 355:788-798, 2006
Inborn Errors of Metabolism

- GC-Mass Spectrometers: organic aciduria
- Tandem Mass Spectrometers: fatty acids oxidation defects
- Congenital Disorders of Glycosylation

22q11 deletion syndrome

- DiGeorge syndrome:
  - cardiac anomalies and immune defect
- Velocardiofacial syndrome:
  - cleft palate and/or velopharyngeal insufficiency, developmental problems, cardiac anomalies, typical face, tapered fingers
- Schizophrenia
- Isolated cleft lip or cardiac anomalies etc
- No Phenotype
Cystic Fibrosis

• Initial description cystic fibrosis of the pancreas, median life expectancy 2 years
• Now in US median life expectancy is 37 years, lung disease and congenital bilateral absence of the vas deferens as well as pancreatic sufficient variants all well recognized
• Changes in treatment (pancreatic enzymes, then antibiotics, then cycled inhaled tobramycin, followed by DN-ase, and now anti-inflammatory agents have made it necessary to study cohorts independently

Correlating Human to Model Organism Phenotypes

• Anatomic differences
• Physiologic differences
• Humans have an uncontrollable environment
• We have limited ability to phenotype humans
• When a human is “diseased”, we intervene to the extent possible
Take Home Messages

• OMIM is easy to link to
• Clinical synopses will be independently searchable soon
• Need a back end thesaurus for synonyms
• Links to ICD-10, Human Phenotype Ontology
  – (should not be hard to relate)
• MGI mammalian phenotype ontology links are also feasible
• We are happy to help with searches
  (joanna@welch.peas.jhu.edu)
• We want to work with you

The End
Using OMIM
Using OMIM

### 7q31.2, CFTTR to 7q32, CATRI

<table>
<thead>
<tr>
<th>Location</th>
<th>Symbol</th>
<th>Title</th>
<th>MIM #</th>
<th>Disorder</th>
<th>Comments</th>
<th>Method</th>
<th>Mouse</th>
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</thead>
<tbody>
<tr>
<td>7q31.2</td>
<td>CFTTR, ABCC7, CF, MRP7</td>
<td>Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette, subfamily C, member 7)</td>
<td>600421</td>
<td>Cystic fibrosis; 216400; [3]; Congenital absence of vas deferens, 221100; [3]; Sodium chloride elevation without CF (3); (Pancreatitis, idiopathic) (3); (Hypertrophismenia, neonatal) (5)</td>
<td>distal and 5' to MET</td>
<td>F, Ff</td>
<td>CffTr</td>
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<td>Testin</td>
<td>600485</td>
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<td></td>
<td>REx</td>
<td>CffTr</td>
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<td>CAPZA2, CAPPA2</td>
<td>Capping protein (acts filament) muscle Z-line, alpha 2</td>
<td>601877</td>
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<td>Phs, REx</td>
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<td>AASS</td>
<td>Alpha-aminoadipic semialdehyde synthase</td>
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<td>Hyperlysinessm, 238700; Sucrhalaminiasis, 261700 (1)</td>
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<td>CADPS2, KIAA1581</td>
<td>Calcium-dependent activator protein for secretion 2</td>
<td>609978</td>
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Using OMIM

Organism: Homo sapiens
Chromosome: 7
Region Shown: 6634.75 6915.25
Available Maps:  
Org: human  
Assembly: reference  
Maps Displayed (left to right):  
--- Sequence Maps ---  
Ab initio  
Assembly  
IES Clone  
Clone Component  
Contig  
CpG Island  
Ensembl Genes

More Options:
- Show Connections
- Verbose Mode
- Compress Map: off
- Auto Compress if > 350 px
- Page Length: 30
- Thumbnail View: default (ideogram) master

OK Apply Close

OMIM - Online Mendelian Inheritance in Man

Welcome to OMIM, Online Mendelian Inheritance in Man. This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. The database contains textual information and references. It also contains comprehensive links to MEDLINE and sequence records in the Entrez system, and links to additional related resources at NCBI and elsewhere.

You can do a search by entering one or more terms in the text box above. Advanced search options are accessible via the Limits, Preview/Index, History, and Clipboard options in the grey bar beneath the text box. The OMIM help document provides additional information and examples of basic and advanced searches.

The links to the left provide further technical information, searching options, frequently asked questions (FAQ), and information on allied resources. To return to this page, click on the OMIM link in the black header bar or on the graphic at the top of any OMIM page.

NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.

OMIM® and Online Mendelian Inheritance in Man® are trademarks of the Johns Hopkins University.
### Using OMIM

The OMIM (Online Mendelian Inheritance in Man) database is a catalog of human genes and genetic disorders. It is maintained by the National Center for Biotechnology Information (NCBI) and serves as a valuable resource for researchers, clinicians, and the general public. OMIM is a comprehensive database that includes information on more than 10,000 genetic disorders, including both rare and common conditions.

#### OMIM Entries

- **Disorder**: Various genetic disorders such as cystic fibrosis, phenylketonuria, and many more.
- **Symbols**: The genetic symbols associated with each disorder.
- **OMIM**: The unique OMIM number for each entry.
- **Location**: Information on the chromosomal location of the disorder.

#### OMIM Features

- **Search Options**: Various search fields including gene symbol, chromosome, and more.
- **Database**: Searchable database with detailed information on genetic disorders.
- **My NCBI**: Personalized settings and alerts for users.

#### OMIM Access

OMIM is accessible through various NCBI databases and tools, providing a wealth of information on human genetics. For more details, visit the NCBI website or contact the Johns Hopkins University for further assistance.

