Consideration of human relevance for developmental effects based on experimental data

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TERMINOLOGY

Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2)

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ABSTRACT **This update (Version 2) of the *Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 1)* incorporates improvements and enhancements to both content and organization of the terminology to enable greater flexibility in its application, while maintaining a consistent approach to the description of findings. The revisions are the result of an international collaboration among interested organizations, advised by individual experts and the outcomes of several workshops. The terminology remains organized into tables under the broad categories of external, visceral, and skeletal observations, following the manner in which data are typically collected and recorded in developmental toxicity studies. This arrangement of the tables, as well as other information provided in appendices, is intended to facilitate the process of specimen evaluation at the laboratory bench level. Only the commonly used laboratory mammals (i.e. rats, mice, rabbits) are addressed in the current terminology tables. The inclusion of other species that are used in developmental toxicity testing, such as primates, is considered outside the scope of the present update. Similarly, categorization of findings as, for example, 'malformation' or 'variation' remains unaddressed, in accordance with the overall principle that the focus of this document is descriptive terminology and not diagnosis or interpretation. The skeletal terms have been augmented to accommodate cartilage findings.**

Key Words: developmental toxicology glossary, developmental toxicology nomenclature, developmental toxicology terminology, external abnormality, skeletal abnormality, visceral abnormality

INTRODUCTION

This publication is the first update (i.e. Version 2) to the *Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 1)* by Wise *et al.* (1997). It builds upon past efforts to assemble an internationally harmonized source of common nomenclature for use in describing observations of fetal and neonatal morphology. Improvements and enhancements to the content and organization of the Version 1 terminology are provided to enable a greater degree of flexibility in its application, while maintaining a consistent approach to the description of findings. The terminology should be of particular use for submissions of developmental toxicity data to regulatory agencies, while also having broader applicability in research.

Version 1 was compiled under the auspices of the International Federation of Teratology Societies (IFTS), which included member groups from North America, Europe, and Asia. It was based on a

THE JAPANESE TERATOLOGY SOCIETY

Japanese

Board of Directors | Annual Meeting | Congenital Anomalies | Secretariat

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Laboratory animal Congenital Anomaly Database

meetings

- 51th Annual Meeting
  Date： July 22-24, 2010
  Place： Sabo Kaikan Tokyo 2-7-5 Hirakawacho, Chiyoda-Ku, Tokyo, 102-0093, Japan
  Chairman： Fumiki Hirahara(Yokohama City Univ.)
  H P：http://www.macc.jp/51jts/index.html

Topics & Whats NEW

- 2011.3.1. The homepage was renewed.

Labolatory animal Congenital Anomaly Database - Top Page

BACK UMIN TOP TOP MENU

All the data are offered by THE JAPANESE TERATOLOGY SOCIETY

Japanese / English

Brief Description	
Display a list of registered observation	Search for observation by category(ex. External/Visceral/Skeletal)
Search	Search by a synonym, related term or definition etc.
Initial regstration (for an administrator)	Add as a new entry. This function is exclusively for an administrator.

問い合わせ先:日本先天異常学会事務局 jts@ac-square.co.jp

Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

- (•) External
- ( ) Visceral
- ( ) Skeletal

next

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Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

Earlier search condition	
External/Visceral/Skeketal	External

Check All Uncheck All

General	Head / Neck	Ear
Eye	Face	Limb (fore- or hind-)
Paw / Digit (fore- or hind-)	Tail	Trunk

Display a list of registered observation next

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Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

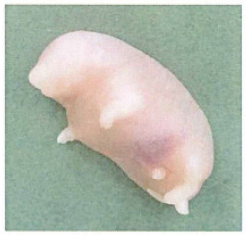
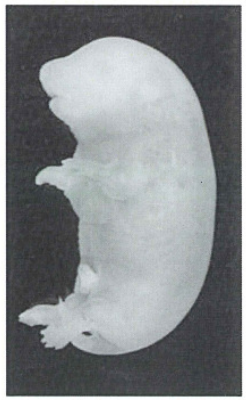
1 2
1-10 / 12

No	Id Number	Code Number	Region Organ Structure	Observation	Synonym or Related Trem	Definition	File
1	S002429	10002	General	General/Conjoined twins	Omphalosite	Monozygotic twins with variable incomplete separation into two during cleavage or early stages of embryogenesis	○
2	S002430	New	General	General/Distended abdomen		Abdomen appears larger than normal	--
3	S002435	10004	General	General/Subcutaneous hemorrhage	Petechia, Purpura, Ecchymosis, Hematoma	An accumulation of extravasated blood beneath the skin	--
4	S002431	New	General	Fetus or pup/neonate/Discolored	Skin discolored	Generalized or localized region of abnormal color (other than pale)	--
5	S002432	New	General	Fetus or pup/neonate/Large			--
6	S002433	New	General	Fetus or pup/neonate/Pale		Generalized absence of color when compared to a normal specimen	--
7	S002434	New	General	Fetus or pup/neonate/Small	Runt		--
8	S000003	10001	General	Subcutaneous edema/Generalized	Anasarca	An accumulation of interstitial fluid in subcutaneous connective tissue	○
9	S002428	10005	General	Subcutaneous edema/Localized		Localized accumulation of fluid	--
10	S002436	10003	General	Skin/Absent	Cutis aplasia	Localized region of no skin development	--

Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10001
External/Visceral/Skeletal	External
Region/Organ/Structure	General
Observation	Subcutaneous edema/Generalized
Synonym or Related Term	Anasarca
Non-Preferred Term	
Definition	An accumulation of interstitial fluid in subcutaneous connective tissue
Note	
Registration date	2010/01/28
Updated date	2010/11/26

Image information		
	species	
	memo	
	species	
	memo	

Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

1 2
1-10 / 17

No	Id Number	Code Number	Region Organ Structure		Observation	Synonym or Related Trem	Definition	File
1	S002909	10328	Kidney	Kidney	Cyst			--
2	S002911	10331	Kidney	Kidney	Large			--
3	S002914	10337	Kidney	Kidney	Misshapen			○
4	S002915	10339	Kidney	Kidney	Small			--
5	S002907	10326	Kidney	Kidney	Absent			○
6	S002910	10330	Kidney	Kidney	Discolored	Infarct		--
7	S002913	10336	Kidney	Kidney	Malpositioned			--
8	S002912	10332	Kidney	Kidney	Fused			--
9	S002916	10342	Kidney	Kidney	Supernumerary			--
10	S002908	New	Kidney	Kidney	Altered texture			--

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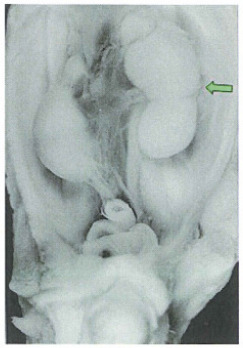
Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10337
External/Visceral/Skeletal	Visceral
Region/Organ/Structure	Kidney
	Kidney
Observation	Misshapen
Synonym or Related Term	
Non-Preferred Term	
Definition	
Note	
Registration date	2010/04/19
Updated date	2011/03/03

Image information		
	species	rat
	memo	

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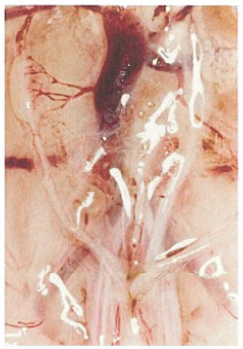
Labolatory animal Congenital Anomaly Database - Details

Observation information	
Code Number	10326
External/Visceral/Skeletal	Visceral
Region/Organ/Structure	Kidney
	Kidney
Observation	Absent
Synonym or Related Term	
Non-Preferred Term	
Definition	
Note	
Registration date	2010/04/19
Updated date	2011/03/03

Image information		
	species	dog
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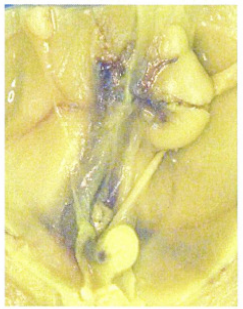
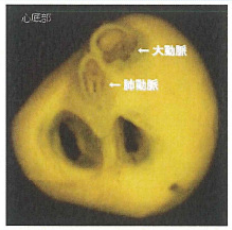
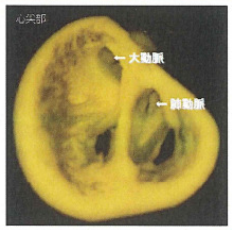
	species	rat
	memo	

Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10224
External/Visceral/Skeletal	Visceral
Region/Organ/Structure	Great vessels
	Great vessels
Observation	Transposition
Synonym or Related Term	
Non-Preferred Term	
Definition	Origin of aorta from right ventricle and pulmonary trunk from left ventricle
Note	
Registration date	2011/03/03
Updated date	2011/03/03

Image information		
	species	rat
	memo	
	species	rat
	memo	

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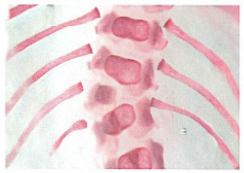
Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10696
External/Visceral/Skeletal	Skeletal
Region/Organ/Structure	Vertebra
	Thoracic vertebra
Observation	Hemivertebra
Synonym or Related Term	
Non-Preferred Term	
Definition	
Note	Absent arch and hemicentrum may be recorded separately
Registration date	2010/04/19
Updated date	2011/03/04

