

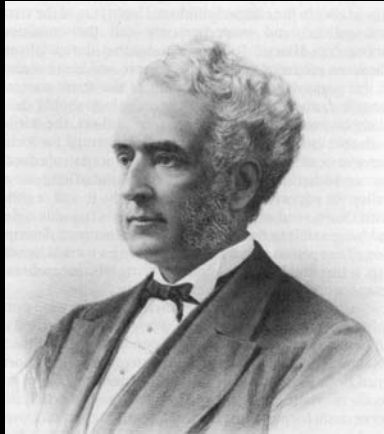
# *Developmental and Medical Aspects of Down Syndrome*

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## Down Syndrome

- Trisomy 21 (3<sup>rd</sup> copy of chromosome 21)
- 350,000 people living with DS in USA, and about 100,000 under age 18.
- Questions:
  - What do we know about Down syndrome?
  - What don't we know?
  - How are we doing with providing healthcare to people with DS?

## Dr. John Langdon Down



- Superintendent of Earlswood Asylum for Idiots, Surrey (1858-68)
- “Ethnic” classification of congenital idiocy: Mongolism
- Distinguished from cretinism (hypothyroidism)
- “Down Syndrome” since 1961

## Down Syndrome

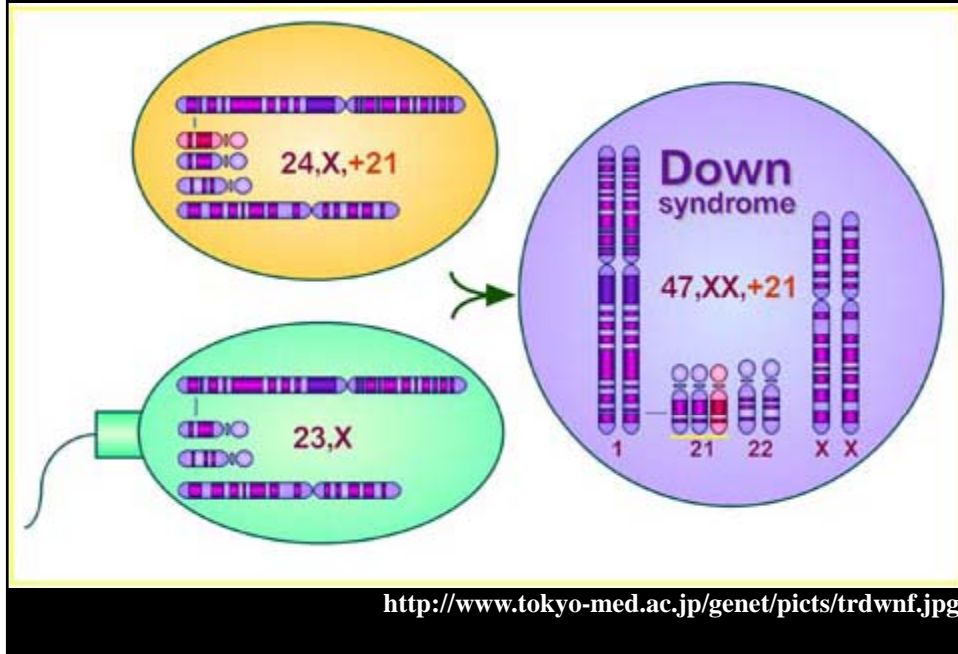
- **Genetics**
- Physical Findings and Systems Involved
- Natural History: Neurodevelopment and Neurodegeneration
- Cognitive Profile
- Brain Findings
- Imaging Findings
- Where from Here?