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Hamosh  July 19, 2004  25
Using OMIM

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Using OMIM

**NOONAN SYNDROME 1; NS1**

**Alternative alleles/symbols**

- **NOONAN SYNDROME**
- **MALE TURNER SYNDROME**
- **FEMALE PSEUDO-TURNER SYNDROME**
- **TURNER PHENOTYPE WITH NORMAL KARYOTYPE**
- **PTERYGOM COLUMellar SYNDROME, INCLUDED**

**Gene map locus**

- **12q24.1**

**TEXT**

A number sign ($) is used with this entry because of evidence that this form of Noonan syndrome (NS1), which maps to chromosome 12q24.1, is due to mutations in PTEN (125790), a gene encoding the tumor suppressor protein (tumor phosphatase 3,2,5), which contains 2 Sm homology 2 (SH2) domains. (Turcotte et al., 2001; Turcotte et al., 2001) found that mutations in the PTEN gene accounted for about half the patients studied. Mutations in the neurofibromatosis gene (NF1; 1622) have been found to cause neurofibromatosis-Noonan syndrome (NFNS; 601212). De novo germline mutations of the KRAS gene (60700) have also been found in individuals with Noonan syndrome (NS3; 604642), but account for less than 1% of Noonan syndrome cases. Other forms of Noonan syndrome, such as NS4 (611721), which is caused by mutation in the SOS1 gene (125795), and NS5 (611721), which is caused by mutation in the RAF1 gene (60700), have been identified. Also see NS2 (602026).

**DESCRIPTION**

Noonan syndrome is an autosomal dominantly inherited syndrome characterized by hypertelorism, a downdrawn cataract, and low-set posteriorly rotated ears (Ghigna et al., 1990). Other features include short stature, a short neck with webbing of the neck, cardiac anomalies, epicanthic folds, clefts, joint contractures, cleft palate, and a bleeding diathesis.

Noonan syndrome has an estimated incidence of 1 in 1,000 to 2,500 live births (Turcotte et al., 2001).
Using OMIM

NOONAN SYNDROME 1; NS1

Clinical Symptoms

INHERITANCE:
- Autosomal dominant

GROWTH:
- Height
  - Short stature (percentile
  - Other
  - Failure to thrive in infancy
  - Specific growth curves are available

HEAD AND NECK:
- Face
  - Triangular face with age
- Ear
  - Low-set posteriorly rotated ear
  - Nerve deafness
- Eyes
  - Hypertelorism
  - Ptosis of upper lid eyelids
  - Epicanthal folds
  - Strabismus
  - Blue-green irides
- Mouth
  - Deeply grooved philtrum
  - High arch palate
  - Micrognathia
  - Dental malocclusion

CARDIOVASCULAR:
- Heart
  - Congenital heart defect
  - Atrial septal defect
  - Ventricular septal defect
  - Pulmonic stenosis
  - Patent ductus arteriosus

CHEST:
- Ribs, sternum, clavicles, and scapulae
  - Short clavicles
  - Pectus carinatum superior
  - Pectus excavatum inferiorly

GENITOURINARY:
- Internal genitalia, male
  - Undescended testes
  - Cryptorchidism
  - Male infertility in individuals with bilateral cryptorchidism

SKELETAL:
- Spine
  - Vertebral abnormalities
- Limbs
  - Calcium deposits
  - Deformities
  - Bone deformities

SKIN, NAILS, HAIR:
- Hair
  - Wooly-like consistency of hair

MUSCLE, SOFT TISSUE:
- Lymphedema
Using OMIM

SKIN, NAILS, HAIR:
- Hair: Wooly-like consistency of hair

MUSCLE, SOFT TISSUE:
- Lymphedema

NEUROLOGY:
- Central nervous system: Articulation difficulties
- Mental retardation (25%)

HEMATOLOGY:
- Aneuploidy: thrombocytopenia
- Von Willebrand disease
- Bleeding tendency

NEOPLASIA:
- Malignant schwannoma

LABORATORY ABNORMALITIES:
- Partial deficiency of factor XCI
- Partial deficiency of factor XIII C
- Thrombocytopenia

MISCELLANEOUS:
- Genetic heterogeneity (see NS2 h05275 and NS3 h09942)
- Atleic with LEOPARD syndrome (151100)

MOLECULAR BASIS:
- Caused by mutations in the protein tyrosine phosphatase, nonreceptor-type, 11 gene (PTPN11, 17h17.60001)

CONTRIBUTORS:
- Joanna S. Amberger - updated: 7/14/2006
- Kelly A. Pritzlaff - revised: 12/7/1999

CREATION DATE:
- John E. Jackson - 6/14/1995

---

.NO001 NOOAN SYNDROME 1 [PTPN11, AAL72SER]

In a family with Noonan syndrome (163950), Tartaglia et al. (2001) found that affected members had a G-to-T transversion at position 214 in exon 3 of the PTPN11 gene, predicting an alan2-to-ser (A72S) substitution in the SH2 domain. This mutation was also identified by Kosaki et al. (2002).

.NO002 NOOAN SYNDROME 1 [PTPN11, AAL72GLY]

In a family with Noonan syndrome (163950), Tartaglia et al. (2001) found that affected members had a C-to-G transversion at nucleotide 215 in exon 3 of the PTPN11 gene, predicting an alan2-to-gly (A72G) amino acid substitution.

.NO003 NOOAN SYNDROME 1 [PTPN11, ASN308ASP] dSnpP

In affected members of 3 families and in a sporadic case of Noonan syndrome (163950), Tartaglia et al. (2001) found a 922A-G transition in exon 8 of the PTPN11 gene, predicting an asn308-to-asp (N308D) amino acid change. This missense mutation affected the phosphotyrosine phosphatase (PTP) domain.

