

Down syndrome

A mental retardation syndrome with specific characteristics

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Down syndrome

- Trisomy of chromosome 21
- Frequency: 1/700 – 1/1000
- Genetic forms
 - Classical: 95%
 - Non disjunction during meiosis
 - Extra chromosome mostly from maternal origin
 - Risk increasing with maternal age
 - Translocation: 3 – 4% (21;14 / 21;13 – 21;15 – 21;22)
 - Balanced translocation in parents (25%): hereditary
 - New mutation
 - Mosaicism: +/- 1%
 - Non disjunction during early embryonic mitosis
 - Duplication of a portion of chromosome 21: very rare



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Contents of the lecture

- Health problems in Down syndrome
- Developmental and behavioral aspects
- Gene overexpression
- Research ideas



General features

- Specific facial characteristics, short neck
- Sandal toe (50%)
- Single transverse palmar crease (40%)
- Hypotonia and joint hyperflexibility
- Delayed development, mental deficiency





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Affected organ systems

- Heart
- Nervous system
- Locomotoric system
- Eyes
- ENT
- Gastro-intestinal system
- Endocrine and reproductive system
- Teeth
- Blood
- Immunological system



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Heart

- Congenital heart disease: 40 – 50%
- Most frequent:
 - AVSD (45 – 50%)
 - VSD (28 – 35 %)
- Later in life
 - Mitral valve prolapse
 - Aortic regurgitation
 - Pulmonary hypertension



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Nervous system

- Delayed development and mental deficiency (mostly moderate)
- Hypotonia
- Epilepsy (8%)
- Autism, obsessive compulsive disorder: 5 – 7%
- Behavioral problems, ADHD: 8 %
- Precocious aging and early (Alzheimer) dementia



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Nervous system: brain

- Macroscopic examination
 - At birth no difference
 - Later: global volume loss
- Microscopic examination
 - Decrease of number of neurons and hypocellularity
 - Decrease of dendrites and synapses
- Neurochemistry
 - Cholinergic deficiency in adult brain
 - Scarce data on catecholaminic and serotonergic transmitters or GABA inhibition



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Locomotoric system

- Hyperflexibility of joints
- Connective tissue disease
- Dislocation of patella, hip
- Atlanto-axial instability (10-15 %)
- Skoliosis



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Endocrine and reproductive system

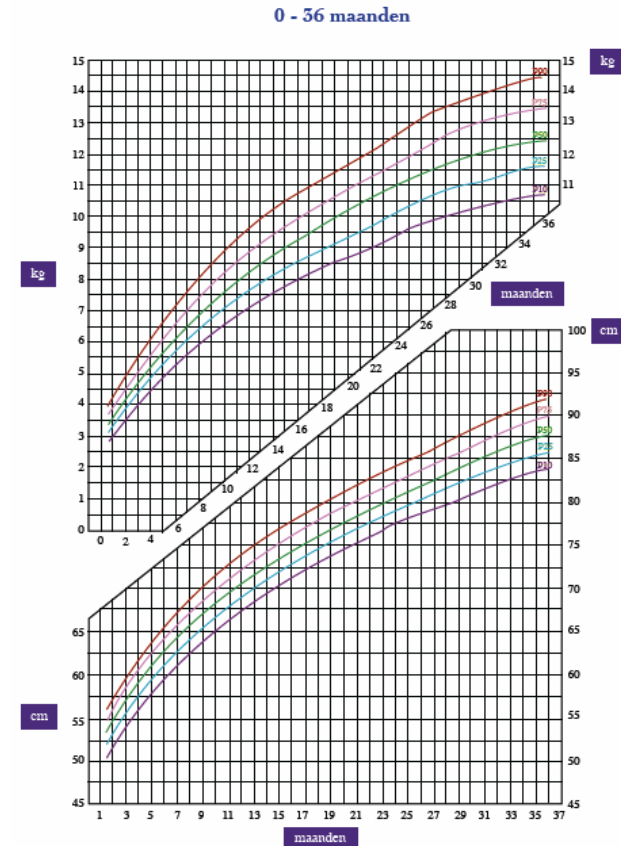
- Thyroid
 - Hypothyroidism: 10 – 20%
 - Subclinical
 - Auto – immune
 - Hyperthyroidism: not frequent
- Diabetes mellitus
 - 10 x more
 - Often in association with other auto – immune diseases (thyroid, celiac disease, alopecia, vitiligo)