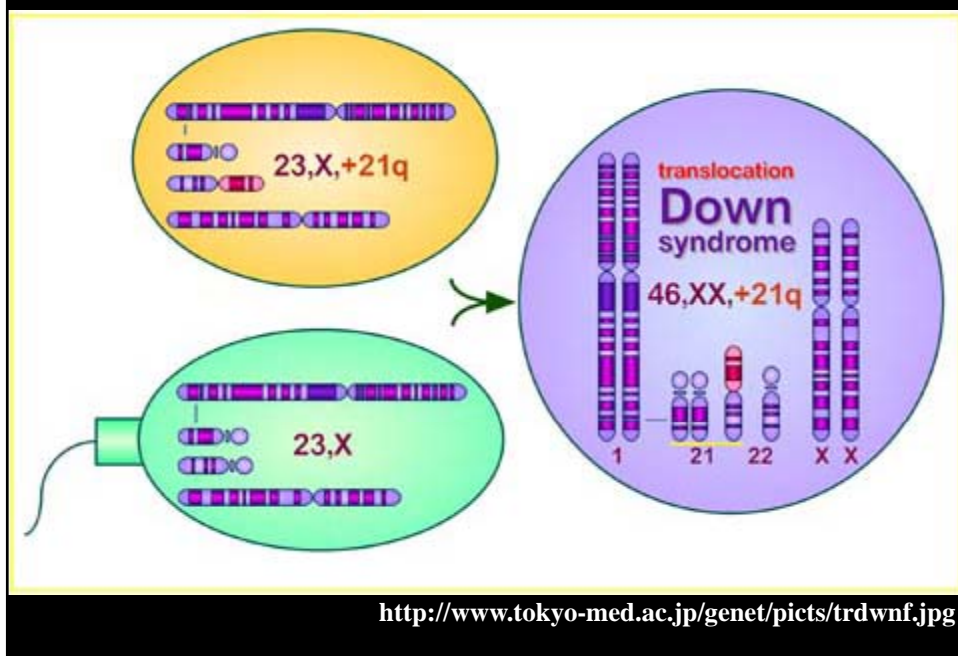
## DS is caused by trisomy 21\*

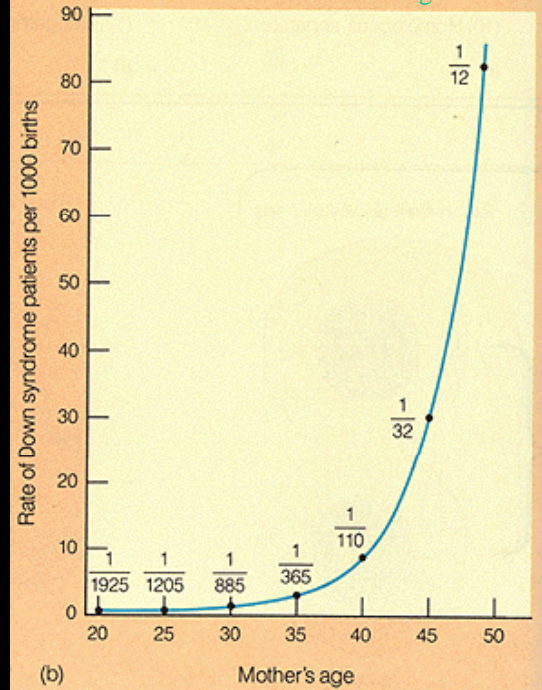
- 95% of DS cases due to full trisomy 21
  - 2-3% translocation
  - 1-2% mosaicism
- **Most commonly maternal non-disjunction in meiosis**
- Overall incidence 1:733
- **Risk increases dramatically with maternal age**
- \*Jerome Lejeune in 1959

### Full Trisomy 21: Fertilization



### Translocation Trisomy 21





## Prenatal testing

- Genetic Counselor is critical in interpreting!
- Ultrasound (11-13 weeks): Increased nuchal fold thickness/translucency (part of 1<sup>st</sup> trimester screen)
- Prenatal maternal serum screens
  - Often tested in pregnant women over 35, now recommended by ACOG for all pregnant women; indicate relative risks as multiples of median (MoM); actual karyotype only by CVS or amniocentesis (or karyotype after birth)
  - ACOG rec controversial in the DS community
  - Increased risk of DS if
    - 1<sup>st</sup> tri (9-13 wk): Elevated beta-hCG level, decreased PAPP-A
    - 2<sup>nd</sup> tri (15-18 wk): Elevated beta-hCG level, Inhibin-A; Decreased AFP, estriol.
    - Often integrated/sequential screening used as improve predictive accuracy
  - For more details, see <http://www.ds-health.com/prenatal.htm>

## Down Syndrome

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## Diagnostic Physical Features

