

# **Humangenetik für Molekulare Medizin**

**Wintersemester 2010/2011**

## **Zytogenetik**

**Dr. rer. nat. Michael Leipoldt**

**Institut für Humangenetik, Univ.Klinikum Freiburg**

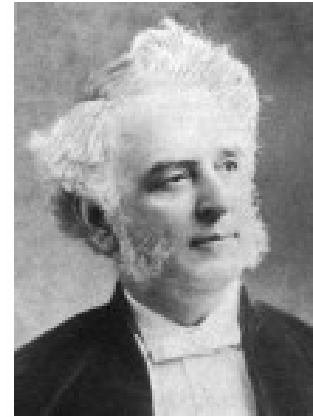
### **2. Down – Syndrom**

OBSERVATIONS ON AN ETHNIC CLASSIFICATION OF  
IDIOTS.

By J. LANGDON H. DOWN, M.D., Lond.

Those who have given any attention to congenital mental lesions, must have been frequently puzzled how to arrange, in any satisfactory way, the different classes of this defect which may have come under their observation. Nor will the difficulty be lessened by an appeal to what has been written on the subject. The systems of classification are generally so vague and artificial, that, not only do they assist but feebly, in any mental arrangement of the phenomena which are presented, but they completely fail in exerting any practical influence on the subject.

The medical practitioner who meets with a child who has, perhaps in a very early condition, a congenital defect of opinion on points of vital importance, is often at a loss as to the probable future of the little one. It is not always easy to answer to the question, whether the supposed defect is the result of a cause subsequent to the birth or not. It is not always easy to meet with a child who has a congenital defect of opinion on points of vital importance, is often at a loss as to the probable future of the little one. It is not always easy to answer to the question, whether the supposed defect is the result of a cause subsequent to the birth or not.



**J. L. H. Langdon – Down**

**“Observations on an ethnic classification of idiots”**

London Hospital Clinical Reports 3, 259–262 (1866)

**“ mongoloid idiocy”**

**J. F. Blumenbach 1775 Theorie d. Menschenrassen**

**W. Weygandt 1911 Entwicklungsstufe d. Mongolen**

**F. D. Crookshank 1924 “Orang-Utan”**

**WHO 1965 Antrag der MVR**

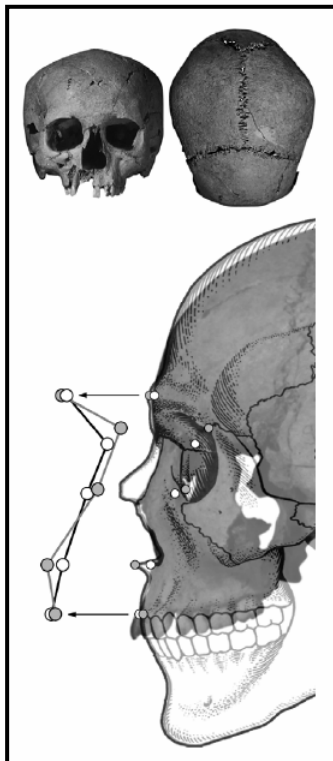
**Bard & Fletcher 1968 “A Down’s is not a person”**







A. Mantegna, 15. Jhdt



550 BC,  
Czarnetzki et al., 2003

# Klinischer Phänotyp beim Down – Syndrom (DS)

Wachstumsdefizit (auch IUGR)

Intelligenzdefekt

## Dysmorphiemuster

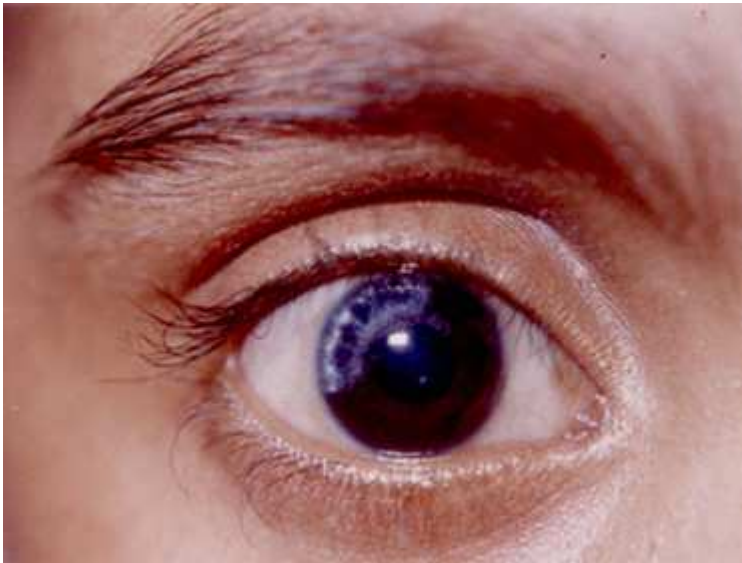
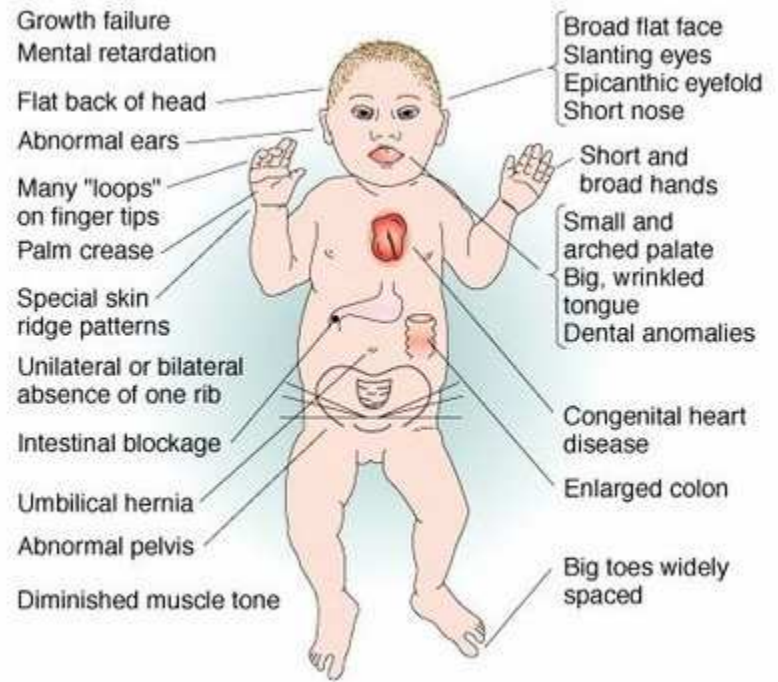
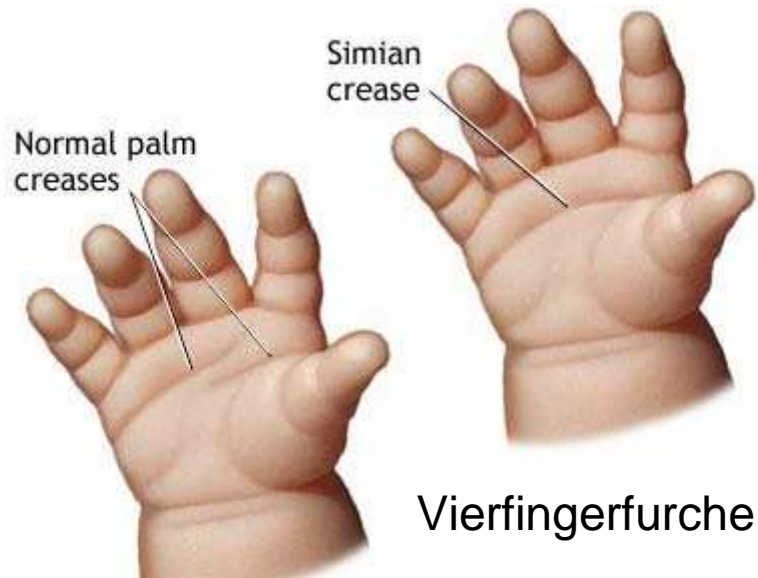
Brachyzephalie	75%
ansteigende Lidachse	82%
Epicanthus	59%
Brushfield-Irisflecken	56%
Vier-Finger-Furche	53%
kurze, breite Hände & Finger	64%
kurze Nase / eingesunkene Nasenwurzel	68%
kurzer Hals mit Hautfalten	81%
offener Mund / Makroglossie	58%

## fakultativ angeborene Fehlbildungen

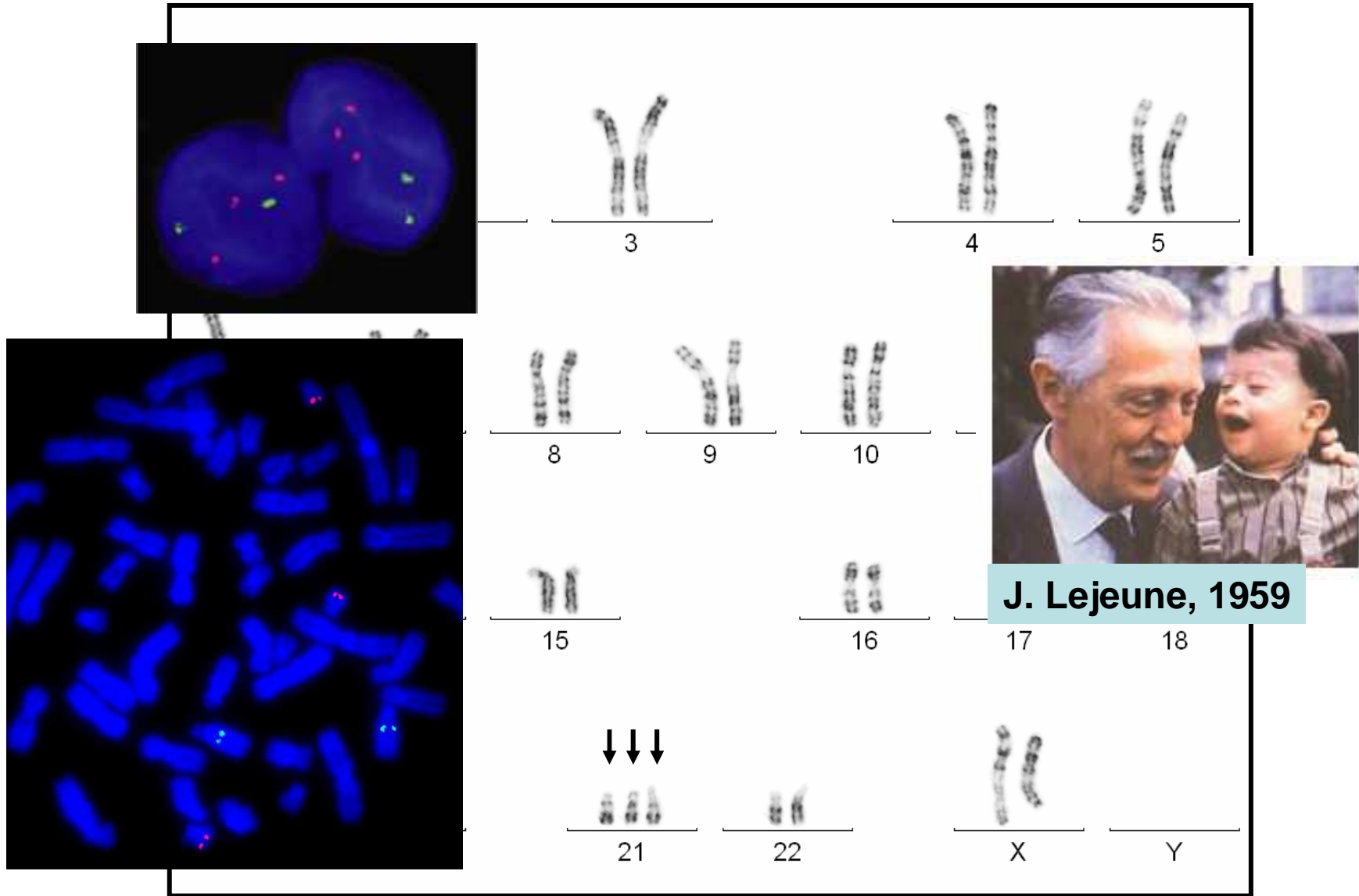
Herzfehler	40%
Gastrointestinal-Trakt	5%

## Verlauf

Hypotonie (Ngb., Kinder & Jugendl.)	100% ?
Infektionserkrankungen	
Leukämien (insbes. frühkindl.)	50x
Morbus Alzheimer	25-100%