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Endocrine and reproductive system

- Growth
 - Small stature
 - Often overweight
 - Specific growth charts
- Fertility
 - Girls: fertile
 - Boys: not fertile?





Eyes

- Congenital cataract
- Refractive disorders
 - Myopia: at 2 yrs: 33%, at 4 yrs 50%
 - Hypermetropia (>4 yrs)
- Infantile glaucoma
- Nystagmus (10%)
- Keratoconus (adolescence or later)
- Blepharitis, lacrimal obstruction



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ENT

- Hearing loss
 - 50% (mild, moderate, severe)
 - Conductive or perceptive
- OSAS
 - >60%; 60-85% hypoventilation
- Narrow auditory canal
- Recurrent upper airway infection, including acute otitis media



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Gastrointestinal system

- Congenital malformation
 - Duodenal atresia, esophageal atresia, anal atresia, etc.
- Hirschsprung's disease, constipation
- Celiac disease: 4 – 17%; 1/330 – 1/1000 (1/2000 in general population)
- Feeding difficulties



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Blood

- Prolonged neonatal jaundice
- Leukemia: 20 x more
 - Transient abnormal myelopoiesis
 - 10% of the neonates
 - Often spontaneous remission
 - 25% develops acute myeloid leukemia
 - Acute lymphoblastic leukemia
 - Generally better response to treatment and less relapses
- Diminished risk of solid tumors



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Immunological system

- Increased frequency of infections and auto-immune disease
- Intrinsically deficient immune system
 - Decreased NK cells
 - Decreased B lymphocytes
 - Decreased T helper lymphocytes
 - Decreased response to vaccines



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Teeth and mouth

- Delayed and abnormal development of teeth
 - Microdontia, malformed teeth
 - Congenitally missing teeth
 - Small and conical roots
- Increased risk of periodontal disease
- Maxillary hypoplasia
- Protruding tongue
- Bruxism



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Developmental and behavioral aspects

Problems with development of:

- Attention, state of alertness
- Initiative, enterprise
- Information processing and short term memory
 - Visual processing is superior to auditory
- Long term memory: difficulties in retrieval and expression
- Correlation and analysis, calculation, abstract thinking
- Expressive language



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Developmental and behavioral aspects

Behavioral problems: ~ 15%

- Obstinacy
- Stubbornness
- ADHD
- Aggressive behavior
- Autism, other psychopathology
- Anxiety disorder



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Developmental and behavioral aspects

- Mental retardation is globally mild to moderate
- Importance of early intervention
 - Enriched environment
 - Physiotherapy
 - Speech therapy
 - Integrated education
 - The less stimulation and educational difficulty, the more isolation and developmental retardation



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10-20 % improvement in cognitive capability





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Multidisciplinary approach: Down team



Leden Downteam

Algemene pediatrie	Dr. Marek Wojciechowski
Diëtiste	Nancy Pyck
Gynaecologie - prenatale diagnostiek	Dr. Paul Ramaekers
Kindercardiologie	Prof. dr. Bert Suys
Kinderendocrinologie	Prof. dr. Raoul Rooman
	Dr. Annick France
Kinderneurologie	Dr. Sandra Kenis
Kinderneurologie revalidatie	Prof. dr. Berten Ceulemans
Kinderpneumologie	Prof. dr. Kristine Desager
Kinesitherapie	Inge Laurent
Logopedie	Miek Claes
Medische Genetica	Prof. dr. Bettina Blaumeiser
	Dr. Martine Biervliet
Neus-Keel-Oorzakten/ revalidatie	Prof. dr. An Boudewyns
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Orthopedie	Dr. Kristof Fabry
Patiëntenbegeleiding	Mariska Waldukat
Psychologe	Saar Van Pottelberghe
Secretariaat	Iris Mallinus
Tandheelkunde (NKO)	Lth. Luc Bensch