In a comprehensive study of Tartaglia et al. (2002), about one-third of the patients who had mutations in the PTPN11 gene had this mutation, which was by far the most common. This was the mutation present in the large 3-generation family that was used originally to establish linkage to the locus on 12q. That codon 308 is a hotspot for Noonan syndrome was further indicated by the finding of an asn308-to-ser (176876.00003) missense mutation in 2 families (Tartaglia et al., 2002). In the cohort of Noonan syndrome patients studied by Tartaglia et al. (2002) noted that in their cohort, no patient carrying the N308D mutation was enrolled in special education.

Kosaki et al. (2002) found this mutation in a Japanese patient.

In 13 (23%) of 56 patients with Noonan syndrome, Jongmans et al. (2005) identified the N308D mutation, confirming the reputation of nucleotide 922 as a mutation hotspot. Among these 13 patients only 3 attended special school. Except for this suspected correlation with normal education, the phenotype observed in patients with the mutation at nucleotide 922 did not differ from the phenotype in patients with other mutations.

.NO004 NOOAN SYNDROME 1 [PTPN11, ASN308SER]

NOOAN-LIKE MULTIPLE GIANT CELL LESION SYNDROME, INCLUDED

Whereas the very frequent N308D missense mutation (176876.0003) is caused by a change of nucleotide 922, 2 families studied by Tartaglia et al. (2002) showed an asn308-to-ser (N308S) missense mutation due to an A-to-G transition at the adjacent nucleotide 923. Thus, codon 308 is a hotspot for Noonan syndrome. One of
Noonan Syndrome

Judith E Allanson, MD

Department of Genetics
Children's hospital of Eastern Ontario
allanson@cheo.on.ca

Last Revision: September 6, 2007.

Summary

Disease characteristics. Noonan syndrome (NS) is characterized by short stature, congenital heart defect, broad or webbed neck, unusual chest shape with superior pectus carinatum, inferior pectus excavatum, and apparently low-set nipples. Developmental delay of variable degree, cryptorchidism, and characteristic facies. Various cardiovascular defects and syndactyly deformities are frequently observed. Congenital heart disease occurs in 50%–60% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%–30% of individuals. Hypertrophic cardiomyopathy, found in 24%–30% of individuals, may be present at birth or appear in infancy or childhood. Other structural defects frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis, and talipes equinovarus.

Length at birth is usually normal. Final adult height approaches the lower limit of normal. Mild mental retardation is seen in up to one-third of individuals. Ocular abnormalities, including strabismus, refractive errors, amblyopia, and nystagmus, occur in up to 45% of individuals.

Diagnosis

Clinical Diagnosis

Diagnosis of Noonan syndrome (NS) is made on clinical grounds, by observation of key features. Despite a lack of defined diagnostic criteria, the cardinal features of NS are well delineated (Allanson, 1987):

- Short stature
- Congenital heart defect
- Broad or webbed neck
- Unusual chest shape with superior pectus carinatum, inferior pectus excavatum
- Apparently low-set nipples
- Developmental delay of variable degree
- Cryptorchidism in males
- Characteristic facies: The facial appearance of NS shows considerable change with age, being most striking in the newborn period and middle childhood, and most subtle in the adult (Allanson et al, 1995). Key features found irrespective of age include low-set, posteriorly rotated ears with highly helical, vivid blue or blue-green irides, and eyes that are often wide-spaced, with epicanthal folds and thick or droopy eyelids.
Table 1. Molecular Genetic Testing Used in Noonan Syndrome

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency</th>
<th>Test Availability</th>
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<tbody>
<tr>
<td>Sequence analysis</td>
<td>PTPN11 mutations</td>
<td>50%</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>FISH (genomic microarray) analysis</td>
<td>PTPN11 deletions</td>
<td>&lt;1%</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>Sequence analysis</td>
<td>KRAS mutations</td>
<td>&lt;3%</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>Sequence analysis</td>
<td>SOSI mutations</td>
<td>10% -13%</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>Sequence analysis</td>
<td>RAF2 mutations</td>
<td>3% - 17%</td>
<td>Clinical Testing</td>
</tr>
</tbody>
</table>

1. Proportion of affected individuals with a mutation(s) as classified by gene and test method
2. The only reported deletion in PTPN11 was a 3-bp deletion in exon 3 in a female infant with severe features of Noonan syndrome, including hydrocephaly and juvenile myelomonocytic leukemia (Yoshida et al 2004); thus, the use of FISH (genomic microarray analysis) seems unlikely to detect/diagnose Noonan syndrome.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

1. PTPN11 sequence analysis of exons 3, 8, 9, and 13
2. If no mutation is identified, sequence analysis of SOSI exons 1-23
3. If no mutation identified in PTPN11 or SOSI, sequence analysis of remaining 11 exons of PTPN11 and of RAF1 exons 7, 14, and 17
4. If no mutation is identified, sequence analysis of remaining RAF1 exons and exons 1-6 of KRAS