Brushfield - Spots



**Down-Syndrom - Trisomie 21**

# Nachweis einer Trisomie 21

Chromosomenanalyse  
FISH / Interphase – FISH  
QF PCR

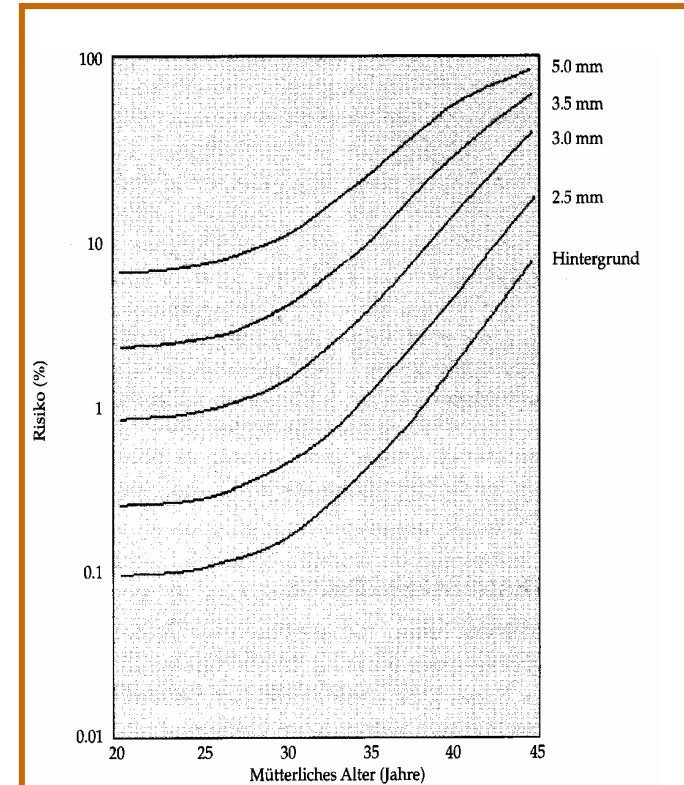
(pränatale Risikomodifikatoren:  
Serum-Marker, Nackentransparenz)

## Veränderungen von (maternalen) Serum – Markern bei fetalen Trisomien

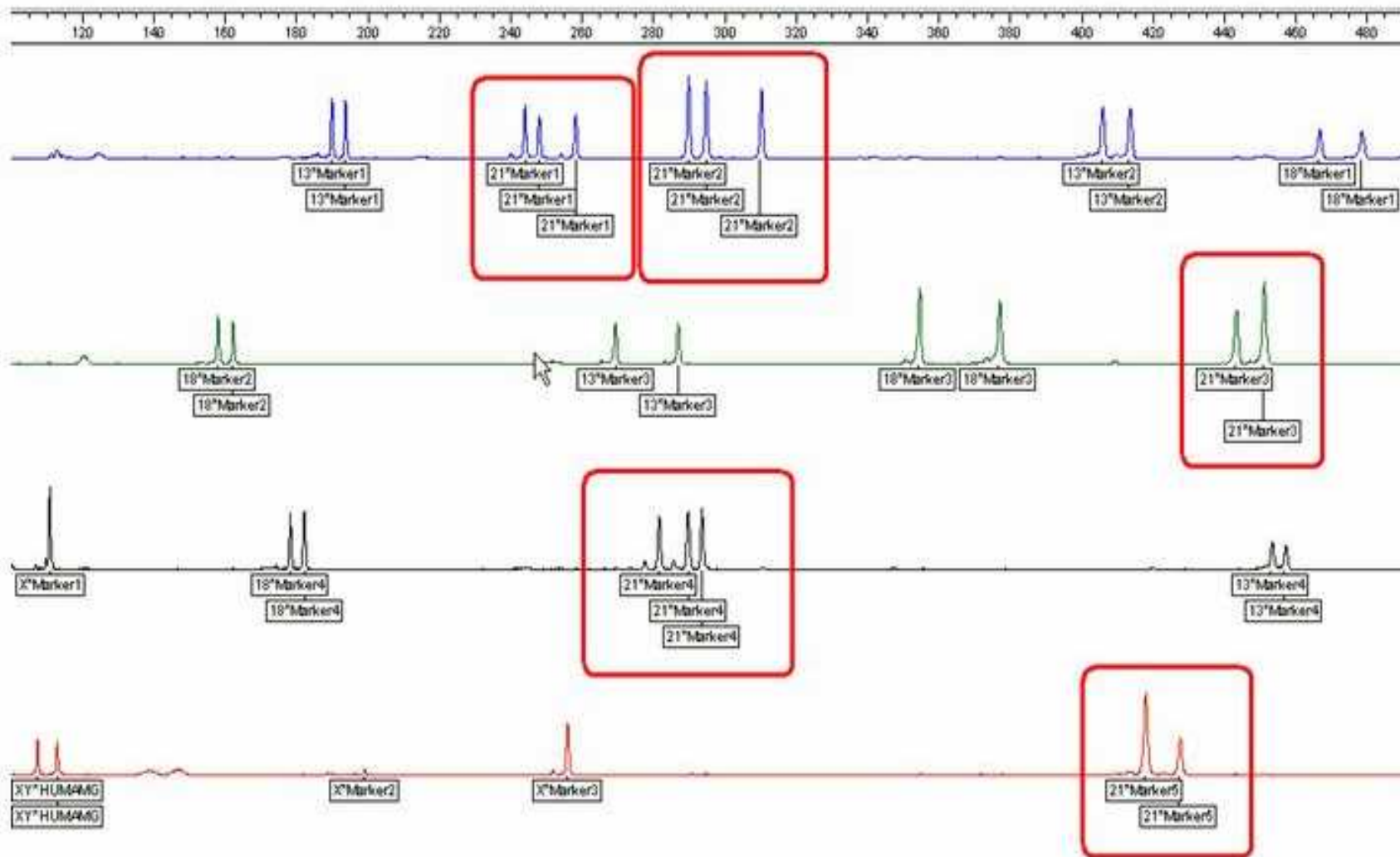
	Tris 21	Tris 18	Tris 13
<b>PAPP-A</b>	↓	↓↓	↓
<b>β-HCG</b>	↑	↓↓	↓
<b>Östriol</b>	↑	↓	?
<b>AFP</b>	↓	↓↓	?

Kagan et al. (2008) Human Reprod 23, 1968

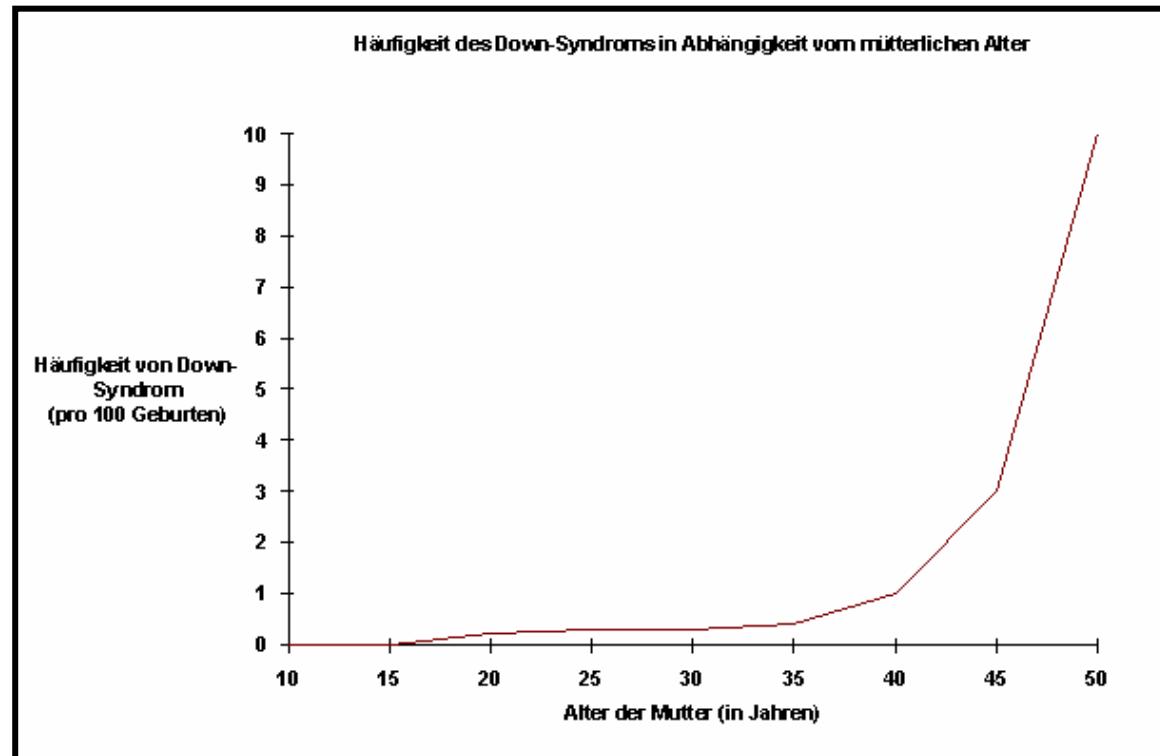
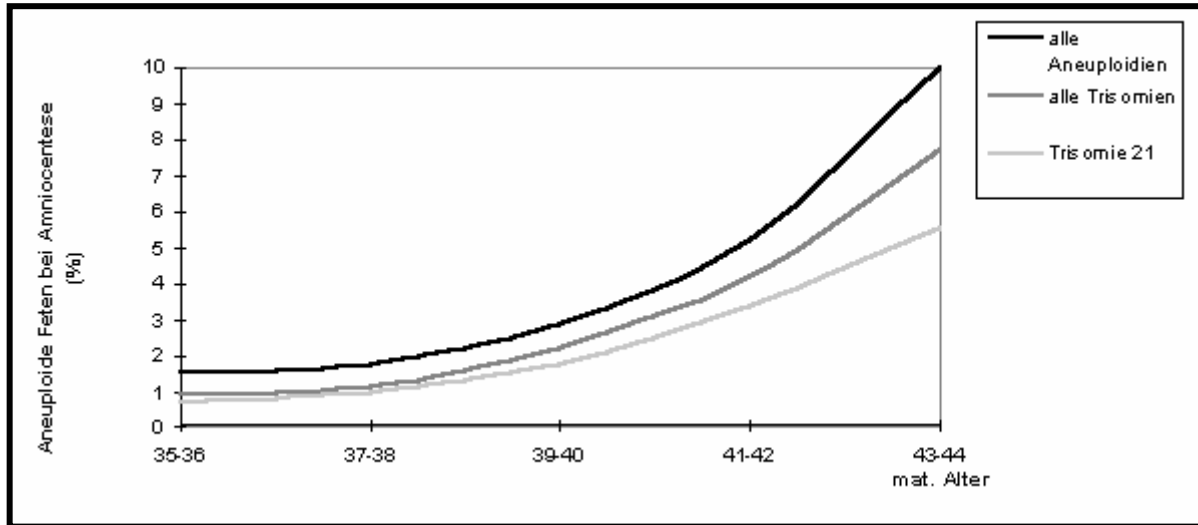
Kagan et al. (2008) Prenat Diag 28, 1209



**Höhe des Risikos für  
ein Down-Syndrom  
in Abhängigkeit von  
Nackentransparenz  
und mütterlichem  
Alter**

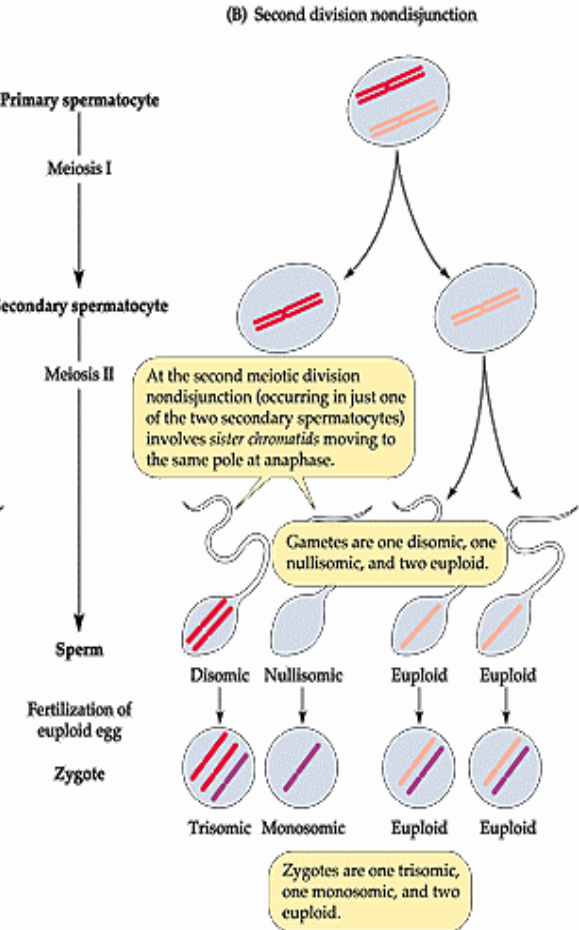
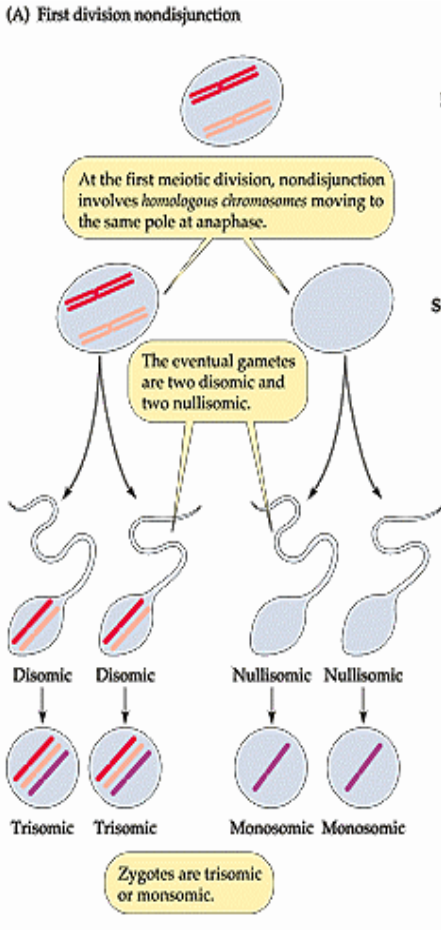