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Multidisciplinary approach: Down team

Schema medisch onderzoek bij kinderen met Down syndroom									
	Geboorte	1 md	3 md	6 - 12 md	12 - 18 md	18 md - 2 jr	2 jr - 6 jr	6 jr - 18 jr	
Algemeen	algemeen klinisch onderzoek, biometrie, ontwikkeling, vaccinaties				jaarlijks algemeen klinisch onderzoek, of meer indien nodig biometrie, ontwikkeling				
Kinderneurologie									
Cardio	Indien klinische aanwijzing ECG, Echo		Klinisch, ECG Echo	In functie van kliniek en planning kindercardioloog Denk ook aan mitralisprolaps in adolescentie, pulmonale hypertensie bij OSAS					
NKO		ALGO	klinisch NKO en gehoor	klinisch NKO en gehoor	jaarlijks klinisch NKO en gehoor of meer indien nodig			klinisch NKO en gehoor jaarlijks	
					denk aan OSAS				
Oftalmo	congenitaal cataract			oftalmologisch onderzoek	jaarlijks oftalmologisch onderzoek			oftalmologisch onderzoek om de 2 jaar	
Gastro-intestinaal	congenitale afwijkingen	voeding, obstipatie			voeding, obstipatie		bloedname celiakie 3-4 jr		
Endo	TSH guthrie kaartje			TSH, T4 anti-TPO		Jaarlijks T4, TSH, anti-TPO			
					cave diabetes				
Voeding	Stimuleren borstvoeding								
			Logopedie Diëtist	mondmotoriek, communicatie Diëtist					
Ortopedie	heupdysplasie		patella luxatie			hyperlaxiteit			
					klinische evaluatie atlanto-axiale instabiliteit				
Fysio					evaluatie en stimulatie ontwikkeling				
Stomato					tanden om de 6 maanden				
Psycholoog Sociaal	bij eerste raadpleging en indien vraag, noodzaak, enz.								
Genetica	diagnostiek				oudergesprek				
Hemato	Bloedbeeld bij andere bloedfanames en zo nodig								
	Geboorte	1 md	3 md	6 - 12 md	12 - 18 md	18 md - 2 jr	2 jr - 6 jr	6 jr - 18 jr	