Funded by the National Institutes of Health

PTPN11-Related Noonan Syndrome

<table>
<thead>
<tr>
<th>Laboratory Offering Clinical Testing</th>
<th>Select All Clinical Laboratories</th>
</tr>
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<tbody>
<tr>
<td>Athena Diagnostics Inc</td>
<td>Athena Diagnostics Inc</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Houston, TX</td>
<td>Houston, TX</td>
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<tr>
<td>Christina H Eng, MD, FACP, William E O'Brien, MD, Lee Ann Wong, MD; Gia M. D'Onofrio, PhD</td>
<td>Christina H Eng, MD, FACP, William E O'Brien, MD, Lee Ann Wong, MD; Gia M. D'Onofrio, PhD</td>
</tr>
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<td>Boston University School of Medicine</td>
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<tr>
<td>Audrey Minsky, MD, OBG</td>
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<td>Center for Human Genetics</td>
</tr>
<tr>
<td>@Leiden University, Netherlands</td>
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<td>Shriners Hospital Philadelphia</td>
<td>Shriners Hospital Philadelphia</td>
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<tr>
<td>Punita Kauri Tawade, MD, FACP</td>
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<td>Shriners Hospital</td>
<td>Shriners Hospital</td>
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</table>

Hamosh  July 19, 2004
PTPN11-Related Noonan Syndrome

References: [1], [2]

Gene Symbol: PTPN11
Chromosomal Locus: 12q24.1
Protein Name: Tyrosine-protein phosphatase non-receptor type 11

Clinical Laboratory

Baylor College of Medicine
Medical Genetics Laboratories
Houston, TX

Director: Christine M Eng, MD, FACP
US Genetic Board Certification: American Board of Medical Genetics (Clinical Molecular Genetics)
Director: William E O'Brien, PhD
US Genetic Board Certification: American Board of Medical Genetics (Clinical Biochemistry/Molecular Genetics)
Director: Su N Cheung, PhD
US Genetic Board Certification: American Board of Medical Genetics (Clinical Cytogenetics)
Genetic Counselor: Patricia A Want, MLS, CGC
US Genetic Board Certification: American Board of Medical Genetics (Genetic Counseling)
email: geneticslab@bcm.tmc.edu  phone: (1-800) 411-GENE  fax: (713) 798-6584
Genetic Counselor: Eri S Schmitt, MS, PhD
US Genetic Board Certification: American Board of Genetic Counseling
email: geneticslab@bcm.tmc.edu  phone: (1-800) 411-GENE  fax: (713) 798-6584
Genetic Counselor: Amber N Purdy, MS
US Genetic Board Certification: American Board of Genetic Counseling
email: geneticslab@bcm.tmc.edu  phone: (1-800) 411-GENE  fax: (713) 798-6584

No direct patient consultation provided.

Method: Analysis of the entire coding region; Sequence analysis
Additional Testing Offered: Clinical confirmation of mutations identified in a research lab; Prenatal diagnosis
CAVEAT EMPTOR

• Alphabetical list
• Provider must determine which lab does the best testing for the best price with the fastest results (if needed)
  – Plus which lab the patient’s insurance will cover (if U.S. patient)
Using OMIM

Laboratory Directory

Research Notice

Clinical trials. For information about clinical trials, see ClinicalTrials.gov.

Clinical testing. Do not contact a research laboratory if you are seeking clinical testing. Research laboratories do not perform clinical testing. Laboratories performing research testing are not subject to CLIA regulation.

Research testing. Check the listing of each laboratory to see if direct patient contact is accepted. Research laboratories may prefer that interested patients work through a healthcare provider or genetics clinic.

Translating a research test into a clinical test. If no clinical laboratory offers a test for mutations in a gene of interest to you, and you have an interest in facilitating such test development, two alternatives are available:

- If you have already spoken with a clinical laboratory or researcher interested in developing the test, go to the CEETT Program Web site (www.ceettprogram.org) to learn how a collaboration between a research laboratory, clinical laboratory, and patient advocacy group can apply for funds to transition a test from a research laboratory to a clinical laboratory.

- If you are willing to promote development of a specific test but are not sure where to start, contact CEETT Program Coordinator Andy Faustelli, MS at wmb@ceettprogram.org to learn how the CEETT Program may be able to identify a clinical laboratory, researcher, and advocate group willing to work together to transition a test from a research laboratory to a clinical laboratory.

"CEETT = Collaboration, Education and Test Translation"

Clinical confirmation of mutations identified in a research laboratory. To locate a laboratory that offers clinical confirmation of mutations identified in a research laboratory, see [CLINIC].
Using OMIM

Noonan Syndrome Resources

- National Library of Medicine Genetics Home Reference
  Noonan syndrome

- The Noonan Syndrome Support Group
  PO Box 145
  Upperco MD 21159
  Phone: 888-686-2224, 410-374-5245
  Email: info@noonansyndrome.org
  www.noonansyndrome.org

- Human Growth Foundation
  917 Glen Cove Avenue Suite 5
  Glen Head NY 11545
  Phone: 800-451-6434
  Fax: 516-671-4055
  Email: hgf1@hgfund.org
  www.hgfund.org

- The MAGIC Foundation
  5645 West North Avenue
  Oak Park IL 60303
  Phone: 800-362-4423, 708-383-0808
  Fax: 708-383-0899
  Email: info@magifoundation.org
  www.magifoundation.org

- Genetic Alliance BioBank
  A centralized biological and data (consent/clinical/environmental) repository to enable translational genomic research on rare genetic diseases.
  Phone: 202-966-5557
  Email: stacey@geneticalliance.org
  www.biobank.org
Using OMIM

GeneTests Resources are identified, evaluated, and selected by staff.
- Consumer health-oriented organizations included in GeneTests:
  - Provide information/services to individuals/families with inheritable diseases
  - Have a medical/scientific advisory board or other mechanism for medical/scientific review
  - Have a regional, national, or international base
  - Do not intentionally include information about specific clinical, educational, or research facilities
  - Are in English or provide an English version
  - Are available at no cost
- Registries included in GeneTests:
  - Have as their primary purpose improving the medical care of patients or increasing scientific/medical knowledge about the disease
  - Have a medical/scientific advisory board or other mechanism for medical scientific review
  - Are not lists of clinical or research facilities
  - May be affiliated with or sponsored by a clinical/research facility

GeneTests does not assume responsibility for information provided by the resources included. Lists are not all-inclusive.