QF - PCR



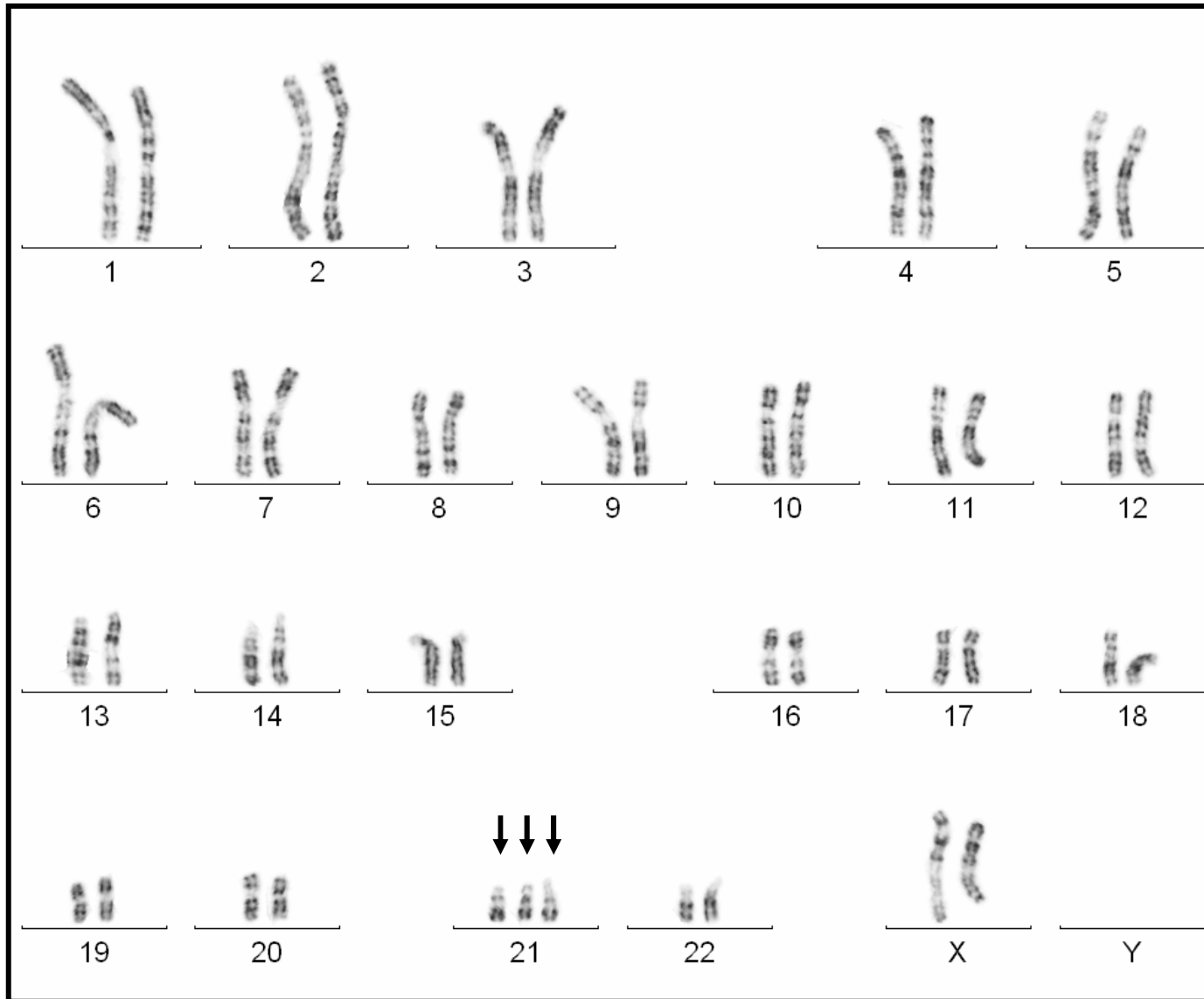
# Meiotisches Nondisjunction

## a) Allgemein



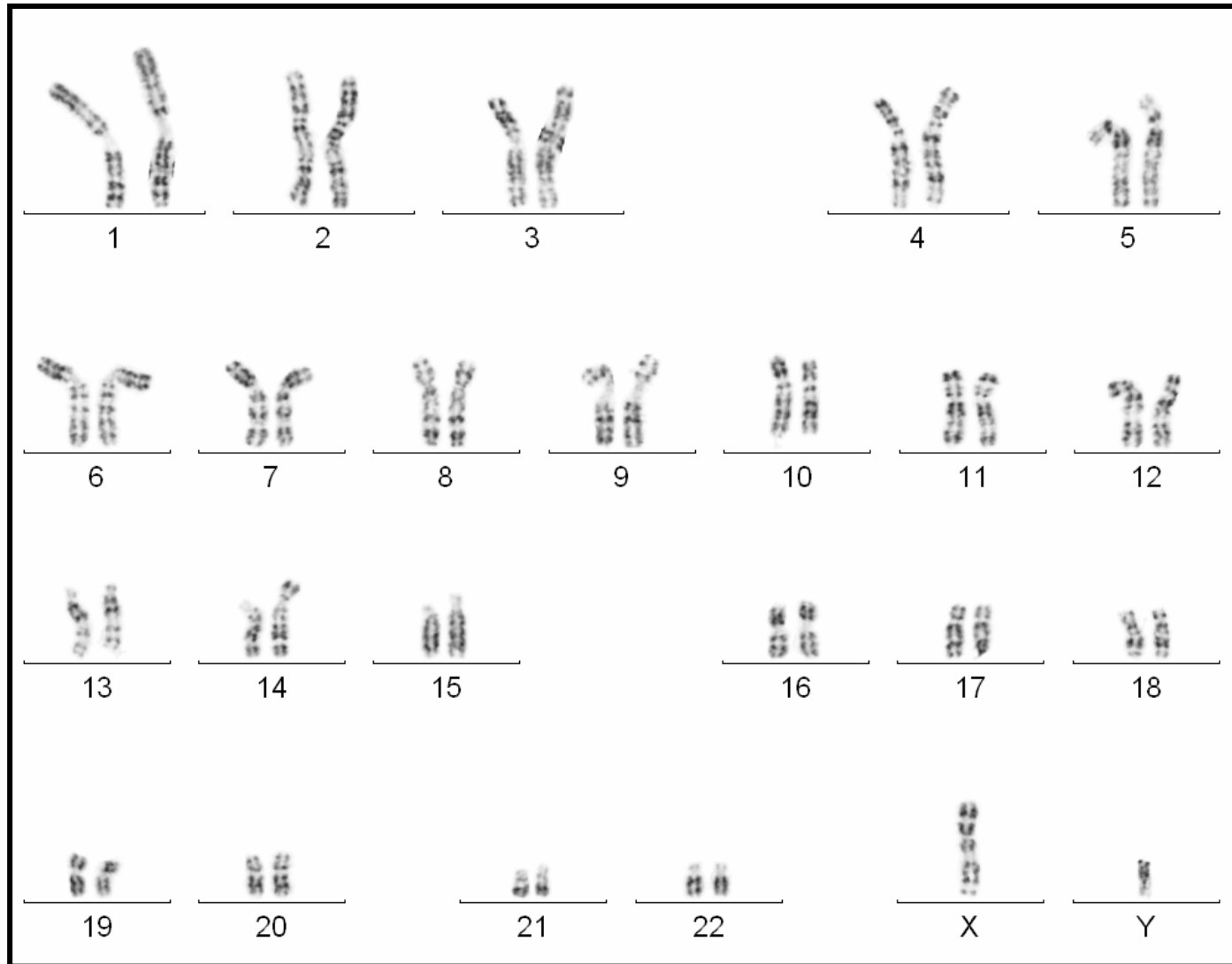
## b) Trisomie 21

	Spermio- genese	Oogenese	
<b>M1</b>	3%	77%	<b>(80%)</b>
<b>M2</b>	2%	18%	<b>(20%)</b>
	<b>(5%)</b>	<b>(95%)</b>	