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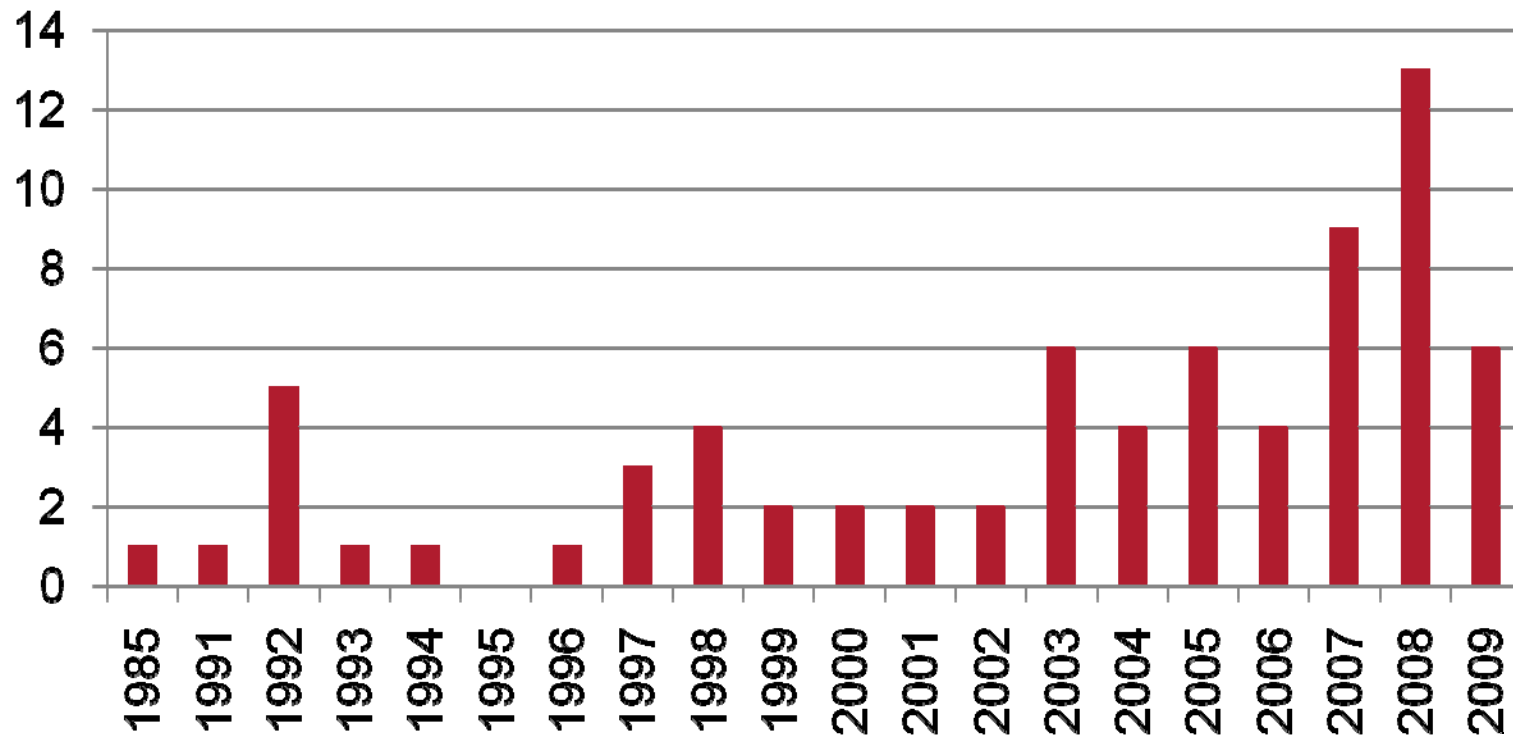