Image information		
	species	rabbit
	memo	

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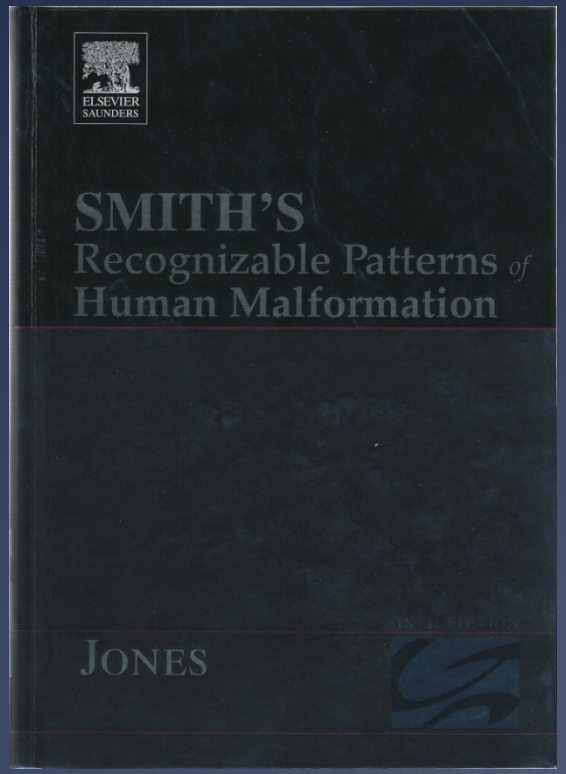
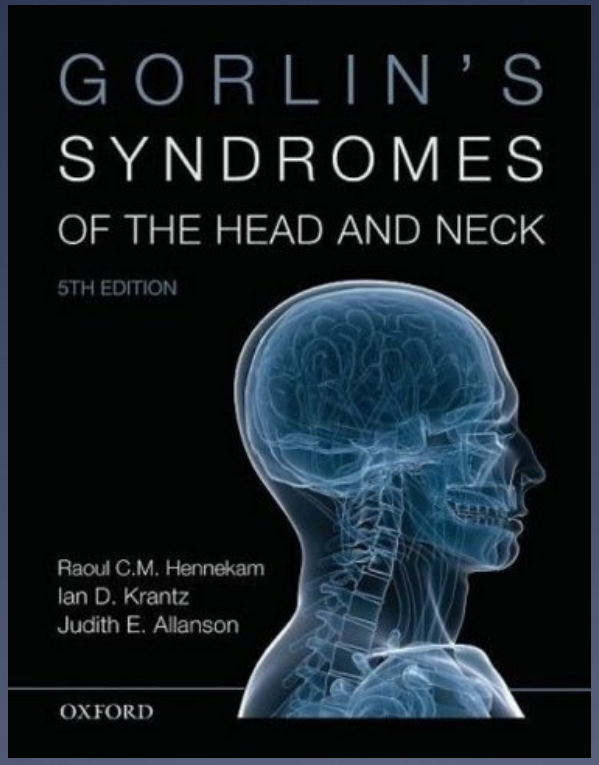
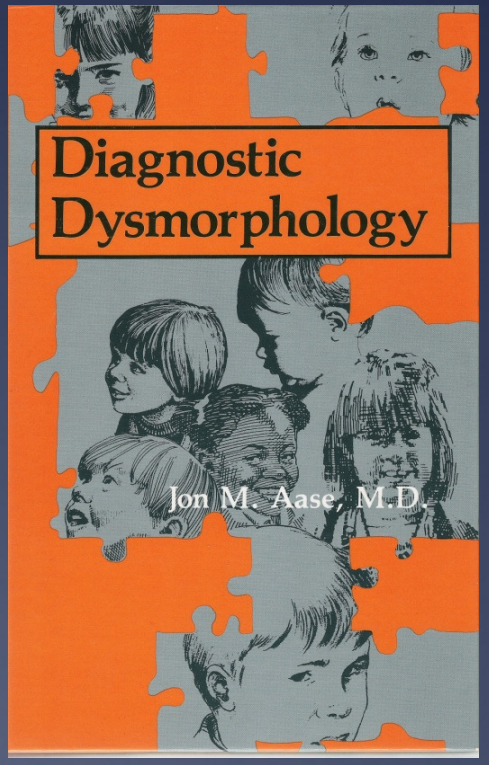
A Discussion Group on Fetal Malformations
in Laboratory Animals, Japan

Dysmorphology textbooks

1) Smith'S Recognizable Patterns of Human Malformation (6th Ed): Kenneth L. Jones
2) Syndromes of the Head and Neck (5th Ed): Raoul C. M. Hennekam, Ian D. Krantz, Judith E. Allanson
3) Diagnostic Dysmorphology: Jon M. Aase