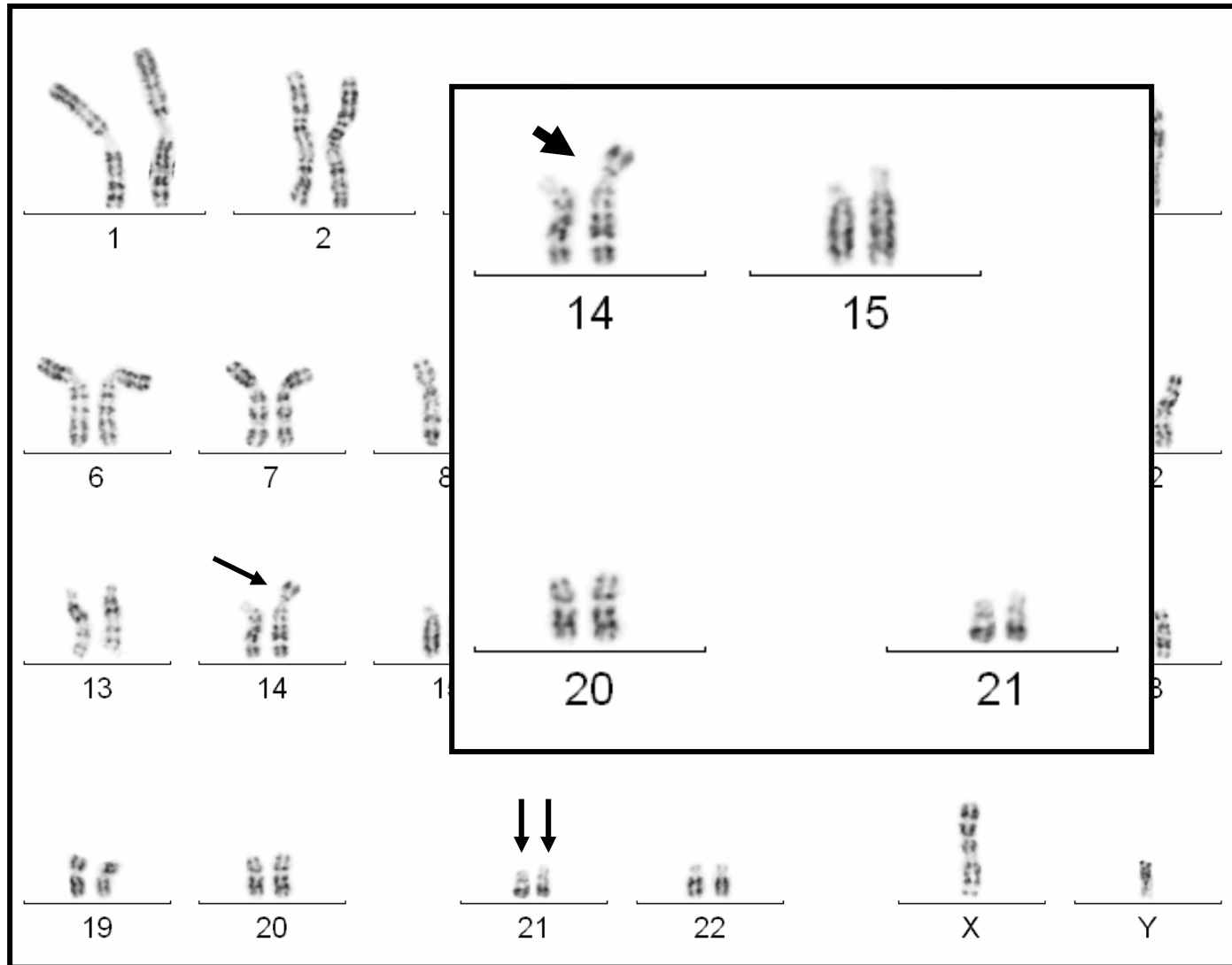


**Karyotyp: 47,XX,+21**

**freie Trisomie 21**

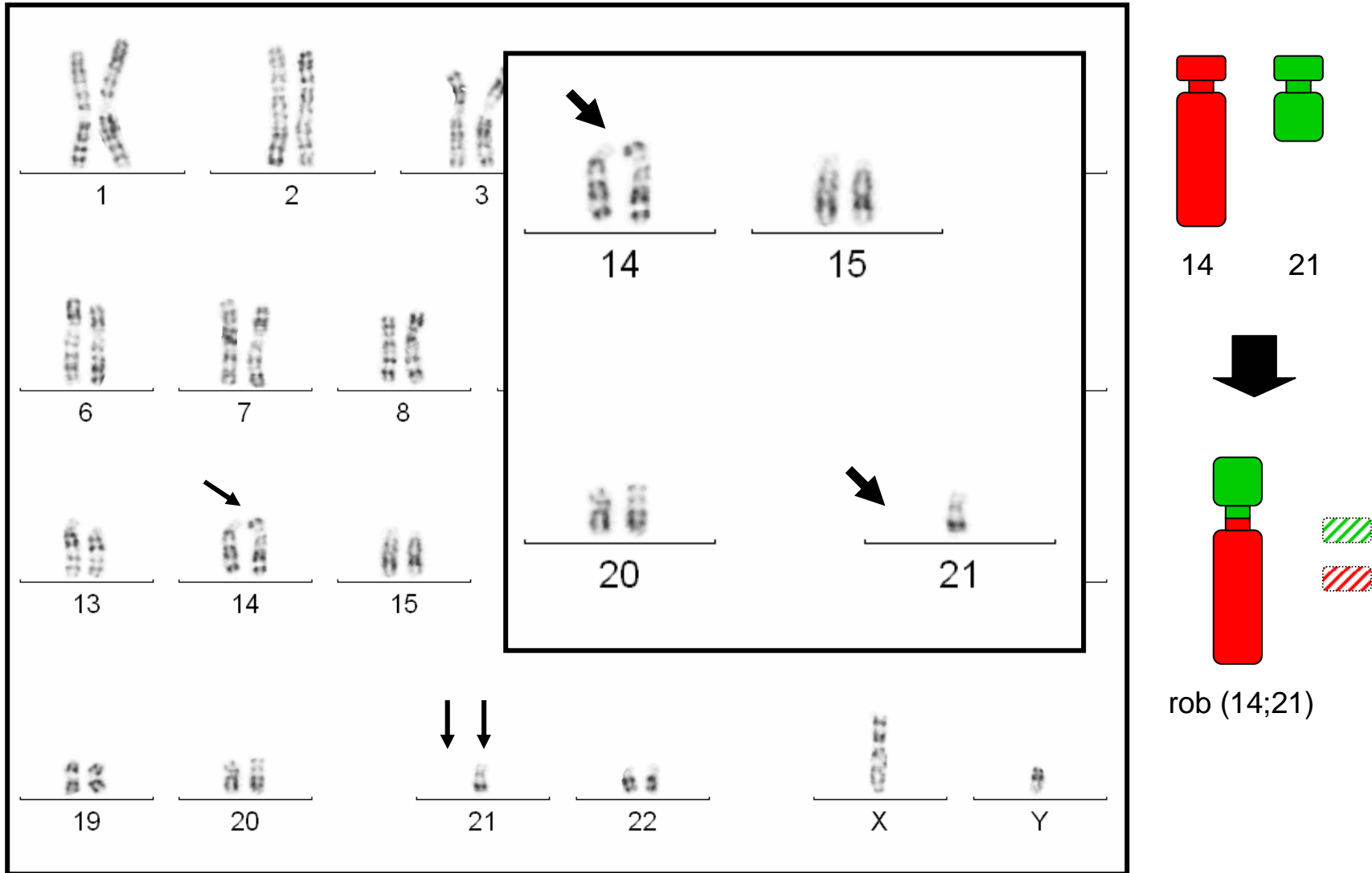


**Karyotyp: 46,XY ??**



**Karyotyp: 46,XY,rob(14;21)(q10;q10),+21**

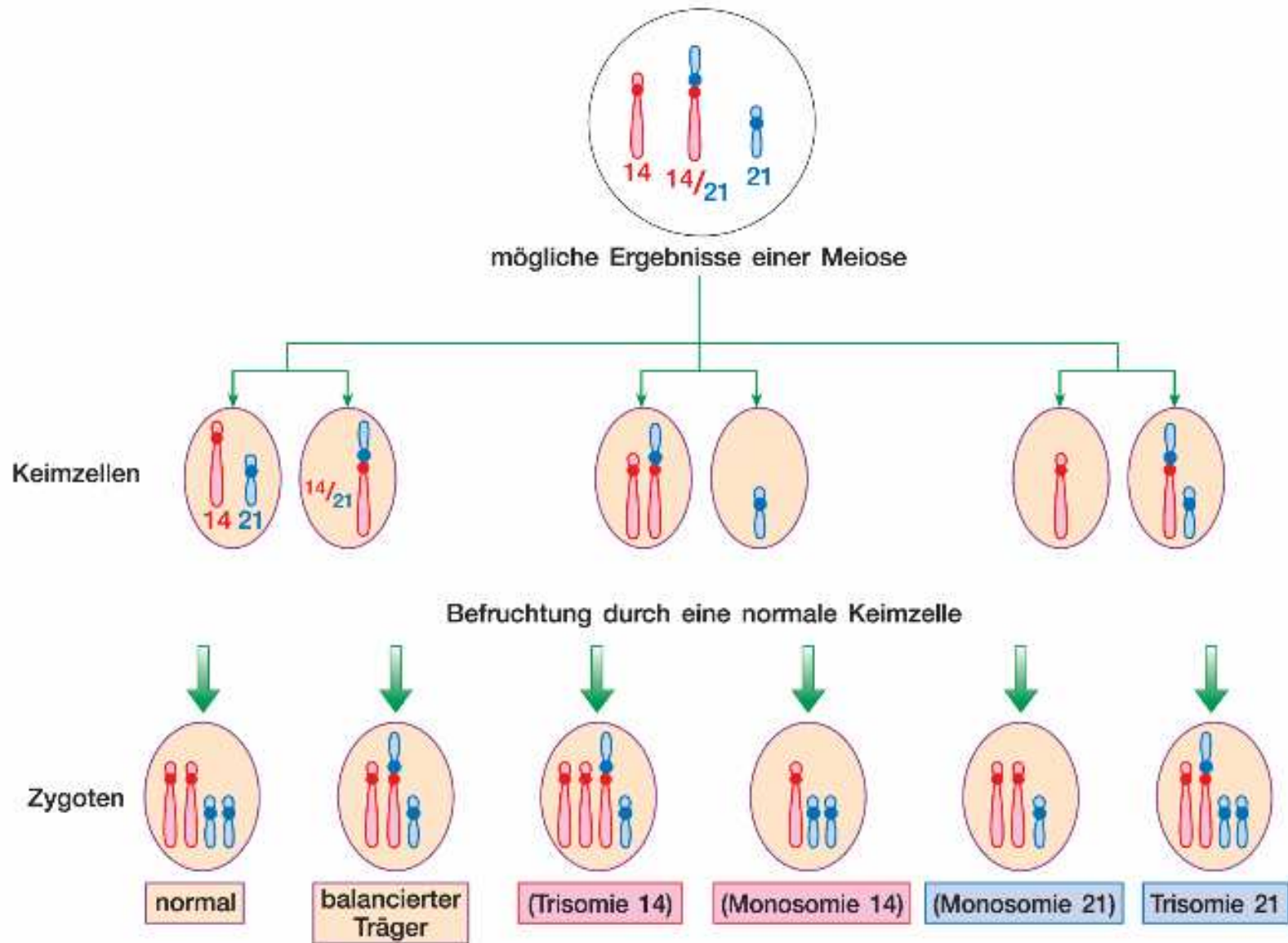
**Translokationstrisomie 21**

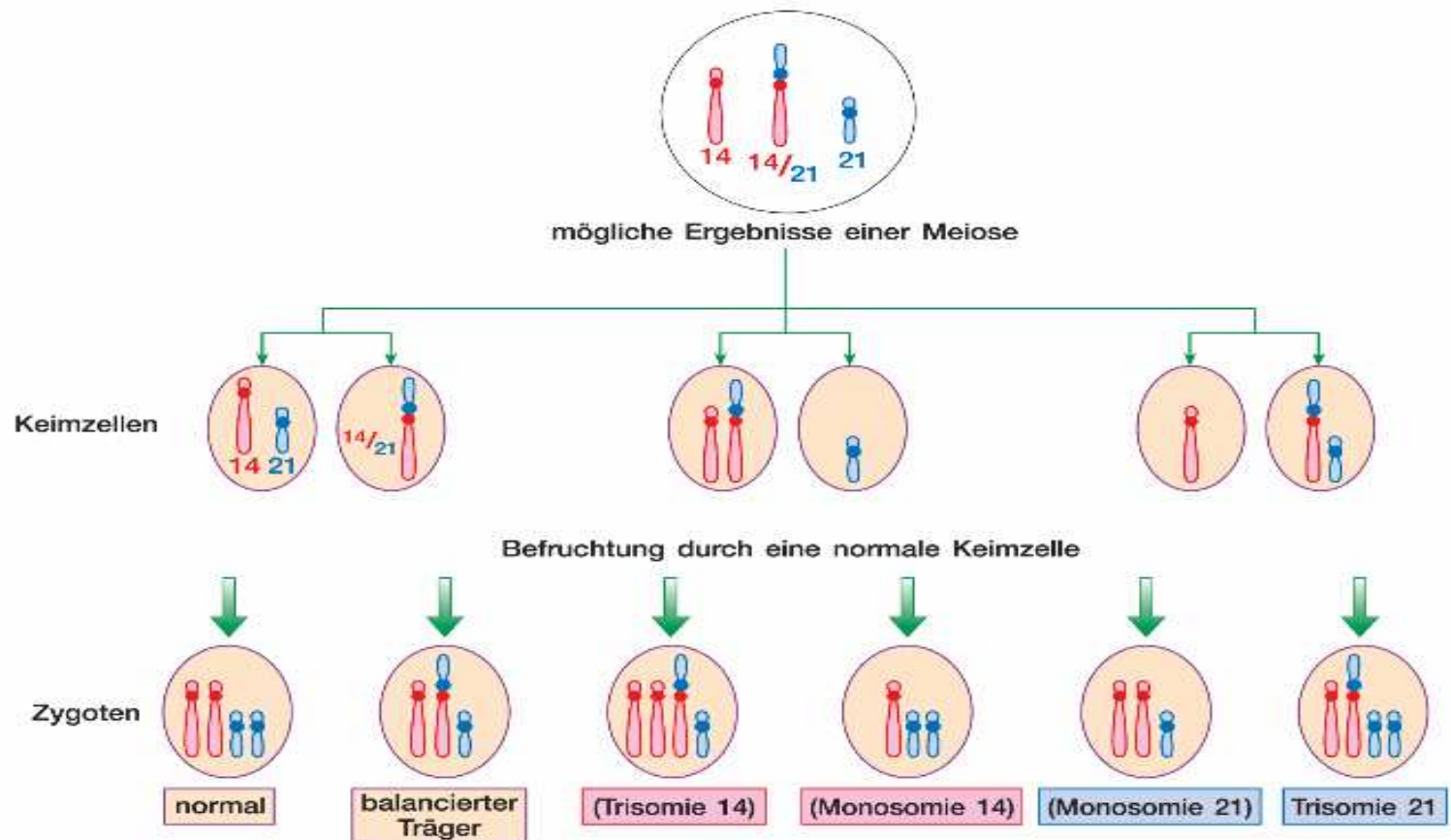


**Karyotyp: 45,XY,rob(14;21)(q10;q10)**

**balanzierte Robertsonsche Translokation 14;21**

# Meiose bei Trägern einer Robertsonschen Translokation





Aus Strachan/Read, Molekulare Humangenetik, 3. Aufl., © 2005 Elsevier GmbH

pränatal letal

+

+

+

lebensfähig

+

+

+

Wahrscheinlichkeit für DS bei Kindern eines TL-Trägers (formal): 33%

Wahrscheinlichkeit (empirisch): 10-12 % bei ♀♀ TL - Trägern

1-2 % bei ♂♂ TL - Trägern

# Chromosomenveränderungen beim DS

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## Freie Trisomie 21

sporadisch,  
meiotisches ND,  
Alterseffekt,  
Mosaik möglich

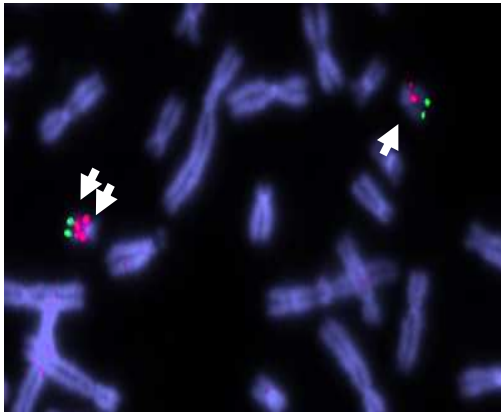
≤ 95%

## Translokationstrisomie 21

Robertsonsche Tl.,  
oft familiär

≤ 5%

## Partialtrisomien



Duplikationen,  
unbalanzierte reziproke  
Translokationen,  
u.U. familiär

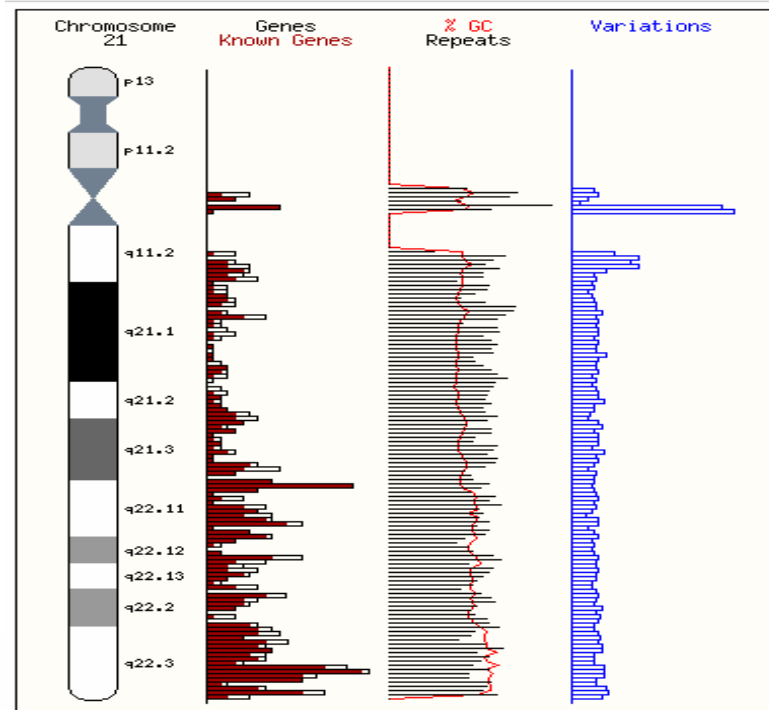
~ 1%

# Chromosom 21

**Kleinstes Autosomes**

**Ca. 1% des Genoms**

**Anzahl Gene (s.u.): 477**



## Chromosome Statistics

Length (bps):	48,129,895
Known Protein-coding Genes:	278
Novel Protein-coding Genes:	2
Pseudogene Genes:	141
miRNA Genes:	16
rRNA Genes:	5
snRNA Genes:	13
snoRNA Genes:	14
Misc RNA Genes:	8

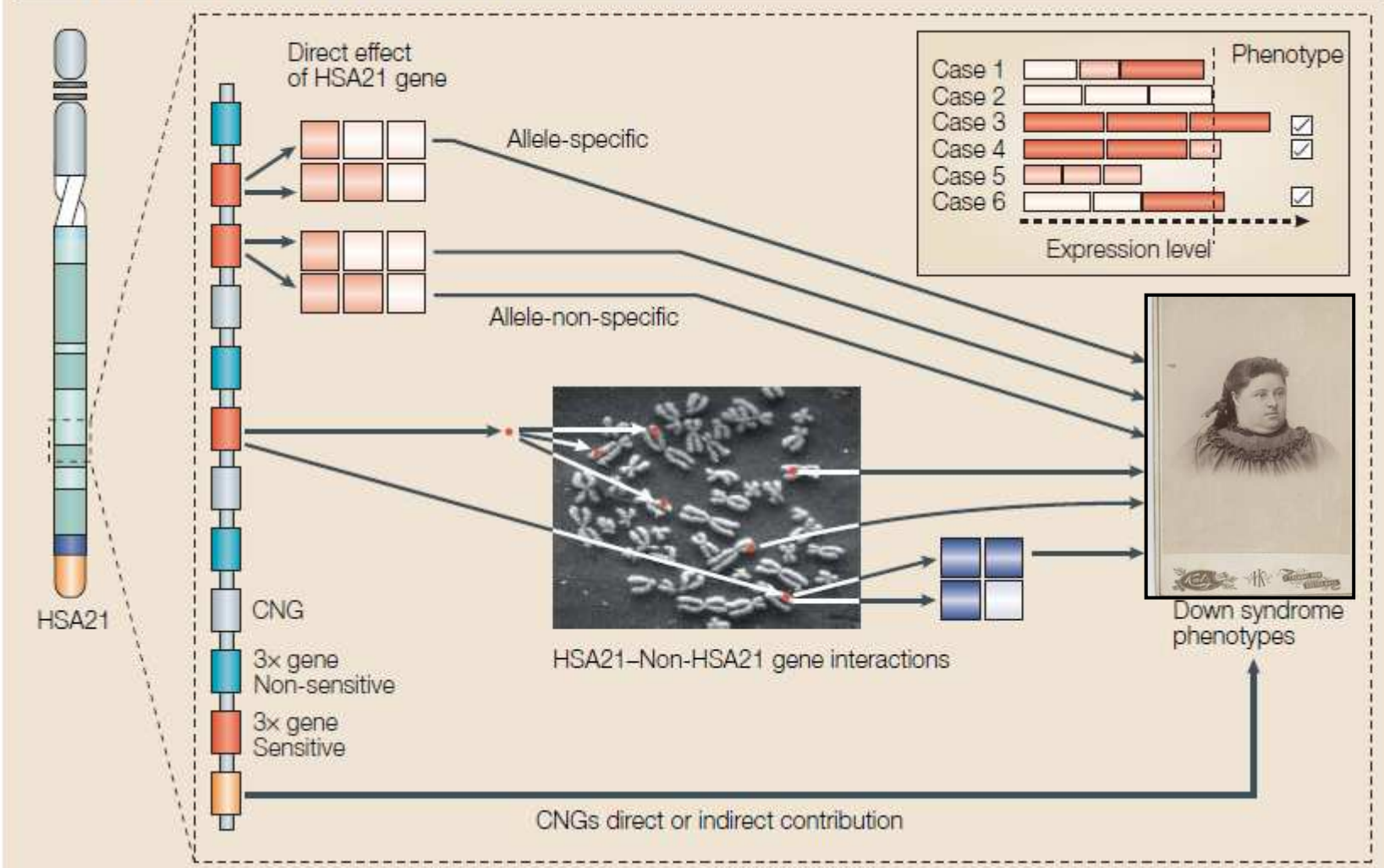
<http://www.ensembl.org>

## **Pathogenese des Down – Syndroms**

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- Down-Syndrom - Gen ?**
- direkte Gendosis – Effekte ?**