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Down team: 74 children

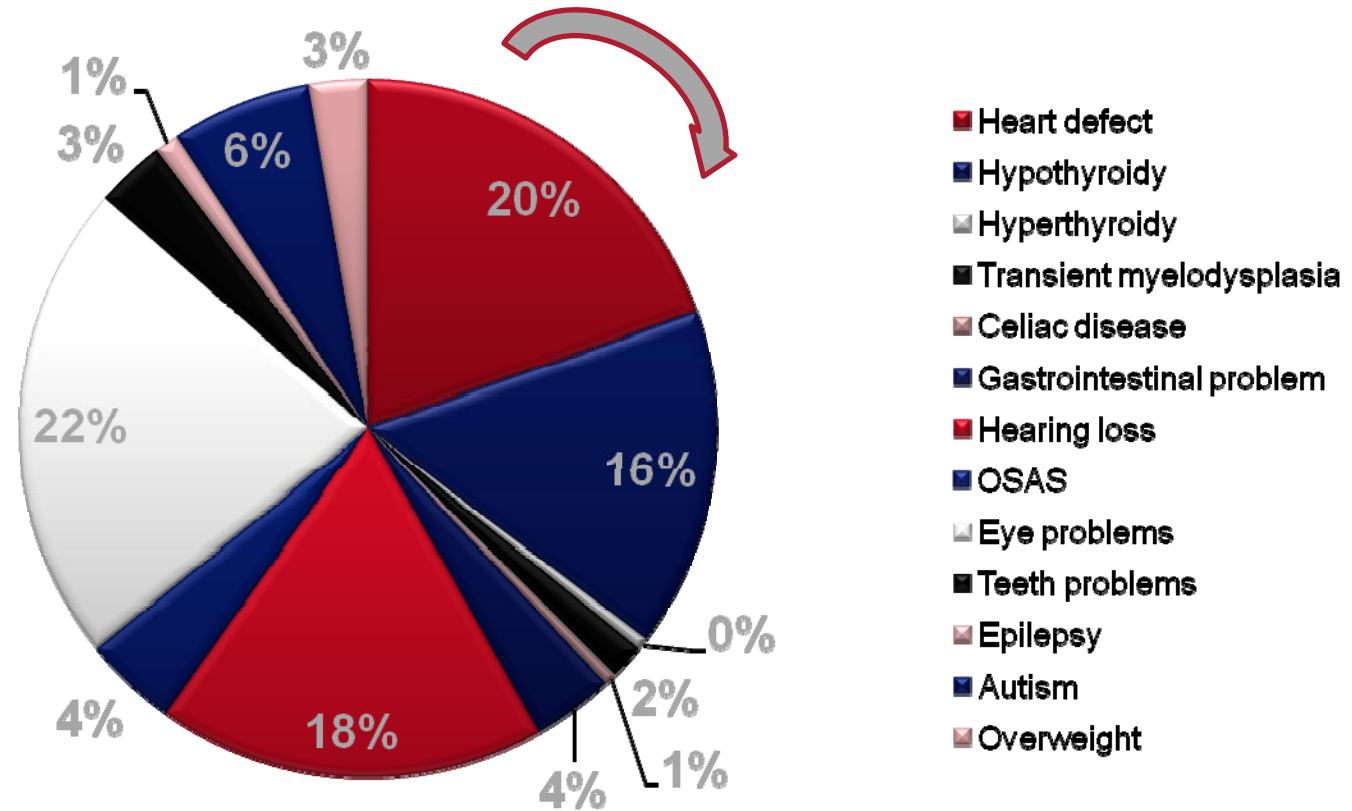
Year of birth





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Overexpression of normal genes

Gene – phenotype relationship:

- Gene dosage hypothesis: phenotype is related to elevated level of expression of certain genes
- Genetic homeostatic hypothesis: phenotype is related to expression of extra genes, regardless of function

Probably: combination of both hypotheses



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Overexpression of normal genes

Mean overexpression = 150 % but:

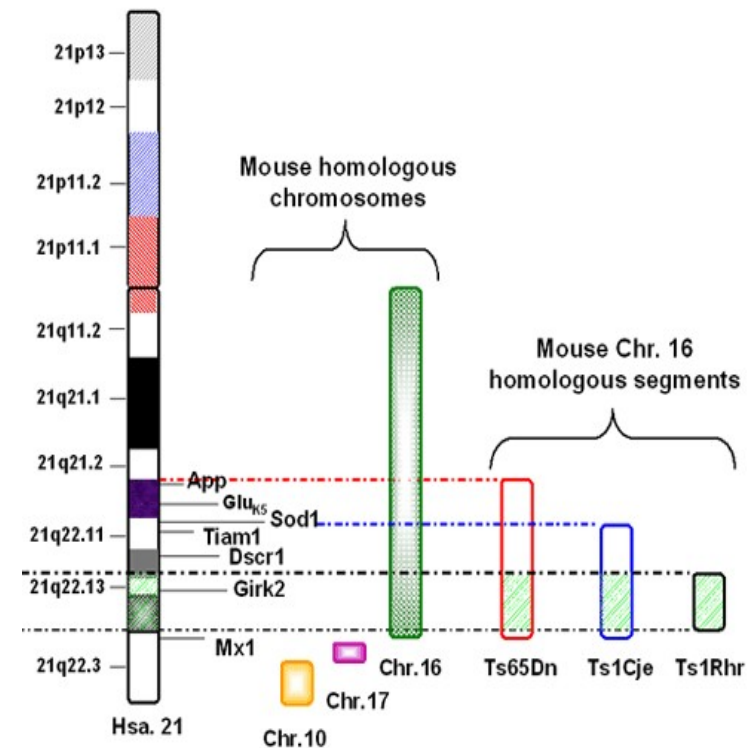
- Variability between genes
- Tissue specificity, e.g. GABPA in brain
- Age effect, e.g. expression of DYRK1A in adult brain but not in infants
- Environmental influence, e.g. possible effect of early stimulation on MAPK pathway (mitogen activated protein kinase) regulated synaptic plasticity



