

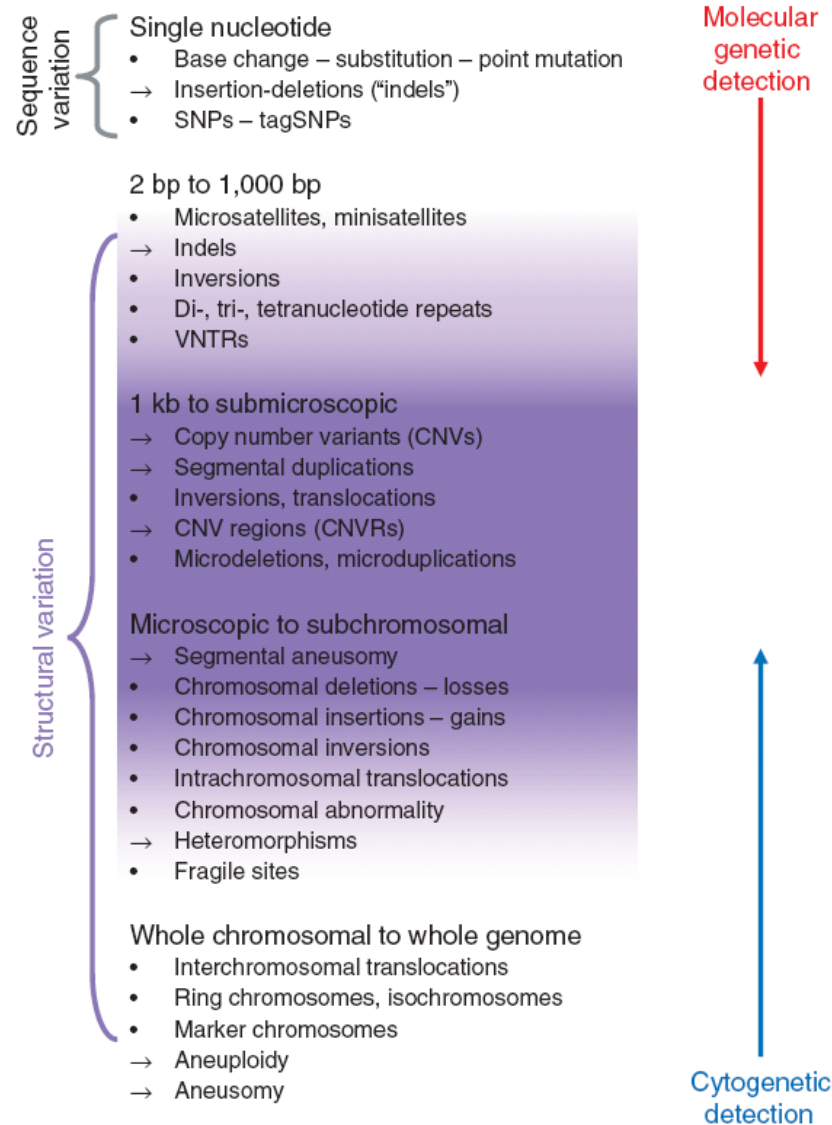
A C G T

DNA-Analytik III

Genetische
Variabilität

Genetische Variabilität

Lexikon



Genetische Variabilität

Sequenzvariation

Mutationen (Mikro~)

Basensubstitution

Insertion + Deletion = InDel

Polymorphismen

SNP („single nucleotide” ~)

Polymorphismen resultieren aus **Mutationen**,
die sich mit einer Häufigkeit $>1\%$ in einer
Population etabliert haben.

SNP-Bestimmung

Methoden

Sanger-Sequenzierung

PyroSequenzierung

Quantitative PCR („TaqMan“)

Massenspektrometrie („Sequenome“)

DNA-Chip („Affimetrix“)

SNP-Bestimmung

Dye Terminator-Sequenzierung

Contig Editor: 1 AF178930.1

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	4330	4340	4350	4360	4370	4380	4390	4400	4410	4420	4430
-1061 5. NO. r27	CATGCTGTGC-C-TGTT										
-168 o404. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
131 o404. NOD2f23	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
-166 1035. 2. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
127 1035. 2. NOD2f23	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
-156 169. s1. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
-161 2103. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGATCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
118 2103. NOD2f23	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGATCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
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-164 1035. 1. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTG										
137 1035. 1. NOD2f23	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
-160 o775. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATG										
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-157 138. s1. NOD2r27	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGATCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
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122 292. s2. NOD2f23	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGATCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
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130 2040. NOD2f23	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										
< > CONSENSUS ***	GATGCTGTGCAAAATGTTATTATTTTAAACATTATGATGCTGTGAAAACCTGGTTAATATTTATAGGTCACITTTGTTTTACTGCTTTAAGTTTATACTCTTTATAGACAACATGGCC										