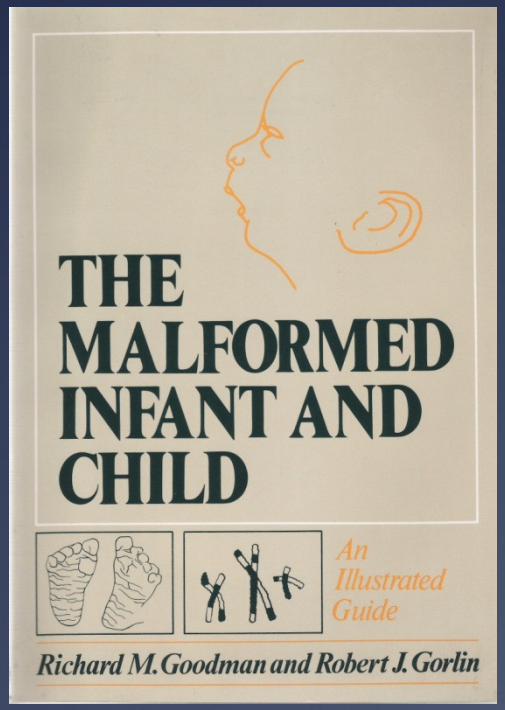


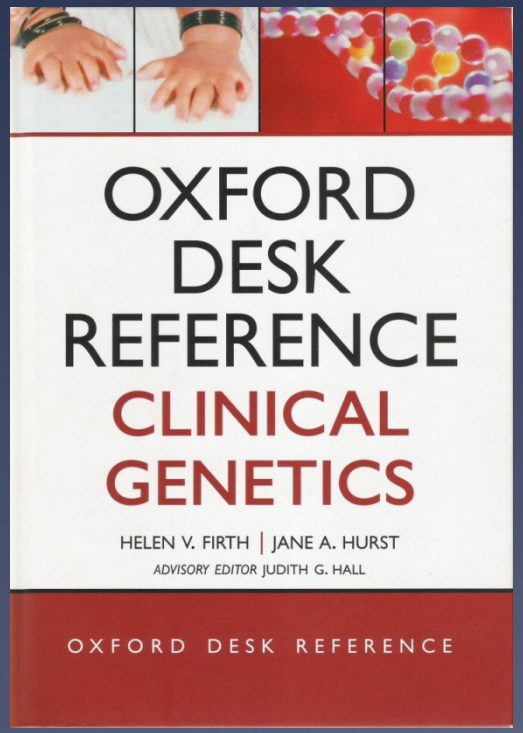


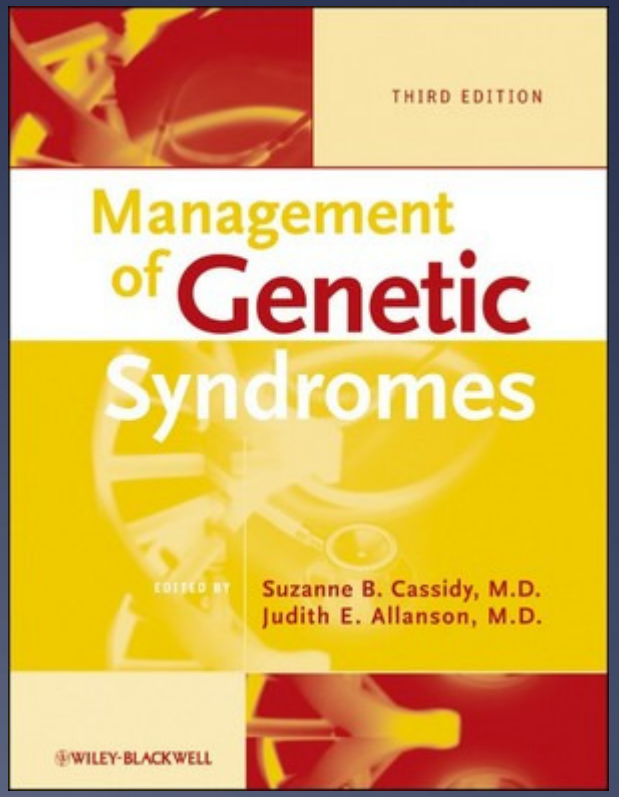


Dysmorphology textbooks

4) The Malformed Infant and Child: Richard M. Goodman, Robert J. Gorlin
5) Oxford Desk Reference: Clinical Genetics: Helen V. Firth, Jane A. Hurst
6) Management of Genetic Syndromes (3rd Ed): Suzanne B. Cassidy, Judith E. Allanson