- **HEAD & FACE:** Flat facial profile, protruding tongue, Brachycephaly & Flat Occiput; Extra neck skin
- **EYES:** Upslanting palpebral fissures, epicanthal folds, Brushfield spots (speckled irises)
- **EARS:** Small, low-set
- **HANDS & FEET:** Single palmar creases (in half, plus 4% of genl pop), wide spaced great toes, unique dermatoglyphics
- **LIMBS:** Hyperflexible joints
- **EXAM FINDINGS:** Hypotonia, Poor Moro

## Diagnostic Physical Features in Newborns with DS

- Flat facial profile 90%
- Poor Moro reflex 85%
- Hypotonia 80%
- Hyperflexible joints 80%
- Excessive neck skin 80%
- Slanted palpebral fissures 80%
- Pelvic dysplasia 70%
- Anomalous auricles 60%
- Dysplastic midphalanx 5<sup>th</sup> digit 60%
- Single palmar crease 45%

## Diagnostic Physical Features in Down Syndrome

- Newborns with 4 or more features  
100%
- Newborns with 6 or more features  
90%

# Systems Affected in Down Syndrome

## NEUROLOGIC (100%)

- **Developmental delays, mental retardation**
- **Seizures:**
  - Infantile spasms (3-5% vs 1 in 4,000...so about 1 of 5 IS has DS)
  - Often easy to treat, relatively good outcome, URGENT referral (\*? Less epilepsy and autism if treated early?)
  - Febrile sz in 5% (vs 3%)
  - Seizures otherwise about 10% (vs 1-2), peak in infancy and again in those with AD.
- **Hypotonia, motor delays**
- Autism in 5-9%
- **Alzheimer-type dementia**
  - 50% by age 50 clinically
  - 100% neuropathologically

\*Eisermann, 2003

## Psychiatric

- Increased incidence of:
  - Depression, sleep disturbances (OSA)
  - Anxiety, ADHD, OCD
  - Autism
  - Dementia
- **Very much under-recognized**
- Consider underlying medical problems (Hypothyroidism)

## Other systems affected in DS

- Cardiac (50%)
- GI (10%)
- Ophthalmologic strabismus, nystagmus, cataracts
- Endo hypothyroidism
- Heme/Onc leukemia, testicular cancer
- ID otitis, URI's
- Audiologic
- Pulmonary/Sleep OSA in at least half
- Orthopedic C1-2 instability (+ knees & hips)

## Cardiac

- 50% with congenital heart defects
- AV canal defects most common (60%)
- Isolated ASD, VSD, PDA (30%)
- Tetralogy of Fallot (7%)
- *Rapid resp, feeding diff, fatigue, congestive heart failure*

## GI

- GI malformations in 12%
- Duodenal atresia/stenosis
- Pyloric stenosis
- Hirschprung's

## Ophthalmologic

- Cataracts in 1-2%
- Nystagmus
- Strabismus
- *Note pseudo-strabismus very common due to epicanthal folds*
- *Poor visual acuity*

## Endocrine

- Short stature
- Microcephaly
  - **USE THE RIGHT CHARTS!**
- Hypothyroidism

## Heme/Onc

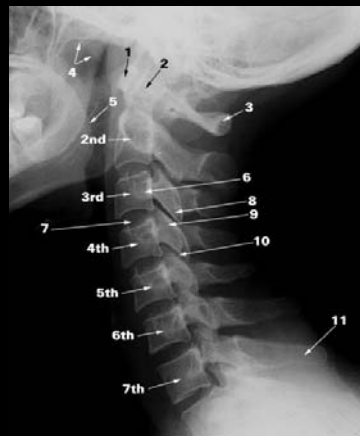
- 10-20 x risk of leukemia in childhood
- Testicular cancer: 5 to 50x risk!
- Less than genl population other types of cancer

## ENT

- Ear Infections
- PE Tubes
- Resp Infections
- **Obstructive Sleep Apnea in 50%**

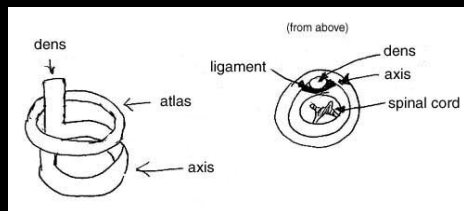
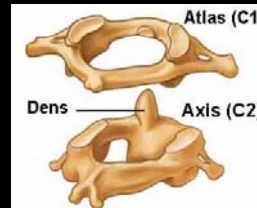
## Orthopedic/Sports Participation