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Human chromosome 21 and orthologous mouse models

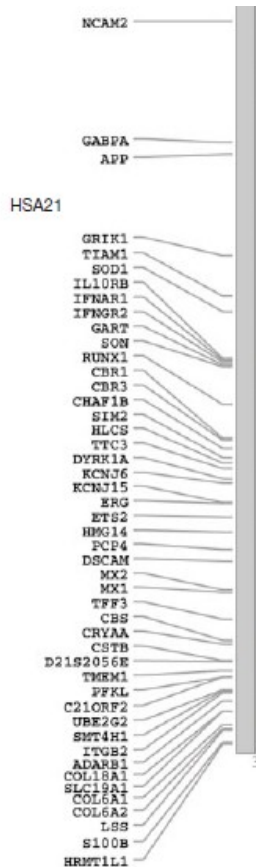
- Year 2000: sequence of long arm of human chromosome 21 ⁽¹⁾
- +/- 300 genes
 - 170 codifying proteins
 - 5 micro RNA genes
 - Function of remainder unknown
 - Distal part of long arm is most active = Down syndrome critical region
- Mouse: 112 orthologous genes on chromosome 16





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Genes on chromosome 21



- Many genes on chromosome 21 encode for proteins that are:
 - Transcription factors or their co-regulators or parts of heteromeric transcription factors
 - Post-translational modifiers
- Several have overlapping specificities
→ perturbation of downstream gene expression, including disomic genes