- Störung der prä- und postnatalen Entwicklung ?  
(indirekte Gendosis – Effekte)**

Box 1 | Hypothesis for Trisomy 21 phenotypes



Antonarakis et al. (2004) NatRevGenet 5: 725-738



**Table 2. Transcriptome analyses of trisomy**

Study	Samples	Tissues	Array or assay type	Number of genes arrayed	Percentage of genes expressed	3n genes <1.2-fold increase <sup>c</sup> (%)	Primary gene-dosage effect <sup>d</sup>	Disomic gene dysregulation <sup>d</sup>
➔ FitzPatrick <i>et al.</i> [7]	Human T21	Cultured amniocytes	cDNA	9126	87%	5-10%	+++	+
➔ Mao <i>et al.</i> [8]	Human T21	Cultured astrocytes	Oligo microarray	15 106	71%	5-10%	+++	-
➔ Mao <i>et al.</i> [8]	Human T21	Cerebrum	Oligo microarray	15 106	54%	5-10%	+++	-
Saran <i>et al.</i> [12]	Mouse Ts65Dn	Cerebellum	Oligo microarray	12 488	55%	24%	+++	++
Amano <i>et al.</i> [9]	Mouse Ts1Cje	P0 brain	Oligo microarray	11 300	37%	0%	+++	-
Dauphinot <i>et al.</i> [15]	Mouse Ts1Cje	Cerebellum	Oligo microarray and/or qPCR	12 488	66%	3-11%	+++	++
Kahlem <i>et al.</i> [10]	Mouse Ts65Dn	Adult tissues	cDNA	520 <sup>a</sup>	82%	~8%	+++	Not applicable
Lyle <i>et al.</i> <sup>b</sup> [11]	Mouse Ts65Dn	P30 and adult tissues	RT-PCR	99 <sup>b</sup>	96%	~9%	+++	Not applicable

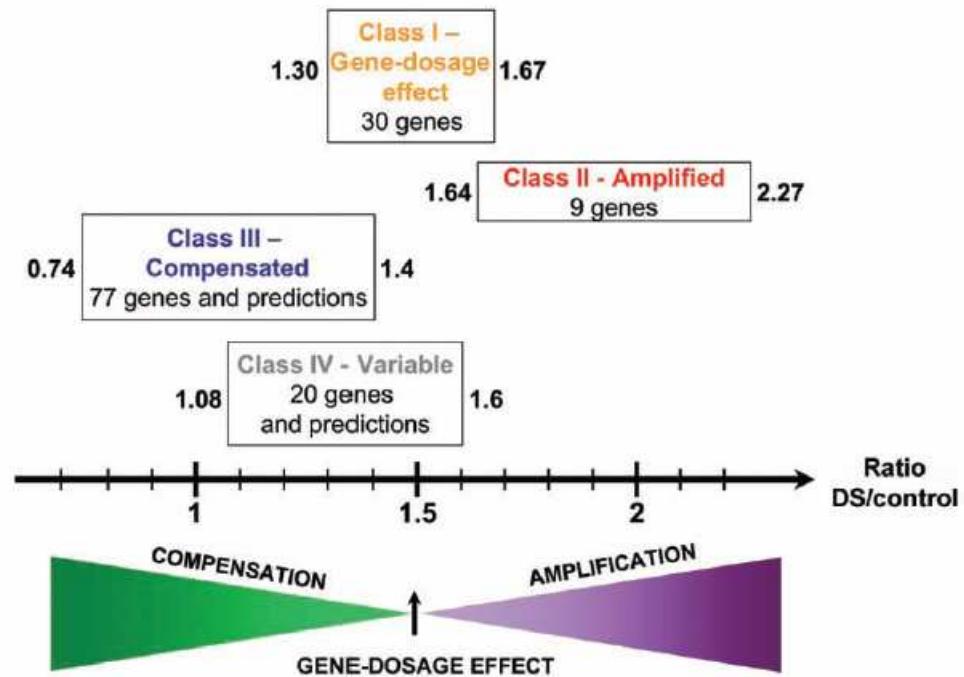
<sup>a</sup>136 mouse genes are orthologous to those on HSA21 (77 are trisomic in Ts65Dn) and 384 non-triplicated genes from elsewhere in the genome.

<sup>b</sup>88 genes are orthologous to those on HSA21 (82 are triplicated in Ts65Dn) and 11 other mouse genes.

<sup>c</sup>Possible dosage-compensation effect.

<sup>d</sup>A strong gene-dosage effect is represented by +++ and a milder gene-dosage effect is represented by ++.