- Atlanto-axial instability common (20%), usually asymptomatic
- **Screening for Special Olympics, etc.**
- Controversial if predicts symptomatic (BUT SCREEN ANYWAY)
- **Ligamentous laxity (also hips, knees)**



## Orthopedic/Sports Participation

- Atlanto-dens interval:  
normal < 3-5 mm
- **Neural canal width:**  
normal > 14 mm
- 1-2% with symptomatic  
AAI or AAS  
(instability/subluxation)
- **Sx: Neck pain, abnl gait,  
weakness, bowel/bladder  
probs**
- Tx: Fusion of C1 and C2



## Healthcare for children with DS

- How are we doing at providing healthcare  
for people with DS?
- Are we meeting familys' needs?
- What strategies are used to assure good  
health maintenance?

## National Survey on Children's Health\* 2005-2006

0-17 years of age

40,000 children with special healthcare needs (SHCN)

**400 with Down syndrome**

Represents 10.2 million kids with special healthcare needs, and

**100,000 with DS**

\*CDC, Natl Center for Health Statistics

## National Survey on Children's Health 2005-2006

	SHCN	DS
4 or more health conditions	11%	42%
Family cut back/stopped work	23.5%	55%
Family provides > 11 hrs/week providing healthcare	9.5%	30%
Financial problems due to child's health needs	18%	36%
One or more unmet health service needs	16%	38%
Have family-centered care	66%	55%

## DS Healthcare Guidelines Stages

- Infancy
- **Childhood**
- Adolescence
- **Adulthood**

<http://www.ds-health.com>

## DS Healthcare Guidelines

- Infancy
  - Karyotype & counseling, cardiac eval + echo, audiology, thyroid screen, monitor growth and development (DS-specific charts); red reflex
- **Childhood**
  - Annual checks of thyroid, hearing, vision
  - C-spine films at 3 and 12 years (ADI and neural canal width)
  - Dental at age 3 then twice yearly

## DS Healthcare Guidelines

- Adolescence
  - Annual: Thyroid
  - Q 2-3 yrs: Hearing, Vision
  - Dental twice yearly, twice daily brushing
  - Regular exercise program & weight
  - Sleep/snoring?
- Adulthood
  - Above + females: gyn exams after puberty
  - C-spine xrays age 18, 30, 40...
  - Mental health/dementia + routine adult care

## Adults with Down Syndrome

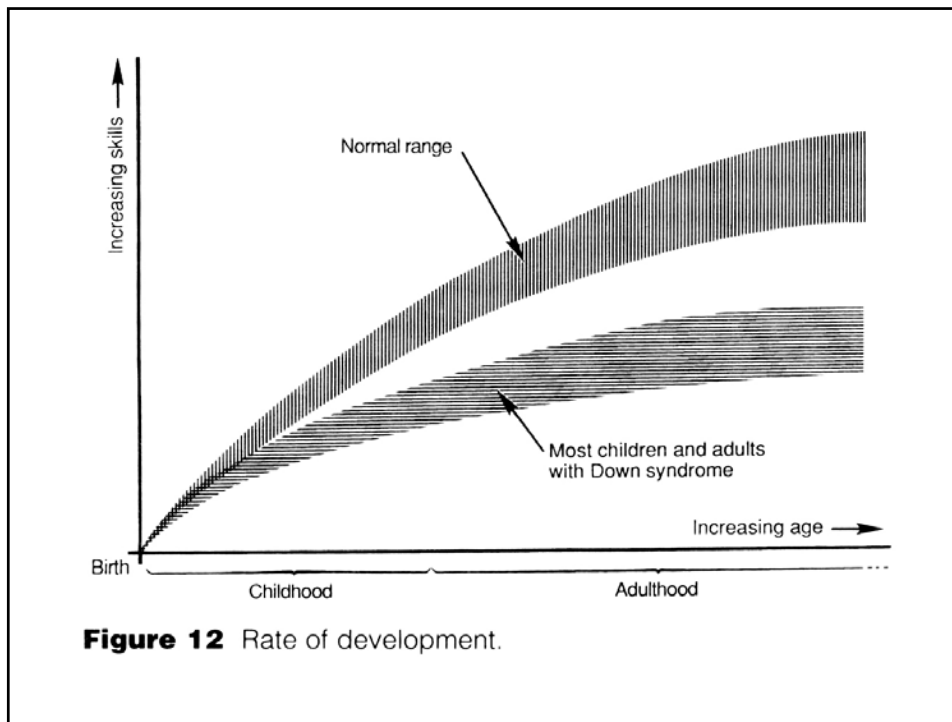
- Be Aware of Medical Problems
  - Thyroid
  - Neck problems (AAI)
  - Psychosocial Issues
  - Psychiatric Issues: Depression
  - Dementia: Early-onset Alzheimer's