Noonan Syndrome Resources

- National Library of Medicine Genetics Home Reference
  - Noonan syndrome
- The Noonan Syndrome Support Group
  - PO Box 145
  - Upperco MD 21159
  - Phone: 888-686-2224; 410-374-5245
  - Email: info@noonansyndrome.org
  - www.noonansyndrome.org
- Human Growth Foundation
  - 917 Glen Cove Avenue Suite 5
  - Glen Head NY 11545
  - Phone: 800-651-6434
  - Fax: 516-671-4055
  - Email: hgf1@hgffound.org
  - www.hgffound.org
- The MAGIC Foundation
  - 5645 West North Avenue
  - Oak Park IL 60303
  - Phone: 800-362-4423; 708-383-0888
  - Fax: 708-383-0899
  - Email: info@magicfoundation.org
  - www.magicfoundation.org
- Genetic Alliance BioBank
  - A centralized biological and data [consent/clinical/environmental] repository to enable translational genomic research on rare genetic diseases.
  - Phone: 202-966-5557
  - Email: storey@geneticalliance.org
  - www.biobank.org

Jun 13 2007 18:40 PDT

Hamosh July 19, 2004
Using OMIM
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Educational Materials

Educational Materials are intended to help healthcare providers understand the appropriate use of genetic counseling and testing.

- The content-sensitive Illustrated Glossary defines over 225 medical genetics terms used on this Web site. Over 70 terms are illustrated, more illustrations are being added regularly.

- GeneticTests: Genetics Through a Primary Care Lens provides resources for primary care teaching, presenting genetics information and concepts in the context of primary care. It includes four main sections: Genetic Concepts & Skills (inheritance, genetic testing, family history, and public health implications); Teaching Cases (31 primary-care-presentations of genetic conditions); Ethical, Legal, Social, & Cultural Issues; and Other Resources (including references and Web resources for patients).

- About Genetic Services explains genetic counseling and testing concepts:
  - What is Genetic Testing?
  - Uses of Genetic Testing
  - Analogy Services
  - What is a Genetic Consultation?
  - Who Should Have a Genetics Consultation?
  - Ordering Genetic Testing

Glossary

affect(s): An individual who manifests symptoms of a particular condition.

allele: One version of a gene at a given location (locus) along a chromosome.

Related Terms: alleles, dominant allele, recessive allele, gene, locus.

allele frequency: (synonym: gene frequency) The proportion of individuals in a population who have inherited a specific gene mutation or variant.

Related Terms: allele, allele frequency, gene frequency, mutation.

allele-specific oligonucleotide testing: (synonym: ASS, AOS testing) The detection of a specific mutation using a synthetic segment of DNA approximately 20 base pairs in length (an oligonucleotide) that binds to and hence identifies the complementary sequence in a DNA sample.

Related Terms: oligonucleotide, gene, mutation.

allelic heterogeneity: (synonym: molecular heterogeneity) Different mutations in the same gene at the same chromosomal locus that cause a single phenotype.

Related Terms: allele, gene, mutation.

allelic variant of unknown significance: An alteration in the normal sequence of a gene, the significance of which is unclear and further study of the geneproduct and corresponding phenotype in a sufficiently large population; complete gene sequencing often identifies numerous (sometimes hundreds) allelic variants for a given gene.

Related Terms: allele, variant, gene, mutation.

alternate paternity: (synonym: false paternity, nonpaternity) The situation in which the alleged father of a particular individual is not the biological father.

Analysis of the entire coding region: Mutation screening: (synonym: mutation scanning, mutation detection) The step-by-step procedure by which the entire coding region of a gene is first analyzed via one of a variety of methods (such as Sanger, BigDye, DTP, DHPLC or TGE) to identify sequence alterations. These methods do not identify the specific nucleotide change(s) and must be followed by further analysis (usually sequencing) to identify the specific sequence alteration.
OMIM

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• Links from the home page
• Links from within a MIM entry
Using OMIM

NOMANN SYNDROME 1; NS1

Alternative db; symbols

NOMANN SYNDROME
MALE TURNER SYNDROME
FEMALE PSEUDO-TURNER SYNDROME
TURNER PHENOTYPE WITH NORMAL KARYOTYPE
PTERYGOM TOMOLL SYNDROME, INCLUDED

Gene map locus: 15q13.1

TEXT

A number (4) is used with this entry because of evidence that this form of Noonan syndrome (NS1), which maps to chromosome 12q24-13, is due to mutations of PTPNNK (17,867,854), a gene encoding the receptor protein tyrosine phosphatase SHP2, which contains 2 SH2 (src homology 2) domains.

Corteglia et al. (2001). Targher et al. (2001)

DESCRIPTION

Noonan syndrome is an autosomal dominant dysmorphic syndrome characterized by hypertelorism, a downward eyelid, and low-set posteriorly rotated ears. Other features include short stature, a short neck with webbing or redundancy of skin, cardiac anomalies, epicanthic folds, asthenia, motor delay, and a bleeding diathesis. g

Noonan syndrome has an estimated incidence of 1 in 1,000 to 2,500 live births (Targher et al., 2001).
Using OMIM

Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome.