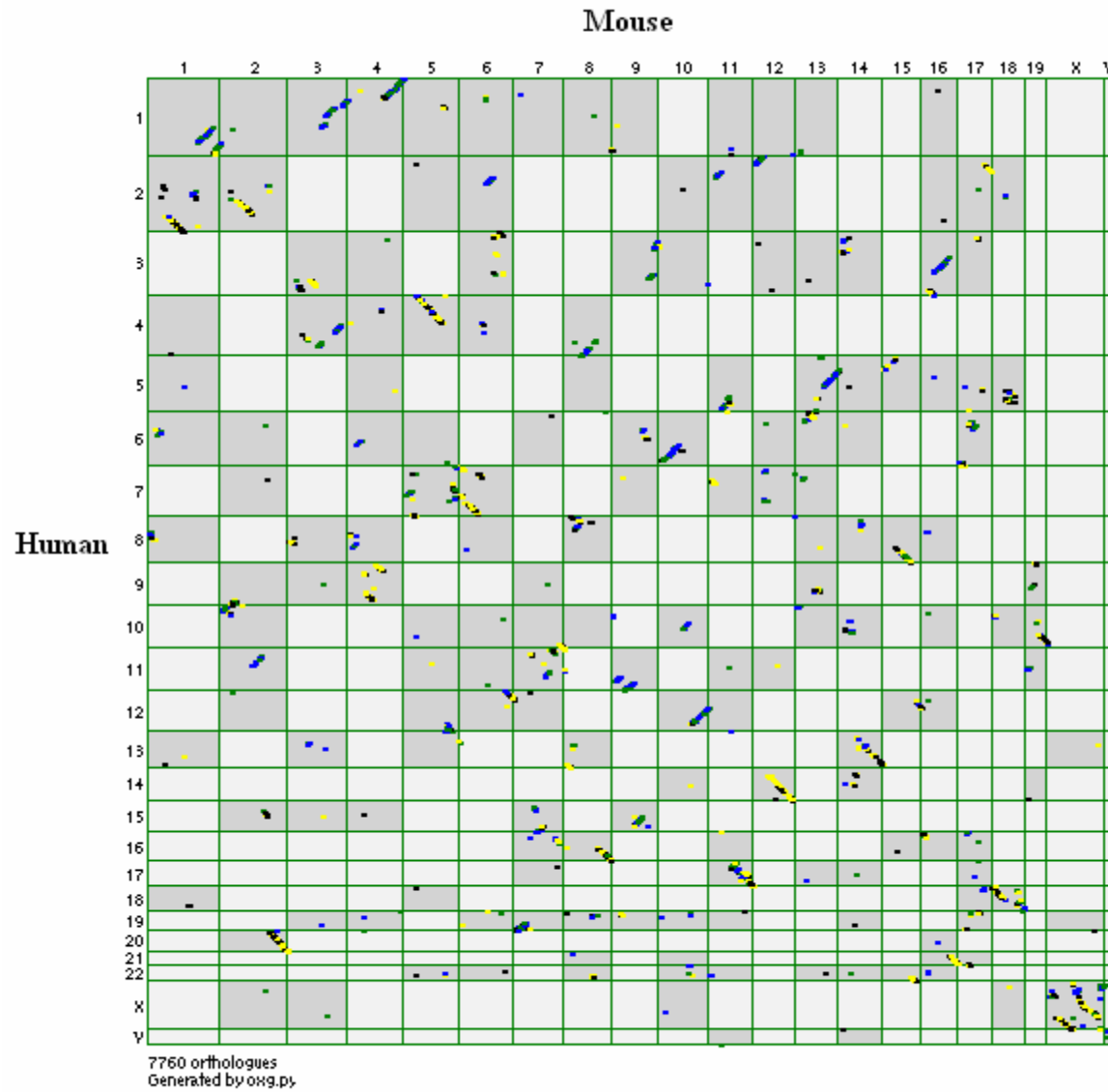
Fitzpatrick (2005) TIG 21, 249



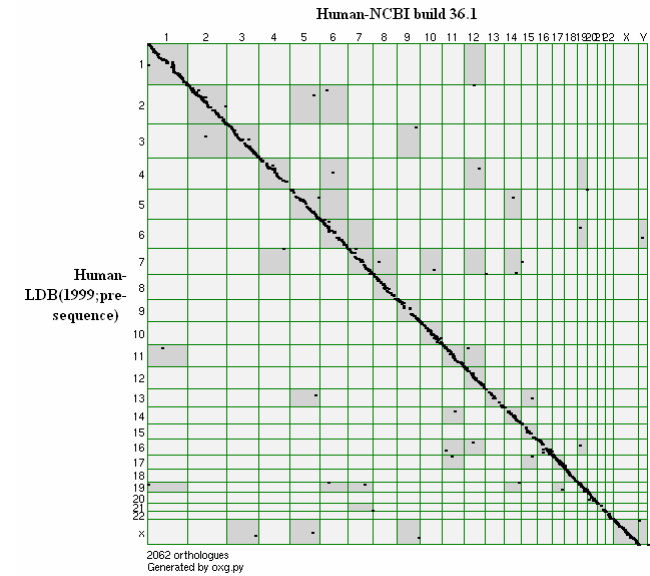
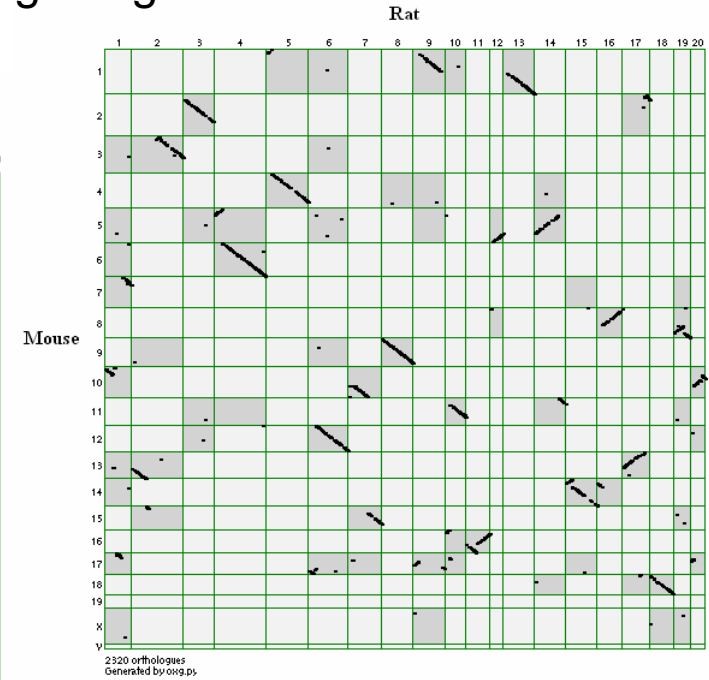
**Figure 1.** Classification of HSA21 genes according to the expression ratio between DS and control LCLs. The sum of classified genes is 136 genes minus 2 (*C21ORF108* and *PRMT2*) that appear twice, depending on the oligonucleotide probe considered (see the “Results” section for details).

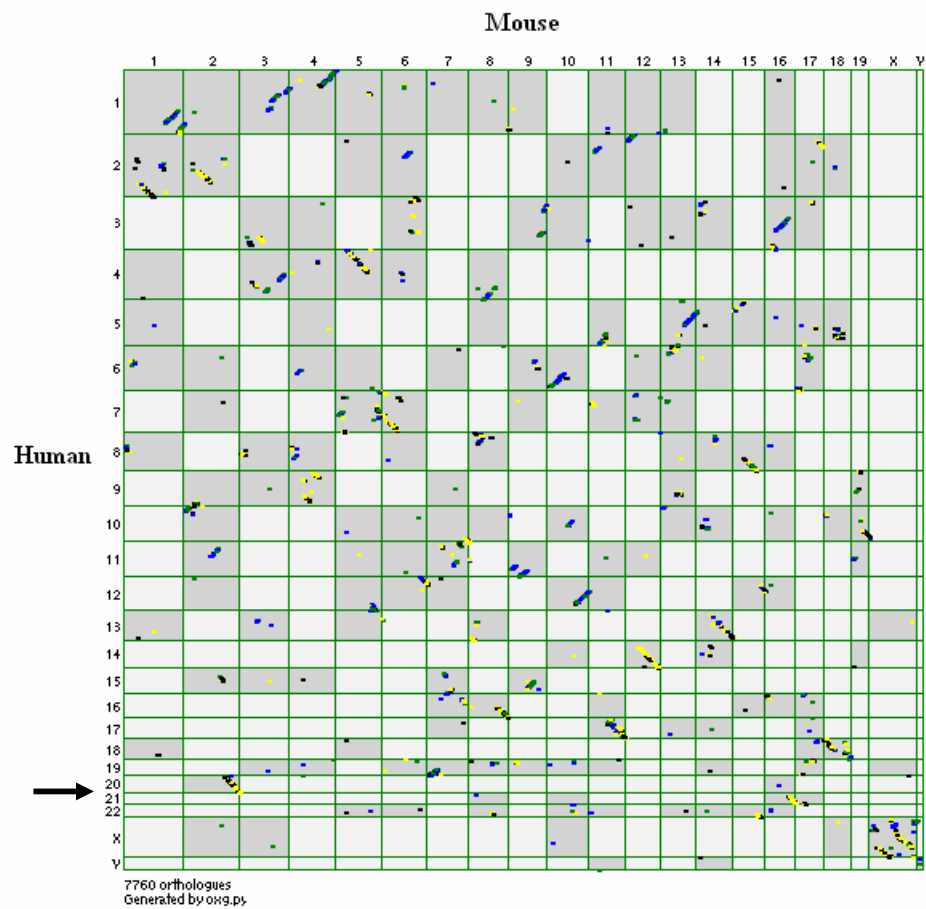
Yahya-Graison et al. (2007) AmJHumGen 81,475