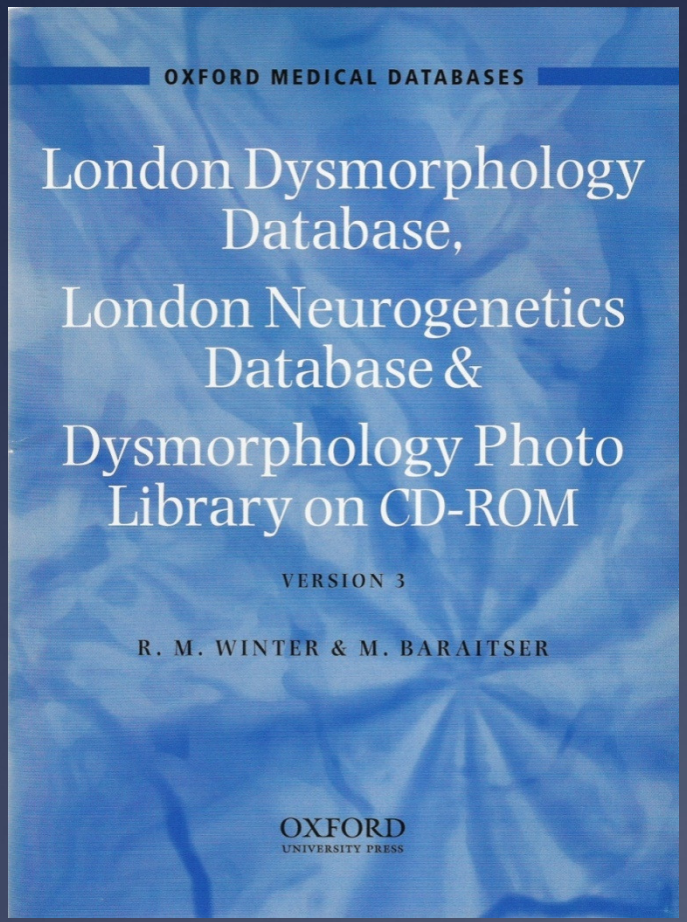


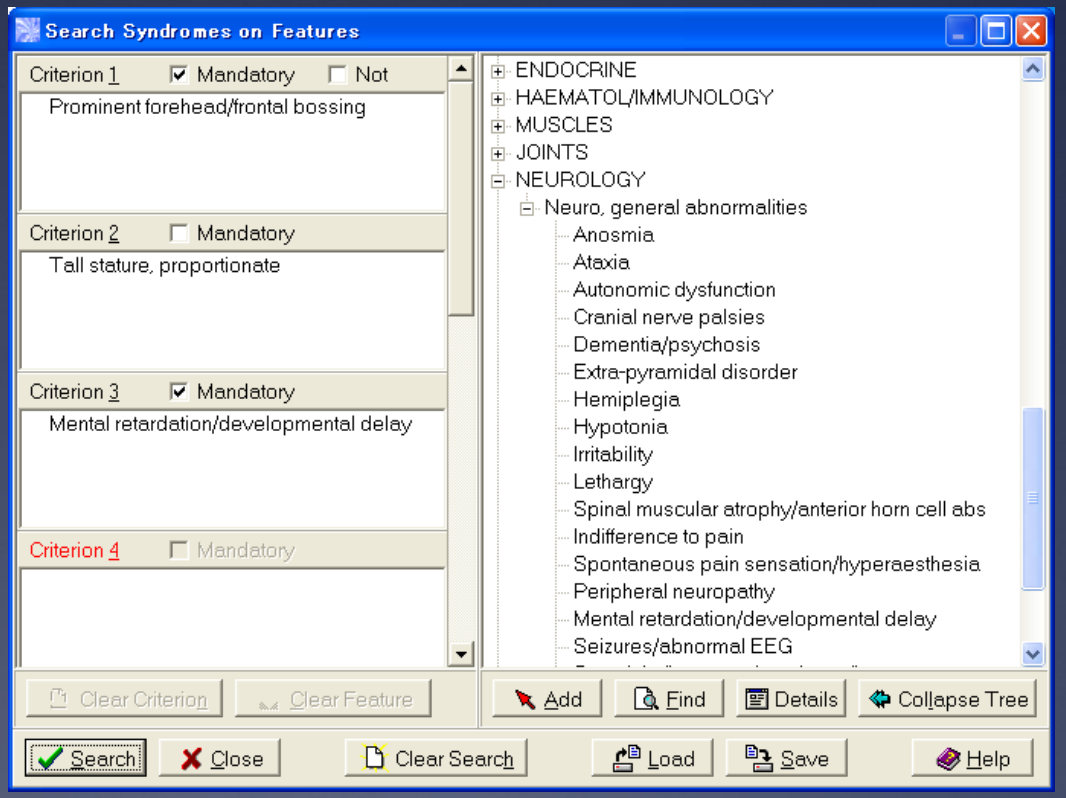




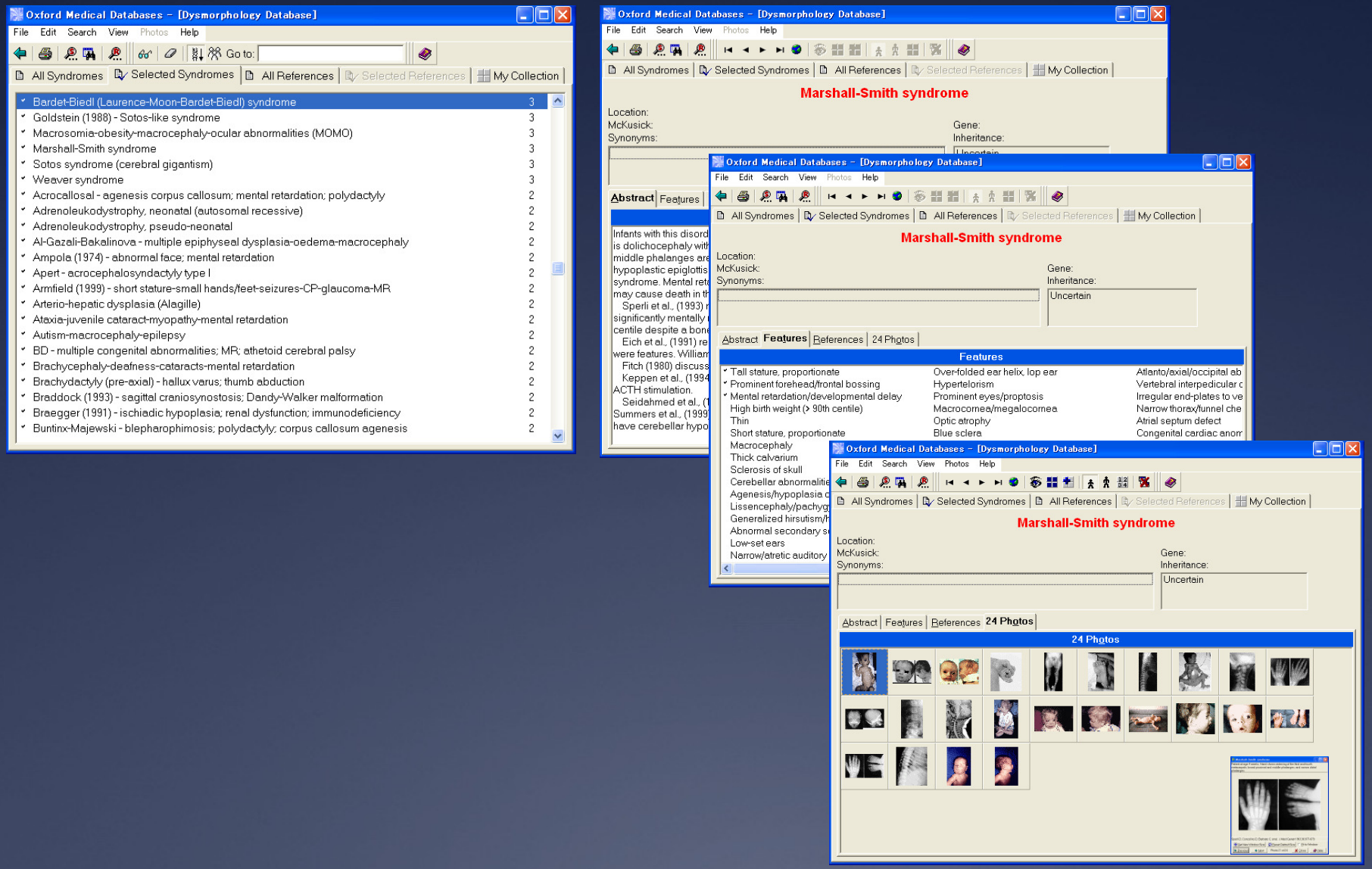
Dysmorphology databases

London Dysmorphology Database, London Neurogenetics Database & Dysmorphology Photo Library on CD-ROM: Oxford University Press 2001





London Dysmorphology Database