Department of Pediatrics, Mount Sinai School of Medicine, New York, New York, 10029, USA. tartam2@msn.com

Noonan syndrome (OMIM 163950) is an autosomal dominant disorder characterized by dysmorphic facial features, proportionate short stature and heart disease (most commonly cardiomyopathy, mitral valve prolapse and hypertrophic cardiomyopathy). Rubella, skeletal deformities, mental retardation and life-threatening disease are often associated with this disease. This syndrome is relatively common, with an estimated incidence of 1 in 1,000-2,500 births. It has been mapped to a 5-Mb region (9q34-q35) on chromosome 9p13.1 and genetic heterogeneity has also been observed. Variability in clinical features and age at onset suggests the presence of multiple disease genes.

Shp2, a member of the protein tyrosine phosphatase (PTP) family, is localized to chromosome 9q34, overlapping the critical region of Noonan syndrome. Shp2 is a bidirectional protein tyrosine phosphatase that removes both activating and inhibitory phosphate groups from tyrosine residues on the cytoplasmic tails of receptors and other proteins. The catalytic domain of SHP-2, which contains two Src homology 2 (SH2) domains, causes Noonan syndrome and accounts for more than 90% of the cases that are confirmed. All PTPN11 missense mutations cluster in domains of the protein - SH2 domain and the phosphotyrosine phosphatase domains, which are involved in activating the protein in inactive and active conformations.

PMID: 1784759 | PubMed - indexed for MEDLINE
NOONAN SYNDROME 1; NS1

Alternative ath; symbols
NOONAN SYNDROME
MALE TURNER SYNDROME
FEMALE PSEUDO-TURNER SYNDROME
TURNER PHENOTYPE WITH NORMAL KARYOTYPE
PTERYGOM COLLI SYNDROME, INCLUDED

Gene map locus: 12p13.1

TEXT
A number of mutations in the PTPN11 gene are associated with Noonan syndrome (NS), which is caused by mutations in the gene encoding the protein tyrosine phosphatase, non-receptor type 11 (PTPN11), in about 35% of affected individuals (McKusick, 2004). In addition to Noonan syndrome, mutations of PTPN11 have been associated with the related disorder Costello syndrome (OMIM 182240), which is characterized by intellectual disability and various developmental abnormalities. Other mutations in PTPN11 have been identified in individuals with Noonan syndrome with multiple lentigines (OMIM 146760), an autosomal dominant disorder characterized by café-au-lait spots, lentigines, and intellectual disability.

DESCRIPTION
Noonan syndrome is an autosomal dominant dysomorphic syndrome characterized by hypotonia, a short stature, and postnatal growth retardation. Other features include characteristic facies, a short neck with or without a mandible, cardiac anomalies, epicanthal folds, deafness, mental retardation, and bleeding disorders.

Noonan syndrome has an estimated incidence of 1 in 1,000 to 2,500 live births (Tamura et al., 2001).
OMIM

- Anatomy of an OMIM entry
- Links from the home page
- Links from within a MIM entry
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Using OMIM

This database is maintained by D.N. Cooper, E.V. Ball, P.D. Stenson, A.D. Phillips, K. Hovells and M.E.Mort with the assistance of N.S.T. Thomas.

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<td>Mutations</td>
<td>The gene symbol (as recommended by the Human Nomenclature Committee) and functional location are recorded for each gene. In cases where a gene symbol has not yet been made official, a provisional symbol has been assigned which is denoted by lower-case letters.</td>
<td>2202</td>
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<td>Single base-pair substitutions in coding regions are presented in terms of a triplet change with an additional letter indicating the affected base, either the first or second position in the triplet.</td>
<td>35433</td>
<td>44775</td>
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<td>Splicing</td>
<td>Minimum is the consequence for mRNA splicing is presented in terms of a triplet change with information specifying the relative position of the lesions with respect to the mammalian (mouse or human) splice site. Positioning of the base pair change refers to an O (downstream) or R (upstream) location.</td>
<td>5477</td>
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<td>Regulatory</td>
<td>Regulatory sequences are presented in terms of a triplet change with information specifying the relative position of the lesions with respect to the mammalian (mouse or human) splice site. Positioning of the base pair change refers to an O (downstream) or R (upstream) location.</td>
<td>776</td>
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<tr>
<td>Small deletions</td>
<td>Micro-insertions &lt;50 bp or less are presented in terms of the deleted bases in lower case plus, in upper case, 50 bp DNA sequence flanking both sides of the lesion. The rambler codon is presented in the given sequence by the cent character (').</td>
<td>9528</td>
<td>12722</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small insertions</td>
<td>Micro-insertions &gt;50 bp or less are presented in terms of the inserted bases in lower case plus, in upper case, 50 bp DNA sequence flanking both sides of the lesion. The rambler codon is presented in the given sequence by the cent character (').</td>
<td>3708</td>
<td>5179</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Model Organisms

FlyBase - *Drosophila melanogaster*; fruit fly
Genome Database (GDB) - *Homo sapiens*; human mapping information
Mouse Genome Database (MGD) - *Mus musculus*
Rat Genome Database - *Rattus norvegicus*
Saccharomyces Genome Database (SGD) - *Saccharomyces cerevisiae*; yeast
WormBase - *Caenorhabditis elegans*; nematode
Zebrafish Information Network (ZFIN) - *Danio rerio*

In addition to the databases above, the NCBI Gene page provides access to genome guides for various organisms, including:

- **Human**
- **Mouse**
- **Rat**
- **Fruit Fly**
- **Zebrafish**
- and others...
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OMIM

• Anatomy of an OMIM entry
• Links from the home page
• Links from within a MIM entry
Welcome to OMIM. Online Mendelian Inheritance in Man. This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. The database contains research information and references. It also contains citations from MEDLINE and sequence records in the Entrez system, and links to additional related resources at NCBI and elsewhere.