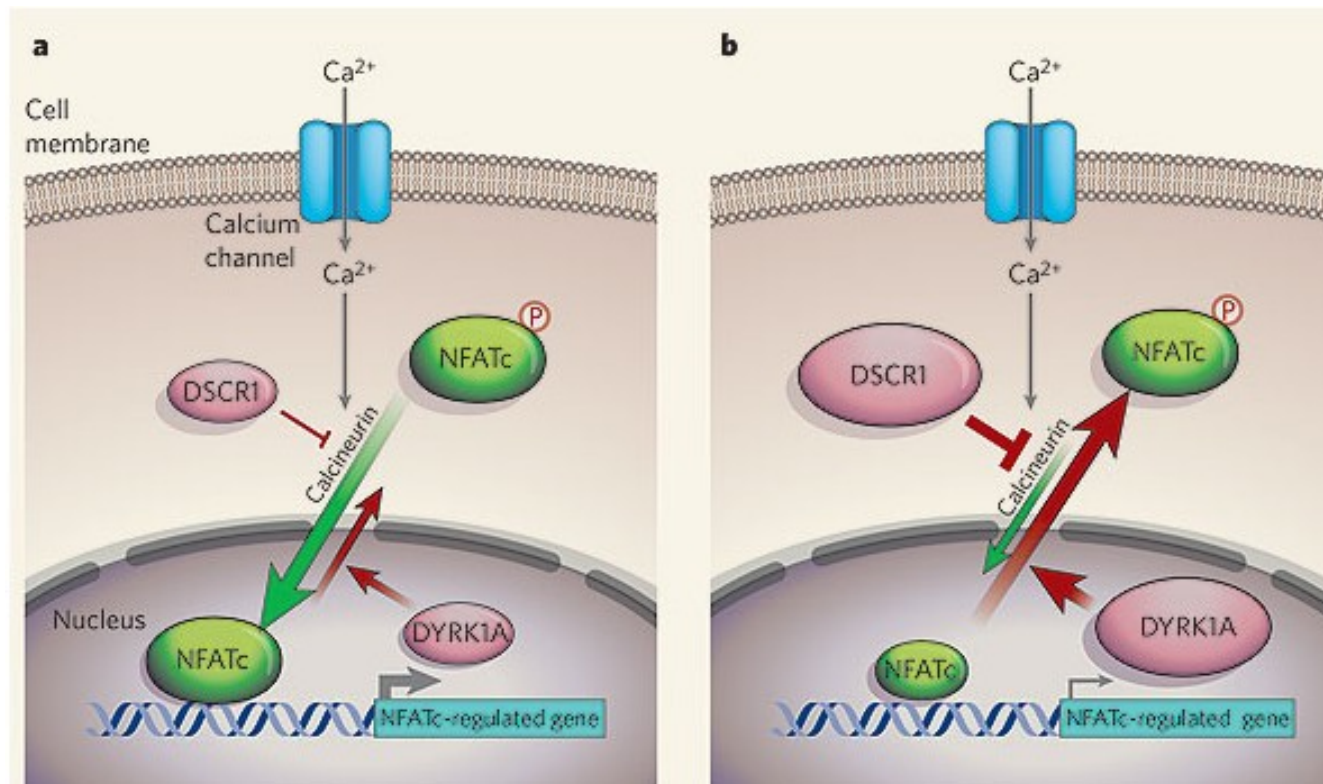
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Transcriptional dysregulation in mental retardation in Down syndrome

Transcription factor	Function	Chromosome locus	Chromosome 21 genes involved
ELK (Etf-like-gene)	Learning Induces nerve growth factor	3	DSCR1, SUMO3, SOD1
CREB (cAMP responsive element binding protein)	Synaptic plasticity	2	DSCR1, DYRK1A, MAPK -genes
BDNF (Brain derived neurotrophic factor)	Neurogenesis Regulated by CREB	11	
ER (Estrogen receptor)	Protection against insult	6	NRIP1, SUMO3
GR (Glucocorticoid receptor)	Stress, learning	5	DYRK1A, NRIP1



DSCR1 and DYRK1A: synergy in control of NFATc phosphorylation





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Some other gene functions

- DSCR1: inhibits calcineurin mediated activation of VEGF
 - Protection against solid tumors?
 - Protection against atherosclerosis?
- Early onset Alzheimer type dementia
 - DYRK1A: phosphorylation of tau protein, may contribute to neurofibrillary degeneration
 - APP gene overexpression
- Congenital heart disease
 - Limited region outside DSCR, including DSCAM (Down syndrome cell adhesion molecule gene)
- Aging:
 - DYRK1A attenuates NOTCH signaling, important in cell proliferation, differentiation and death
 - GABPA: heteromeric transcription factor for several genes involved in cell control



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Research / Projects: endothelial dysfunction

Background

- Increased pulmonary vascular reactivity and hypertension is known in Down syndrome
- Peripheral endothelial dysfunction has been demonstrated by endovascular methods
- Less atherosclerosis and solid tumors

Projects

- Study of endothelial dysfunction by peripheral arterial tonometry (endo-pat)
- Endothelial progenitor cells and endothelial microparticles
- Markers of oxidative stress
- To be linked ultimately with interventions: thyroid, sports,..