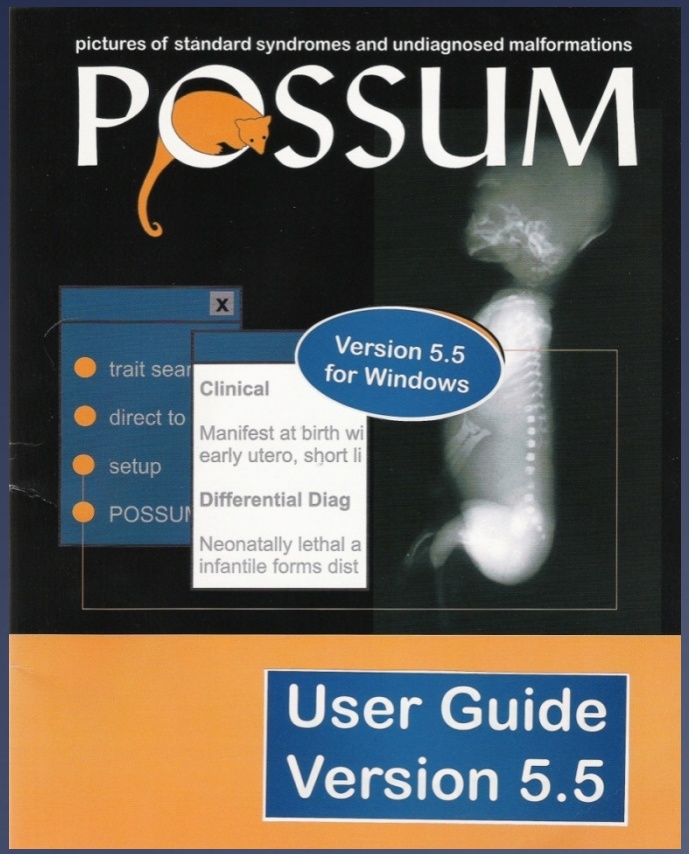


Dysmorphology databases

Possum

(Pictures of Standard Syndromes and Undiagnosed Malformations)

The Murdoch Institute and the Telemedia Software Labs, 2002



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Pictures of Standard Syndromes and Undiagnosed Malformations