You can do a search by entering one or more terms in the text box above. Advanced search options are accessible via the Limits, Preview/Index, History, and Clipboard options in the gray bar beneath the text box. The OMIM help document provides additional information and examples of basic and advanced searches.

The links to the left provide further technical information, searching options, frequently asked questions (FAQs), and information on allied resources. To return to this page, click on the OMIM link in the black header bar or on the graph at the top of any OMIM page.

NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetic researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for advice in personal questions.

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Cystic fibrosis transmembrane conductance regulator (CFTR), a 1,480 amino acid protein that is encoded by the CFTR gene, is a member of the ATP-binding cassette (ABC) family of transporters.

The ABC family of transporters are characterized by a shared nucleotide-binding fold and include a diverse set of transporters that share a common mechanism of active transport.

The CFTR gene is located on chromosome 7 and is composed of 27 exons. It is expressed in a variety of tissues, including the pancreas, lungs, and sweat glands.

Cystic fibrosis is a genetic disorder caused by mutations in the CFTR gene.

The most common mutation is the deletion of three nucleotides (delF508), which results in a premature stop codon and a truncated protein.

There are currently over 1,500 known mutations in the CFTR gene, and each mutation leads to a different clinical phenotype.

Treatment for cystic fibrosis includes lung clearing maneuvers, pancreatic enzyme supplements, and antibiotics to prevent infections.

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ALLELIC VARIANTS

Selected examples

Allelic variants are given a 10-digit number: the 6-digit number of the parent locus followed by a decimal point and a unique 4-digit variant number.

Note that for most genes, only selected mutations are included as specific subentries. Criteria for inclusion include: the first mutation to be discovered, high population frequency, distinctive phenotype, historic significance, unusual mechanism of mutation, unusual pathogenic mechanism, and distinctive inheritance (e.g., dominant with some mutations, recessive with other mutations in the same gene).

Most of the allelic variants represent disease-producing mutations. A few polymorphisms are included, many of which show a positive statistical correlation with particular common disorders.
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There are currently 1544 mutations listed in this CFTR mutation database.

Statistics by mutation type:

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Count</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>645</td>
<td>41.77</td>
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<tr>
<td>Frame shift</td>
<td>243</td>
<td>15.74</td>
</tr>
<tr>
<td>Splicing</td>
<td>197</td>
<td>12.76</td>
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<tr>
<td>Nonsense</td>
<td>149</td>
<td>9.55</td>
</tr>
<tr>
<td>In frame ins/del</td>
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<td>2.01</td>
</tr>
<tr>
<td>Large ins/del</td>
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<td>2.85</td>
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<tr>
<td>Promoter</td>
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<td>0.52</td>
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<tr>
<td>Sequence variation</td>
<td>225</td>
<td>14.57</td>
</tr>
</tbody>
</table>

Statistics by region:

<table>
<thead>
<tr>
<th>Region Name</th>
<th>Count</th>
<th>Distribution %</th>
<th>Density %</th>
</tr>
</thead>
<tbody>
<tr>
<td>promoter</td>
<td>16</td>
<td>1.04</td>
<td>N/A</td>
</tr>
<tr>
<td>5UTR and exon 1</td>
<td>28</td>
<td>1.81</td>
<td>15.14</td>
</tr>
<tr>
<td>exon 2</td>
<td>29</td>
<td>1.85</td>
<td>26.13</td>
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</table>
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Cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride channel and controls the regulation of other transport pathways. Mutations in the CFTR gene have been found to cause cystic fibrosis (OMIM 602421) and congenital bilateral aplasia of the vas deferens (OMIM 217950).

CLOTHING

Rudolph et al. (1989) isolated overlapping cDNA clones from epithelial cell libraries with a generic DNA segment containing a portion of the cystic fibrosis gene. Transcripts of approximately 6,500 nucleotides in size were identified in the tissues affected in patients with CF. The predicted protein product of 12 similar cDNA clones was analyzed by cloning and sequencing. The N-terminus of a deduced polypeptide sequence occurs at the center of the predicted first nucleotide-encoding site (NRE). The predicted polypeptide has 1,480 amino acids with a molecular mass of 165,131 Da. The characteristics are remarkably similar to those of the sodium-coupled multispecific organic anion transporter (P-glycoprotein, P-gp), which also maps to 5q33, and to a number of other membrane-associated proteins. To avoid confusion with the previously named CF antigen (OMIM 602421), referred to as the present term, cystic fibrosis transmembrane conductance regulator (CFTR).

Cystic fibrosis represents the first genetic disorder elucidated entirely by the process of reverse genetics (i.e., positional cloning), i.e., on the basis of map location but without the availability of chromosome breakpoints or deletions such as those that have greatly facilitated previous success in the cloning of human disorders, e.g., Duchenne muscular dystrophy (OMIM 310200), retinitis pigmentosa (180800), and chronic granulomatous disease (OMIM 600208), for example. By use of a combination of chromosome walking and jumping, Zimman et al. (1989) succeeded in covering the CF region on 5q. The jumping technique was particularly useful by bypassing ‘recombilant’ regions, which are estimated to constitute 5% of the human genome. Once artificial chromosome (YAC) vectors amounted an alternative strategy. The identification of endonucleotides (Cox’s method, acc. 3.5kb) another set of 5’ by RNAi screen, constructed from...
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CTFTR, Cystic Fibrosis Transmembrane Conductance Regulator

Alternative titles; symbols
ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 7; ABCC7

Cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride channel and controls the regulation of other transport pathways. Mutations in the CFTR gene have been found to cause cystic fibrosis (CF; 219750) and congenital bilateral aplasia of the vas deferens (CBVA; 271800).