Research / Projects: OSAS

Background:

- Majority of children with Down syndrome have OSAS
- Etiology is complex, classic therapy with adenotonsilectomy is less successful

Sleep endoscopy in all children with documented OSAS
and comparison of children with and without Down
syndrome

Possibly to be linked with non ENT interventions



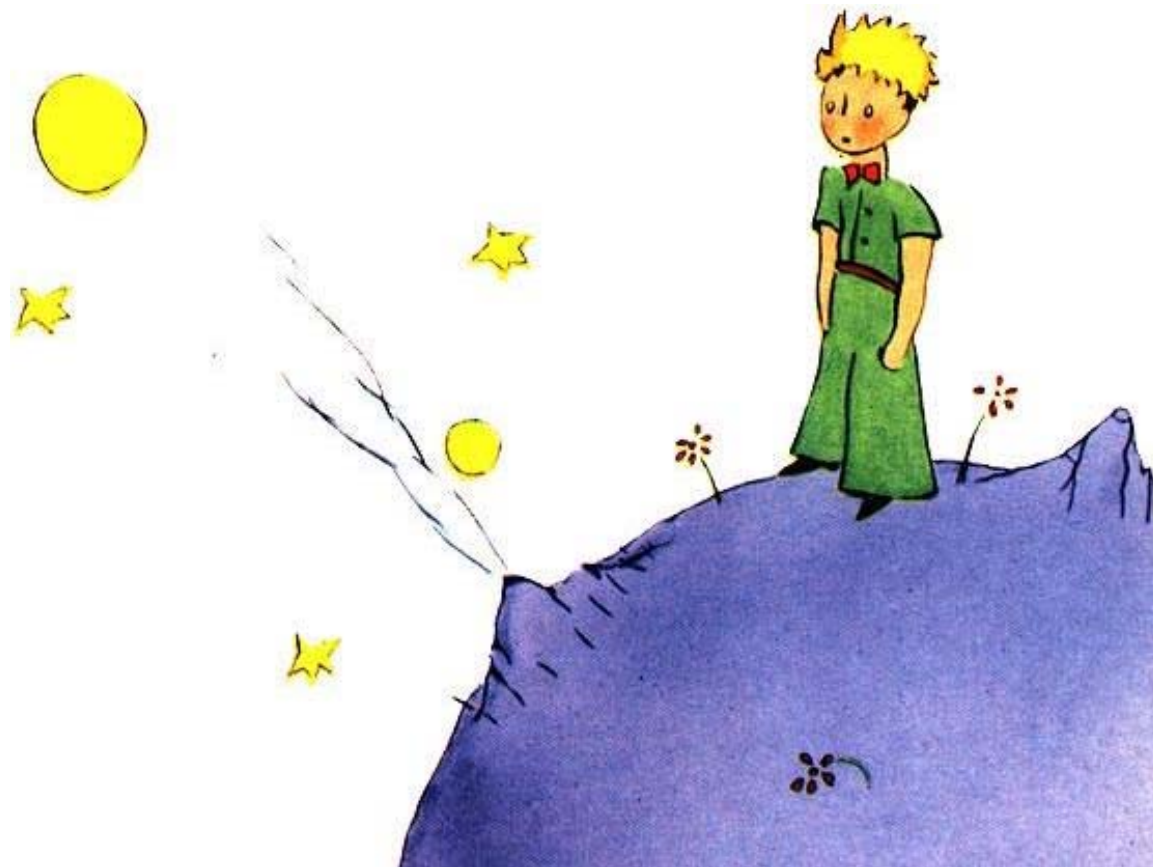
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Research / Projects

- Outcome after interdisciplinary follow – up
- Early signs of autism in Down syndrome
- Health pass for adult Down patients
- Body composition of children with Down syndrome
- Sports?
 - Evaluation of physiological effects of sport in children with Down syndrome
 - Sport as intervention
 - Sport advice: scientific base?



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On ne voit bien qu'avec le coeur
Antoine de Saint-Exupéry

Thank You for Your attention