# Oxford grid (J.Edwards, 1984) <http://oxgrid.angis.org.au/>



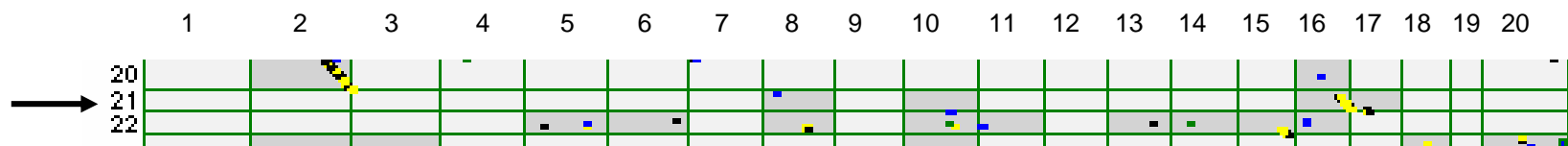
7760 orthologues

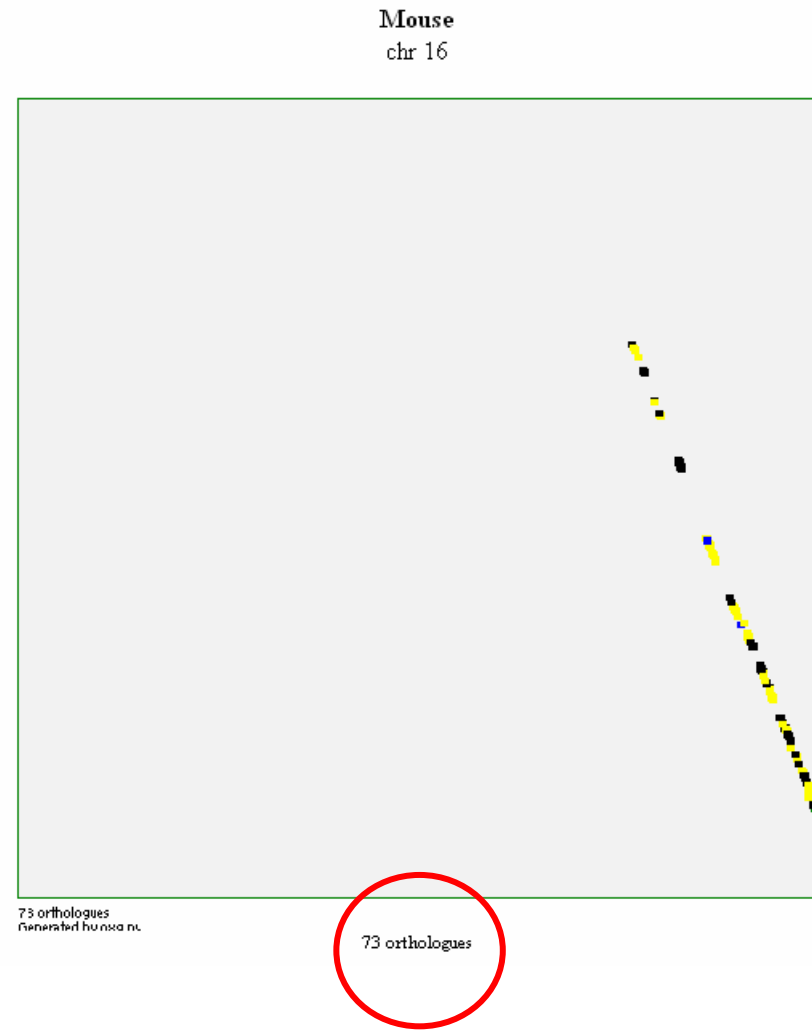
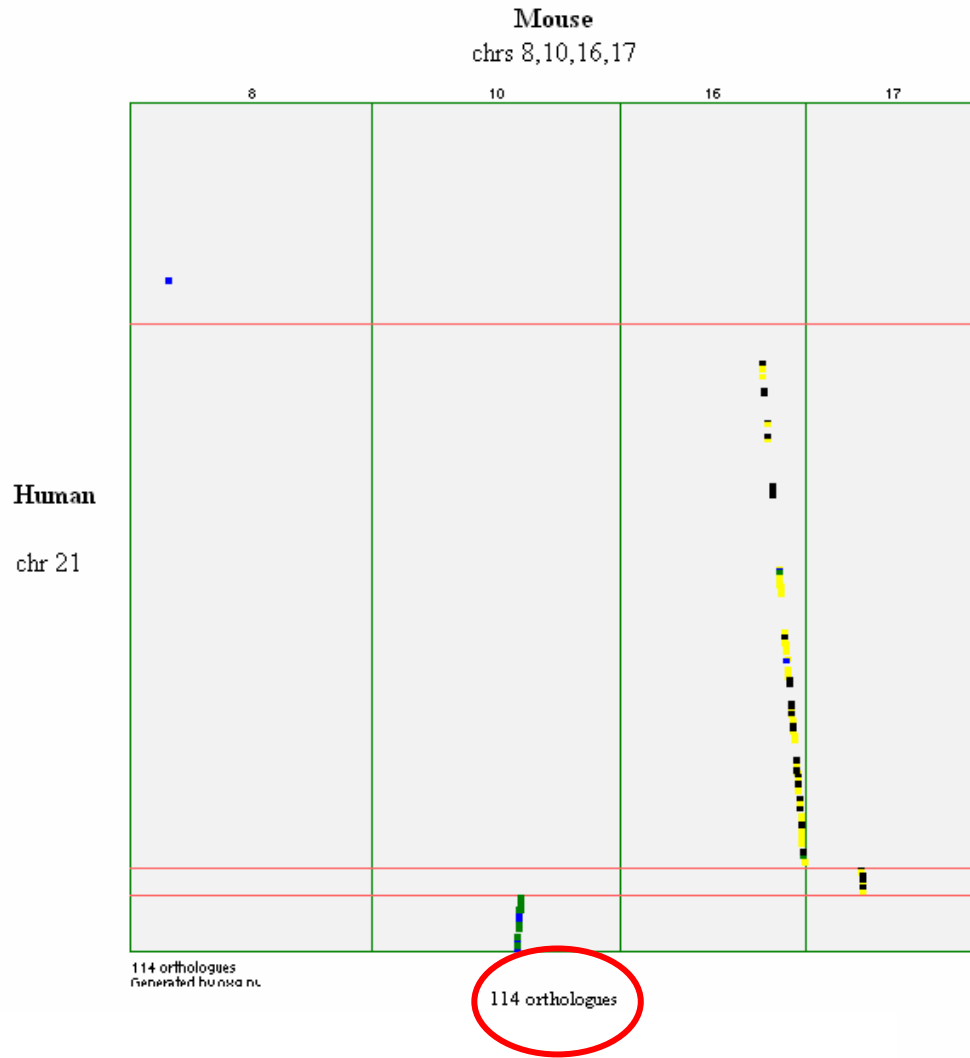




7760 orthologues

### Maus







All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Books

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All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

## 1: DYRK1A dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A [ *Homo sapiens* ]

GeneID: 1859

updated 02-Aug-2009

### Summary

**Official Symbol** DYRK1A

provided by [HGNC](#)

**Official Full Name** dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A

provided by [HGNC](#)

**Primary source** [HGNC:3091](#)

**See related** [Ensembl:ENSG00000157540](#); [HPRD:09018](#); [MIM:600855](#)

**Gene type** protein coding

**RefSeq status** REVIEWED

**Organism** [Homo sapiens](#)

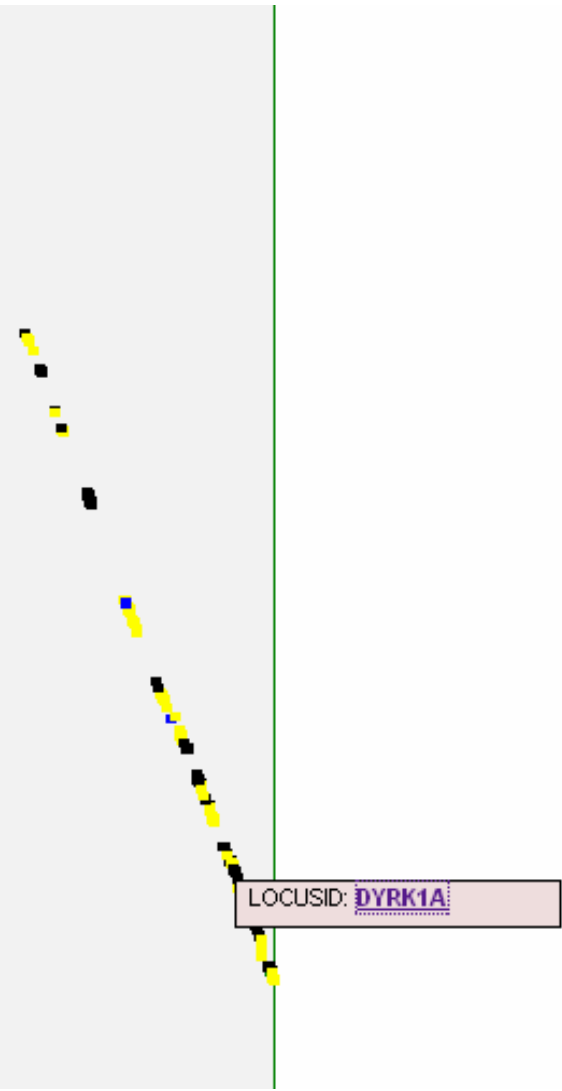
**Lineage** *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo*

**Also known as** MNB; DYRK; HP86; MNBH; DYRK1; DYRK1A

#### Summary

This gene encodes a member of the Dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family. This member contains a nuclear targeting signal sequence, a protein kinase domain, a leucine zipper motif, and a highly conservative 13-consecutive-histidine repeat. It catalyzes its autophosphorylation on serine/threonine and tyrosine residues. It may play a significant role in a signaling pathway regulating cell proliferation and may be

transcript variants differing from each other either in the 5' UTR or in the 3' coding region. These variants encode



## Die Ts65Dn – Maus [ Ts(17<sup>16</sup>)65Dn ]

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- Segmentale (partielle) Trisomie 16

ausgehend von einer Translok. 16;17

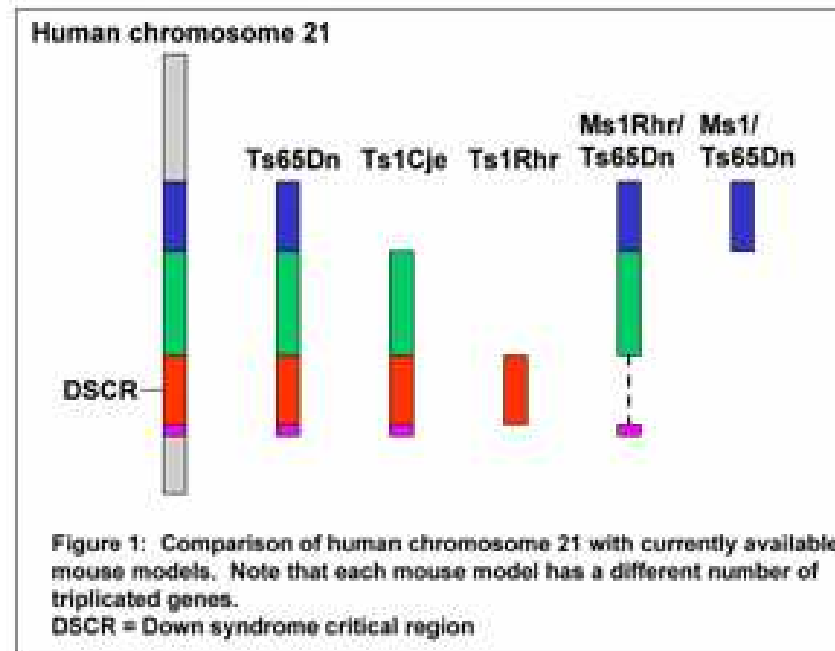
- Orthologe für ca. 50% der bekannten

Gene des humanen Chr. 21

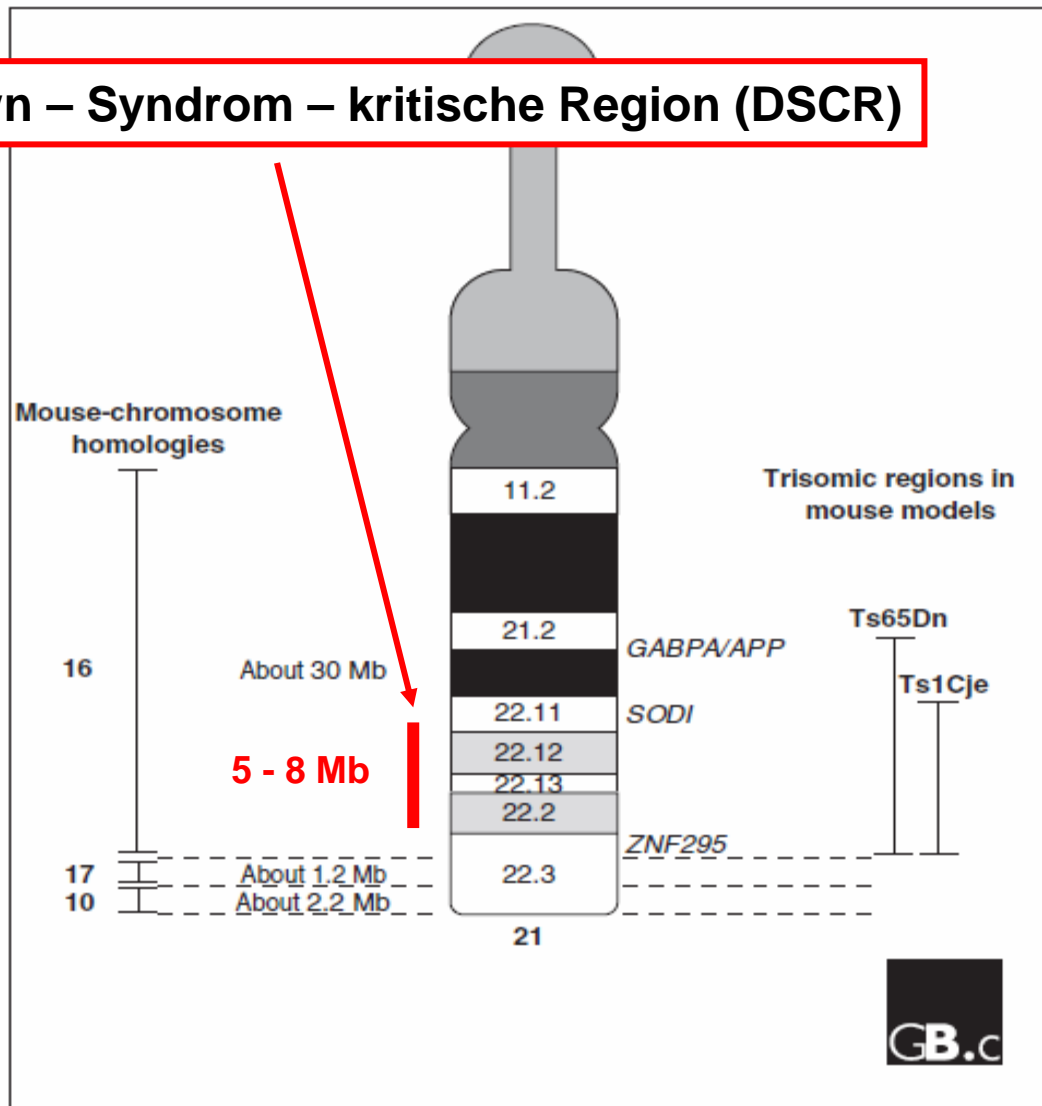
(entspricht ~ 28Mb = 72%)

Entwicklungsstörung  
Craniofaziale Auffälligkeiten  
Hirnfehlbildungen  
Lern – und Verhaltensauffälligkeiten