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Hironao NUMABE

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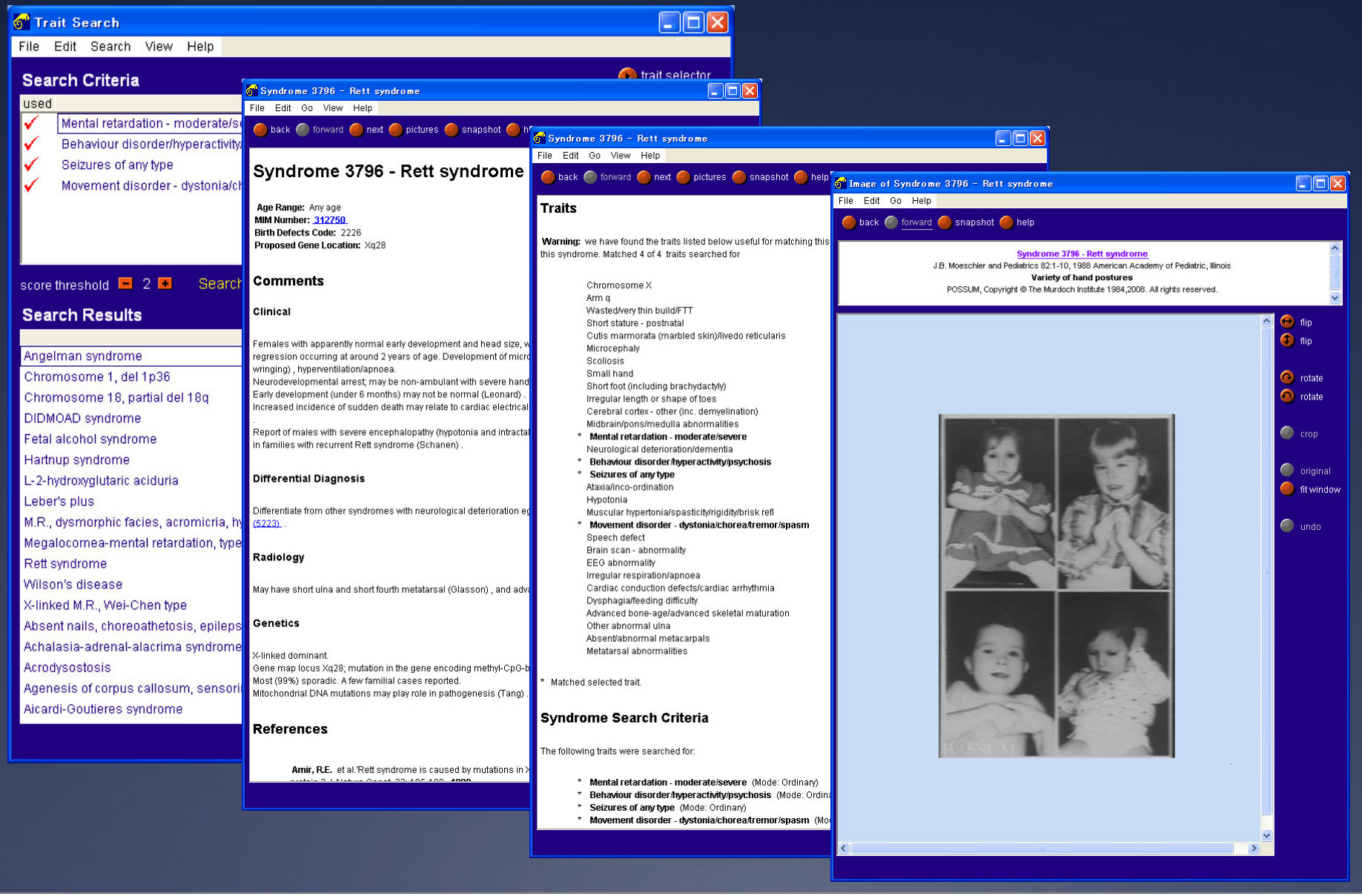
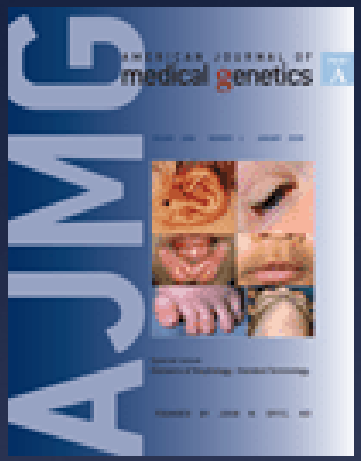