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## **DS: Neurodevelopment**

- Later acquisition of most milestones
- **Language is especially affected (syntax, articulation)**
- Memory deficits
- **Relatively strong visuospatial skills**



## Down Syndrome

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## **Down Syndrome Cognitive Profile**

- Developmental Delays
- **Memory deficits (short and long-term)**
- Language deficits (especially syntax and articulation) out of proportion to IQ
- **Poor set-switching, perseveration**
- Attention Problems
- **Relative strength in visuospatial skills**

## **DS: Cognitive Profile**

- *Forest vs Trees* cognitive profile
- **Global > Local**
- Key studies have compared DS with Williams Syndrome, with an almost opposite pattern of language & spatial skills

## Cognitive Deficits Across the Lifespan

- Language & memory problems; variable degrees of impairment
- **Known: All develop AD neuropathology by their 40's (probably 20's)**
  - Amyloid plaques
  - Basal forebrain cholinergic atrophy
- About 50% by age 50 (also = median) with clinical dementia (? 100% by age 70\*): need evaluate adults with DS regularly for signs of dementia --cholinesterase inhibitors (Aricept = Donepezil) improve dementia as well as language in non-demented DS

Kishnani, 1999; Heller 2003

\*25-30% in 55-60's in Netherlands

Coppus et al, 2006

## Down Syndrome

- Genetics
- Physical Findings and Systems Involved
- Natural History: Neurodevelopment and Neurodegeneration
- Cognitive Profile
- **Brain Findings**
- Imaging Findings
- Where from Here?

## Neuropathology in Adults with DS

- Mostly based on autopsies
- **GROSS:**
  - Very small overall, brachiocephalic
  - Cerebellum, frontal lobes esp small
  - Superior temporal gyrus very narrow
- Senile plaques and neuritic tangles identical to those in Alzheimer Disease
- **Basal forebrain cholinergic degeneration**

## Cognitive Deficits Across the Lifespan

- Unknowns:
  - Why do some NOT become clinically demented early?
  - What are the neuroanatomical bases for the cognitive deficits seen at any point in DS?
  - Are plaques important in DS?
  - Or is it the cholinergic (?NGF) deficit?
  - Is DS important to AD research?

## Dementia in DS

### Special Considerations

- **Depression can result in pseudodementia**, a progressive deterioration of function that is reversible with proper treatment.
  - Symptoms of depression frequently are present in the early stages of AD.
  - The use of antidepressants at this stage may result in some temporary improvement; however, it does not change the ultimate prognosis of the disease.
- **Hypothyroidism**, observed in almost 30% of individuals with DS, may simulate dementia.
  - Hypothyroidism frequently is present in people with DS and AD; however, treatment with hormone replacement does not change the course of the underlying disease.

## Neuropathology in Babies with DS

- Mostly based on autopsies
- **Normal volumes first 2 trimesters**
- Small from birth on
- **Very small: cerebellum, frontal lobes, superior temporal gyrus very narrow**
- Histologic studies reveal fewer, less dense neurons in layers 2, 4 (interneuronal zones)

## Down Syndrome

- Genetics
- Physical Findings and Systems Involved
- Natural History: Neurodevelopment and Neurodegeneration
- Cognitive Profile
- Brain Findings
- **Imaging Findings**
- Where from Here?