>> transgene Mäuse

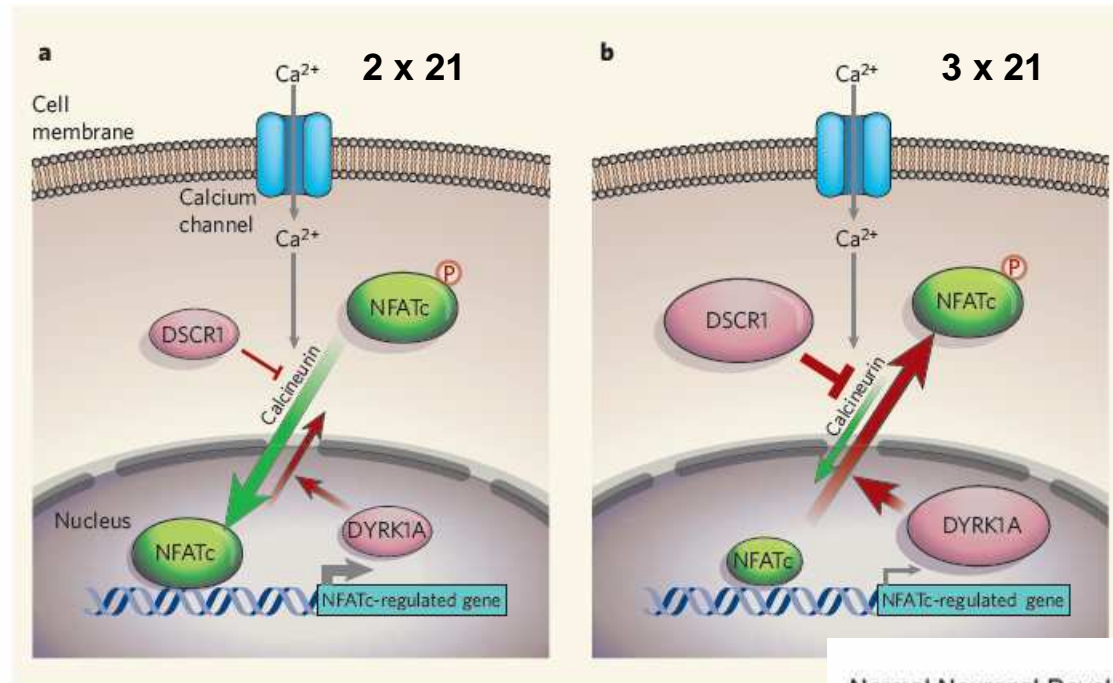


# Down – Syndrom – kritische Region (DSCR)

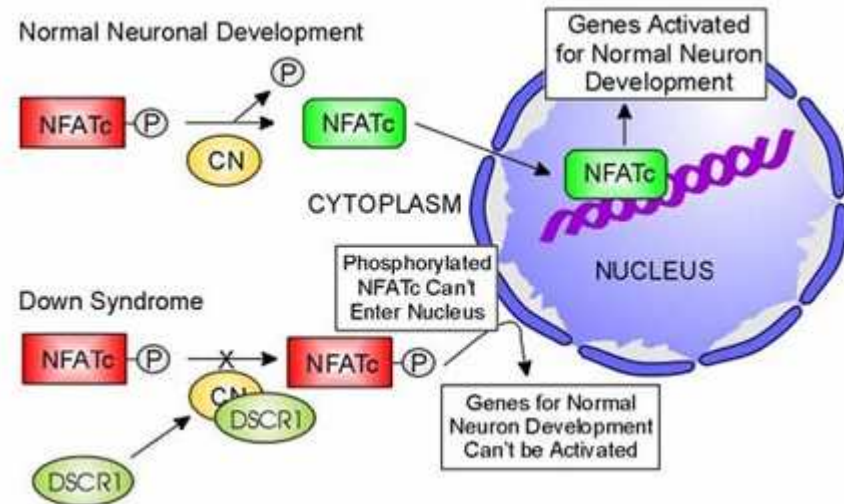


Gardiner, 2004

# NFAT signalling (nuclear factor of activated T-cells)



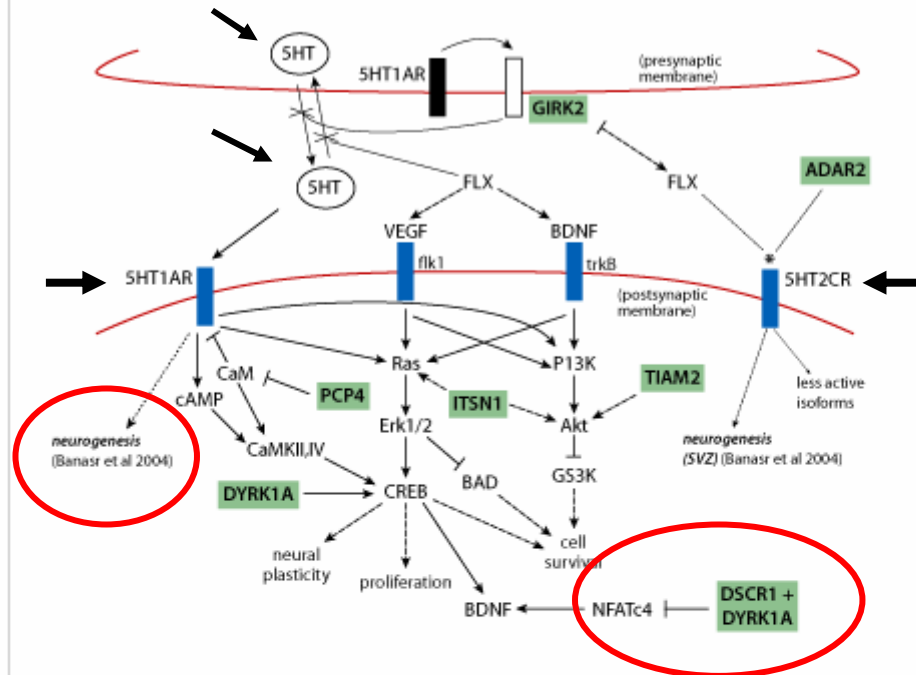
Epstein (2006) Nature 441: 582-583  
 Arron et al. (2006) Nature 441: 595-600



Crabtree 2001, O'Day 2009



## Serotonin (Neurogenesis)



5HT: Serotonin

5HT1AR: Serotonin type 1A receptor

5HT2CR: Serotonin type 2C receptor

CREB: cAMP response element-binding protein

Figure 3 | Pathways relevant to adult neurogenesis: predicting perturbations in Down syndrome and effects of fluoxetine. Signalling through 5HT1AR is required for neurogenesis; VEGF and BDNF are required for proliferation of neural precursors and survival of newborn neurons, respectively. Serotonin (5HT) levels are decreased in Down syndrome, possibly due to GIRK2 activation by 5HT1A autoreceptors causing hyperpolarisation of the presynaptic membrane and inhibition of 5HT release. Fluoxetine (FLX) blocks reuptake of 5HT and thus increases 5HT concentrations and resultant signaling through the integrated pathways that involve cAMP, Ras/Erk and PI3K/Akt, and that converge on CREB. Several chromosome 21 proteins (shaded) interact with pathway components and are predicted to affect pathway flux when overexpressed. Fluoxetine also alters functional properties of 5HT2CR (\*) which may also be affected by increased ADAR2(\*). Solid arrows, activation; dashed arrows, indirect activation; blunt lines, inhibition; dotted lines, alters functional properties. (Figure is a composite from

## Reversion von DS – Phänotypen in der Ts65Dn - Maus

Treatment	Target	Phenotypic feature	Outcome	Reference	Advantages	Limitations
Memantine ●	NMDAR	Hippocampal-based learning deficit (CFC)	Rescue of CFC deficit	Costa et al. <a href="#">[17]</a>	Approved for use in AD	Not tested in children
Pentylentetrazole (PTZ)	GABRA	Hippocampal-based learning deficits (NOR; MWM)	Rescue of NOR, MWM deficits	Fernandez et al. <a href="#">[16]</a> ; Rueda et al. <a href="#">[18]</a>	Effects lasted 3 months after last drug exposure	Not approved for human use; can induce seizures
Fluoxetine (Prozac) ●	Serotonin	Impaired neurogenesis (hippocampus)	Improved neurogenesis	Clark et al. <a href="#">[19]</a>	Approved for human use (mood disorders)	Not tested in children; effects on learning/memory not tested
Nerve growth factor (NGF)	TrkA, p75	Neurodegeneration	Rescue of cellular abnormality	Cooper et al. <a href="#">[20]</a>	-	Effects on learning/memory not tested; no drug available
Activator of sonic hedgehog (SHH)	SHH	Cellular abnormalities in the cerebellum	Rescue of cellular abnormality	Roper et al. <a href="#">[21]</a>	-	Effects on learning/memory not tested; increased cancer risk
Genetic reduction of APP (chr21 gene) ●	APP (chr21)	Failed NGF transport, neurodegeneration	Partial rescue of cellular abnormality	Cataldo et al. <a href="#">[22]</a> ; Salehi et al. <a href="#">[23]</a>	-	Effects on learning/memory not tested; no drug available

Tests of hippocampal-based learning: CFC: Contextual Fear Conditioning; NOR, Novel Object Recognition; MWM, Morris Water Maze. AD, Alzheimer's Disease

Table 1 | **Successful interventions using Ts65Dn mice: pharmacological, biochemical and genetic**



Feature	Frequency in Down syndrome	Chromosome 21 gene associations	Non-chromosome 21 gene associations
Cognitive deficits	Normal distribution; mean IQ = 45; range, 25-70	RCAN1, ITSN1, SYNJ1, DYRK1A, TIAM1, PCP4, BACH1, SOD1, APP; microRNAs; *S100B; SIM2; DSCAM	NMDAR, MAPK, calcineurin, Ras, Elk, BDNF, GABRA; + 300 gene mutations associated with cognitive deficits
Memantine response	Unknown*	RCAN1, ITSN1, SYNJ1, DYRK1A, TIAM1, PCP4, BACH1, SOD1, APP	NR1, NR2a,b, calcineurin, calmodulin, GSK3B, Akt, Erk1/2
Autism	7%	CXADR-BTG3-NCAM2 region	NLGN3, NLGN4X; GABRA4; NRXN1(?)
Seizures	7%	*CSTB, GRIK1 (JAE), GRIK2, HLCS,	+401 gene mutations associated with seizures
Hearing impairment	15%	CLDN14 (DFNB29), *TMPRSS3 (DNFB8,10), KCNE1 (JLNS1)	+277 gene mutations associated with deafness
Vision impairment	40%	*CRYAA, *CBS,* LSS	+155 gene mutations associated with vision impairment
Alzheimer's pathology	All	APP, BACE2	APPL1, APPL2, BACE1, PS1, PS2, APOE, MAPT
AD-like dementia	50% at age 50	APP, BACE2	APPL1, APPL2, BACE1, PS1, PS2, APOE, MAPT
Anxiety	?	*SUMO3, *NRIP1; MRAP	GR, BDNF; MC2R
Early menopause	?	*SUMO3, *NRIP1	ER
Inflammation	?	IFNAR1,2, IL10RB, IFNGR2,* S100B	IL1

Down syndrome features and frequency <sup>[29-33]</sup>. Chromosome 21 and non-chromosome 21: Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>). \*, genes that are not present in the Ts65Dn model and thus their study requires development of new mouse models.

Table 2 | Down syndrome features and variable frequency and candidate gene associations

## **Zusammenfassung**

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**Down – Syndrom (DS) zählt zu den komplexesten genetischen Erkrankungen und stellt die häufigste genetische Ursache für geistige Behinderung dar (1 : 600 Ngb.).**

**In 95% der Fälle mit DS liegt ursächlich eine freie Trisomie 21 vor, die i. d. R. durch meiotisches Non-Disjunction entsteht, und deren Häufigkeit mit dem mütterlichen Alter korreliert ist.**

**Familiäre Robertsonsche Translokationen (insbes. 14;21) können zu Translokationstrisomie 21 bei den Nachkommen eines Translokationsträgers führen (ca. 4 – 5 % aller Fälle von DS).**

**Das Krankheitsbild ist sehr variabel, sowohl was den Grad der geistigen Behinderung als auch das Auftreten fakultativer Auffälligkeiten / Fehlbildungen betrifft.**

**An der Pathogenese des DS sind Gen – Dosis – Effekte von Chr.21 – Genen direkt und indirekt beteiligt (Genexpressions – Studien, Maus – Modell).  
Therapeutische Ansätze sind für die nähere Zukunft zu erwarten.**