Trait Search
File Edit Search View Help
Search Criteria
used
Mental retardation - moderate/s
Behaviour disorder/hyperactivity
Seizures of any type
Movement disorder - dystonia/c
trait selector
score threshold 2
Search
Search Results
Angelman syndrome
Chromosome 1, del 1p36
Chromosome 18, partial del 18q
DIDMOAD syndrome
Fetal alcohol syndrome
Hartnup syndrome
L-2-hydroxyglutaric aciduria
Leber's plus
M.R., dysmorphic facies, acromicria, hy
Megalocornea-mental retardation, type
Rett syndrome
Wilson's disease
X-linked M.R., Wei-Chen type
Absent nails, choreoathetosis, epileps
Achalasia-adrenal-alacrima syndrome
Acrodysostosis
Agenesis of corpus callosum, sensori
Aicardi-Goutieres syndrome
Syndrome 3796 - Rett syndrome
File Edit Go View Help
back forward next pictures snapshot
Syndrome 3796 - Rett syndrome
Age Range: Any age
MIM Number: 312750
Birth Defects Code: 2226
Proposed Gene Location: Xq28
Comments
Clinical
Females with apparently normal early development and head size,
regression occurring at around 2 years of age. Development of micr
wringing) , hyperventilation/apnoea.
Neurodevelopmental arrest; may be non-ambulant with severe hand
Early development (under 6 months) may not be normal (Leonard) .
Increased incidence of sudden death may relate to cardiac electrical
.
Report of males with severe encephalopathy (hypotonia and intracta
in families with recurrent Rett syndrome (Schanen) .
Differential Diagnosis
Differentiate from other syndromes with neurological deterioration eg
(5223) .
Radiology
May have short ulna and short fourth metatarsal (Glasson) , and adv
Genetics
X-linked dominant.
Gene map locus Xq28; mutation in the gene encoding methyl-CpG-b
Most (99%) sporadic. A few familial cases reported.
Mitochondrial DNA mutations may play role in pathogenesis (Tang) .
References
Amir, R.E. et al.'Rett syndrome is caused by mutations in
Syndrome 3796 - Rett syndrome
File Edit Go View Help
back forward next pictures snapshot help
Traits
Warning: we have found the traits listed below useful for matching this
this syndrome. Matched 4 of 4 traits searched for
Chromosome X
Arm q
Wasted/very thin build/FTT
Short stature - postnatal
Cutis marmorata (marbled skin)/livedo reticularis
Microcephaly
Scoliosis
Small hand
Short foot (including brachydactyly)
Irregular length or shape of toes
Cerebral cortex - other (inc. demyelination)
Midbrain/pons/medulla abnormalities
* Mental retardation - moderate/severe
Neurological deterioration/dementia
* Behaviour disorder/hyperactivity/psychosis
* Seizures of any type
Ataxia/inco-ordination
Hypotonia
Muscular hypertonia/spasticity/rigidity/brisk refl
* Movement disorder - dystonia/chorea/tremor/spasm
Speech defect
Brain scan - abnormality
EEG abnormality
Irregular respiration/apnoea
Cardiac conduction defects/cardiac arrhythmia
Dysphagia/feeding difficulty
Advanced bone-age/advanced skeletal maturation
Other abnormal ulna
Absent/abnormal metacarpals
Metatarsal abnormalities
* Matched selected trait.
Syndrome Search Criteria
The following traits were searched for:
* Mental retardation - moderate/severe (Mode: Ordinary)
* Behaviour disorder/hyperactivity/psychosis (Mode: Ordina
* Seizures of any type (Mode: Ordinary)
* Movement disorder - dystonia/chorea/tremor/spasm (Mo
Image of Syndrome 3796 - Rett syndrome
File Edit Go Help
back forward snapshot help
Syndrome 3796 - Rett syndrome
J.B. Moeschler and Pediatrics 82:1-10, 1988 American Academy of Pediatric, Illinois
Variety of hand postures
POSSUM, Copyright © The Murdoch Institute 1984,2008. All rights reserved.
flip
flip
rotate
rotate
crop
original
fit window
undo



American Journal of Medical Genetics
Volume 149A, Issue 1, Pages 1–127, 2009

Special Issue:
Elements of Morphology: Standard Terminology

- Head and Face
- Periorbital region
- Ear
- Nose nad philtrum
- Lips, mouth and oral region
- Hands and feet

- Over 3,000 agents have been shown to have embryotoxic/teratogenic effects in one or more animal species.

- Only a limited number of agents are embryotoxic/teratogenic in humans.

- Many human teratogens were suspected by clinicians when they observed a small number of patients with birth defects

↓

How accurately can preclinical animal studies predict the embryotoxic/teratogenic risk in humans?

Causes of species difference in teratogenesis

1) Phylogenetic difference in reproduction and pregnancy

2) Different susceptibility of embryonic tissues to the exogenous agent

3) Species difference in pharmacokinetics in the mother-placenta-embryo complex

Absorption, tissue distribution, metabolism and excretion

4) Conditions of exposure

Timing of exposure

Dose of exposure

Comparison of pharmacokinetics between the human and laboratory animals*

	Similarity to the human in terms of metabolic pattern			
Species	Good	Fair	Poor	Invalid
Rat	29%	12%	20%	42%
Dog, Rabbit Guinea pig	32%	27%	9%	32%
Rhesus monkey	73%	19%	4%	4%

* Nau (1986)

Teratogenicity of major human teratogens in laboratory animals

Teratogenic agent	Major anomalies induced in humans	Species					
		Mouse	Rat	Giunea pig	Hamster	Rabbit	Nonhumana primate
Ethanol	Craniofacial anomalies, cardiovascular defects	++	+	+		+	++
Aminopterin	Skeletal defects	+	++			-	-
Androgenic hormones	Masculinization in female babies	++	++	++	++	++	++
Coumarin	Nasal dysplasia, skeletal anomalies	-	-			-	
Diethylstilbestrol	Uterine malformations	++	++		-	-	+
Methyl mercury	Microcephaly, neurological disorders	++	++		+	-	+
Streptomycin	Inner ear anomalies	-	++	-		-	
*							
Valproic acid	Neural tube defects, raniofacial anomalies	++	+	+	+	+	+
Thalidomide	Limb reduction defects	+	+	-	+	++	++

-: Not teratogenic; +: Teratogenic; ++: Induces similar anomalies as in humans.

Proof of teratogenesis*

1. Majority of epidemiological studies demonstrate an increased incidence of a particular group of malformations in exposed populations.

2. The incidence of patients prenatally exposed to the agent is significantly higher in the population having the particular group of malformations.

3. An animal model is developed which mimics the human situation.

4. The embryotoxic effects are dose-related.

5. The critical period and mechanism of teratogenesis are biologically plausible.

* Modified after Shepard.

For better assessment of embryotoxicity/teratogenicity of exogenous agents

- Well-designed laboratory studies
- Detailed, careful observation
- Description of observed results
- Proper data analysis

- Data interpretation and extrapolation to the human
- Assessment of human risk

- *Knowledge on normal and abnormal development*
- *Data on pharmacokinetics*