CLOSING

Rossifelt et al. (1999) isolated overlapping, lDNA clones from epithelial cell libraries with a genuine DNA segment containing a portion of the putative CF gene. Transcripts approximately 6,500 nucleotides in size were detected in the lesion affected in patients with CF. The predicted proteins encoded by 2 similar mRNAs encode a putative polypeptide chain of 1,480 amino acids with a molecular mass of 169,138 Da. The characteristics are remarkably similar to those of the cloning mutator enzyme Pseudomonas (123750), which also maps to 7q, and to a number of other membrane-associated proteins. To avoid confusion with the previously named CF antigen (219750), Rossielt et al. (1999) referred to the protein as cystic fibrosis transmembrane conductance regulator (CFTR).

Cystic fibrosis represents the first genetic disorder elucidated entirely by the process of reverse genetics (also called positional cloning), i.e., on the basis of map location but without the availability of chromosomal rearrangements or deletions such as those that have greatly facilitated previous success in the cloning of human disease genes. In Duchenne muscular dystrophy (DMDX), attempt to construct a human gene that codes for a muscle-specific protein (DMDX), for example, by use of a combination of somatic cell hybridization and mapping. Hemiemann et al. (1989) succeeded in covering the CF region on 7q. The jumping technique was particularly useful in bypassing 'nucleotides' regions, which are estimated to constitute 5% of the human genome. (Four artificial chromosomes (YAC) vectors were used as alternative substrates.) The identification of chromosome 7 locus, however, still awaits a screening of 234 DNA libraries, constructed from...
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Cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride channel and controls the regulation of other transport pathways. Mutations in the CFTR gene have been found to cause cystic fibrosis (ICD: 219800) and congenital bilateral aplasia of the vas deferens (ICD: 272180).

Cystic fibrosis is a genetic disorder characterized by the presence of thick, sticky mucus, which blocks the ducts and organs of the body. This mucus can affect the lungs, pancreas, and other organs. People with cystic fibrosis face many health challenges, including frequent lung infections, digestive problems, and a higher risk of diabetes and other conditions.

The gene that causes cystic fibrosis is called CFTR (cystic fibrosis transmembrane conductance regulator). It produces a protein that helps control the flow of salt and water in the body. When the CFTR gene is mutated, the protein doesn’t work properly, leading to the symptoms of cystic fibrosis.

Cystic fibrosis affects people of all ages and is genetic in nature. It is caused by mutations in the CFTR gene, which is located on the long arm of chromosome 7 and is responsible for producing a protein that helps control the movement of sodium and chloride ions across cell membranes.

The symptoms of cystic fibrosis can range from mild to severe, and the severity can vary from person to person. Common symptoms include recurrent lung infections, digestive problems (such as problems with the pancreas), and an increased risk of certain types of cancer.

There is currently no cure for cystic fibrosis, but treatments are available to manage symptoms and improve quality of life. These treatments include antibiotics to treat lung infections, enzymes to help digest food, and medications to relieve nasal congestion.

In conclusion, cystic fibrosis is a serious genetic disorder that affects many aspects of a person’s health. By understanding the cause and symptoms of cystic fibrosis, we can better support those who are affected and develop new treatments to help improve their lives.

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Cystic fibrosis transmembrane conductance regulator (CFTR), formerly known as a chloride channel and controls the regulation of other transport pathways. Variations in the CFTR gene have been found to cause cystic fibrosis (IC: 219790) and congenital bilateral aplasia of the vas deferens (OMIM: 274869). The protein is encoded by the CFTR gene, located on chromosome 7 (OMIM: 219790) and is expressed in a wide range of tissues, including the lung, intestine, pancreas, and sweat glands. It is also found in the testis, where it may play a role in sperm motility.

The protein consists of 12 transmembrane domains and is localized to the apical membrane of epithelial cells. The protein is phosphorylated by protein kinase A and C, which modulate its activity. The protein contains several conserved motifs, including a C-terminus ATP-binding cassette domain, a cystic fibrosis transmembrane conductance regulator domain, and a transmembrane domain. The protein is regulated by the intracellular calcium concentration and is involved in the regulation of chloride and bicarbonate ion transport.

The protein is localized to the apical membrane of epithelial cells and is involved in the regulation of chloride and bicarbonate ion transport. The protein is also involved in the regulation of pancreatic fluid secretion and the production of mucus in the respiratory tract.

The protein is encoded by the CFTR gene, located on chromosome 7 (OMIM: 219790) and is expressed in a wide range of tissues, including the lung, intestine, pancreas, and sweat glands. It is also found in the testis, where it may play a role in sperm motility.
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Cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride channel and controls the regulation of other transport pathways. Mutations in the CFTR gene have been linked to cystic fibrosis (CF, 219700) and congenital bilateral absence of the vas deferens (CBAVD, 277180).

CLOSING

Due to the overlap of CFTR with other genes, the protein is now referred to as cystic fibrosis transmembrane conductance regulator (CFTR).

Cystic fibrosis is a rare genetic disorder characterized by the presence of a defective protein known as the cystic fibrosis transmembrane conductance regulator (CFTR). This protein is responsible for the malfunction of glands in the lungs, pancreas, and other organs, leading to recurrent lung infections, digestive issues, and other health problems.
**OMIM: a knowledgebase**

- Aimed at clinicians and molecular biologists
- Free text, literature based
- Comprehensive, timely, authoritative
- Easy to use
- Rich links out, easy to link to us
- Flexible, adaptable
The End