## Volumetric MRI in Down Syndrome

- Overall decreased brain volume (18% smaller), with disproportionate reduction of cerebellar and hippocampal volumes  
*(both important in language and memory)*
- Relatively preserved parietal gray matter  
*(preserved visuospatial abilities)*
- “Enlarged” subcortical gray matter volumes (no difference in uncorrected volumes)  
*(consistent with 3<sup>rd</sup> trimester onset of structural differences)*

## Down Syndrome

- Genetics
- Physical Findings and Systems Involved
- Natural History: Neurodevelopment and Neurodegeneration
- Cognitive Profiles
- Brain Findings
- Imaging Findings
- **Where from Here?**

## Genetics in DS (Not just prenatal anymore)

- Genomic/Gene Expression Studies (RNA) have potential for biomarkers for specific problems within DS
- **Not all genes expressed at 1.5 x normal on chromosome 21 (copy number variation (CNV) may account for some of variability**
- Not all genes on other chromosomes normally expressed
- **DS with heart disease: extra-21 cardiac genes overexpressed**

## From Trisomy 21 to Cognitive Deficits

- Brain Imaging Studies
  - fMRI
  - Diffusion Tensor Imaging
- Genetic/Genomic Studies
  - Copy number variation (not exactly 150% of chromosome 21 gene dosage)
  - Gene expression (RNA expression)
  - Looking beyond Chromosome 21
- Clinical Studies correlating behavior/development/mental retardation with MRI or genetic variation
- Animal Studies
  - Ts65Dn mouse and other models

*COLLABORATIVE RESEARCH WILL BE CRITICAL!*

## The future of DS treatments

- AD-based treatments (cholinergic, beta amyloid modifiers)
- Intensive education/training programs
- Gene therapy (NGF, APP, other targets)
- Individualized gene-profile-targeted Rx
- Prenatal therapy: with diagnosis in 1<sup>st</sup> trimester could affect course of later fetal brain development
- Is there a “folate” for the DS brain?

## DS research at OHSU

- Clinical Research
  - Cognitive Testing Development (*Maslen*)
  - Cardiovascular Genetic Studies (*Maslen*)
  - National Survey of Children's Health/CAHMI (*Child & Adolescent Health Measurement Initiative – Bethell, Read, Krahn, Phelps, Pinter*)
  - DS fitness intervention program (*Necia Davis, PT*)
  - Diffusion Tensor Imaging (*Pinter, with Hopkins/KKI*)
  - Functional MRI (*Pinter*)
  - Gene expression in aging in DS (*Pinter, with UCD*)

## DS Clinic at OHSU

- CDRC Multidisciplinary Clinic for Down syndrome
  - *Pediatric Neurology*
  - *Speech Therapy (Candace Ganz)*
  - *Physical Therapy (Necia Davis)*
  - *Occupational Therapy (Margaret Wolfe)*
- Referrals accepted from babies to young adults
- Striving to work with and for Northwest families with members with Down Syndrome

## Resources: Internet

- <http://www.ndss.org/>
  - National Down Syndrome Society
- <http://www.nwdsa.org/>
  - Northwest (Portland area) DS Association
- <http://www.dsnor.org>
  - Down Syndrome Network Oregon
- <http://downsyndromeinfo.org/>
  - Down Syndrome Information Alliance (Sacramento area)
- <http://www.kennedykrieger.org/>
  - DS health guidelines and good links
- <http://www.ndscenter.org/>
  - National Down Syndrome Congress
- <http://www.ds-health.com/>
  - Excellent site by Dr. Len Leshin, parent of a child with DS and a pediatrician; critical reviews of articles and lots of links.
  - \*\*\*(<http://www.growthcharts.com/> For DS growth charts)

<http://www.karengaffneyfoundation.com>

En español: <http://www.downcantabria.com/>  
<http://www.downcantabria.com/articulos.htm>

Youtube.com, search Down Syndrome dreams

## Dr. Jerome Lejeune

- **Trisomy 21 as cause of DS (1959)**
- "Of course, they must be provided with a protected environment, a job within their abilities, and always limitless affection. But that applies to us all" (Prof. J. Lejeune).

<http://www.fondationlejeune.org/>