Base confidence:10 (Probability 0.900000) Position 4394

SNP-Bestimmung

Dye Terminator-Sequenzierung

Contig Editor: 1 AF178930.1

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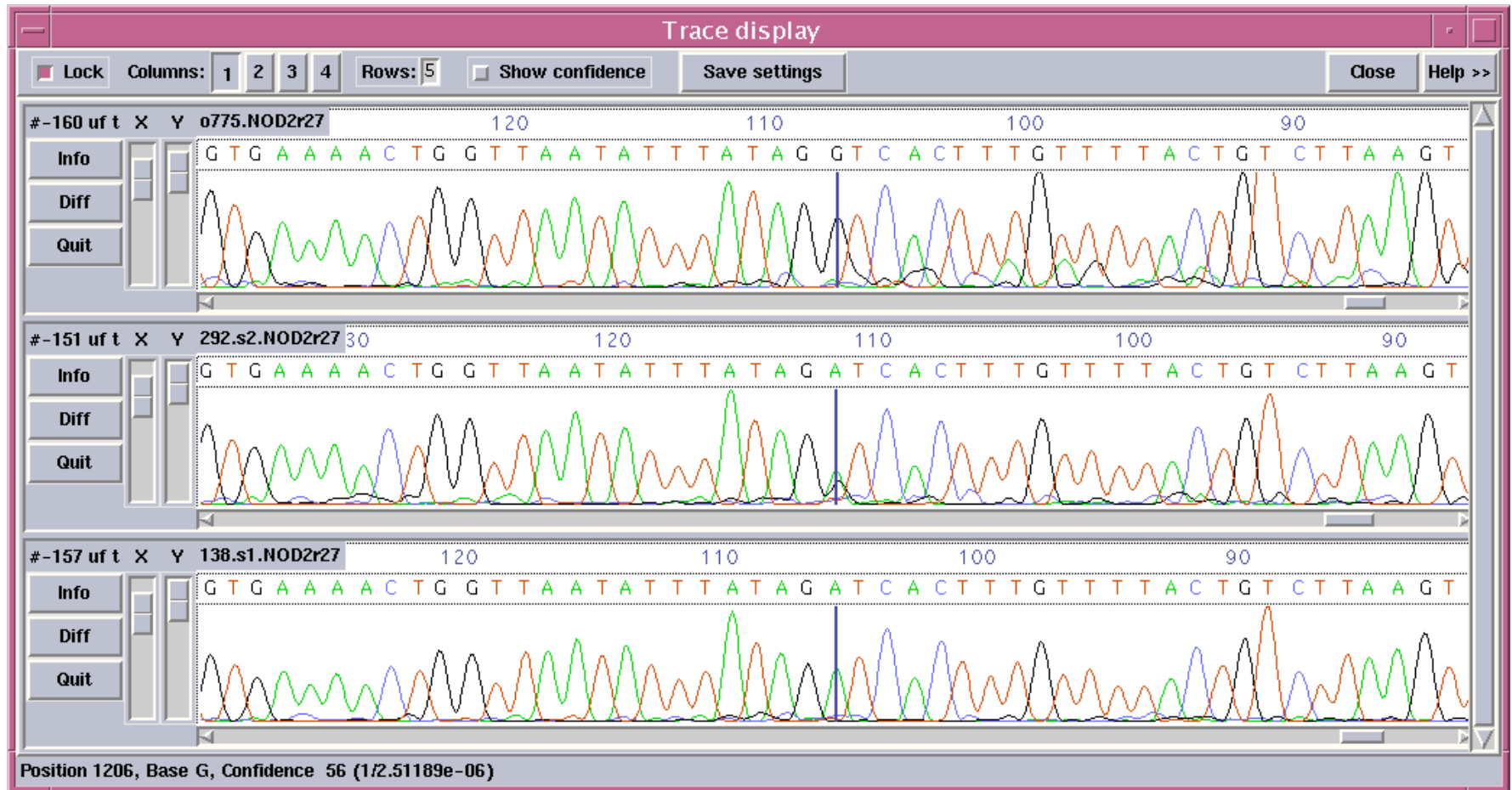
30 4340 4350 4360 4370 4380 4390 4400 4410 4420 4430 4440

-1061 5. NO. r27 ...-C-...
-168 o404. NOD2r27
131 o404. NOD2f23
-166 1035. 2. NOD2r27
127 1035. 2. NOD2f23
-156 169. s1. NOD2r27
-161 2103. NOD2r27 A
118 2103. NOD2f23 A
-153 o826. NOD2r27 A
138 o826. NOD2f23 A
-164 1035. 1. NOD2r27
137 1035. 1. NOD2f23
-160 o775. NOD2r27
117 o775. NOD2f23
-157 138. s1. NOD2r27 A
140 138. s1. NOD2f23 A
-152 367. s1. NOD2r27
123 367. s1. NOD2f23
-145 311. s2. NOD2r27
126 311. s2. NOD2f23
-144 o589. NOD2r27
119 o589. NOD2f23
-142 341. s1. NOD2r27
-151 292. s2. NOD2r27 A
122 292. s2. NOD2f23 A
-167 o288. NOD2r27
134 o288. NOD2f23
-165 2040. NOD2r27
130 2040. NOD2f23
< > CONSENSUS ---- TGCAAAATGTTATTATTTTAAACATTATGATGTGTGAAAAC TGGTTAATATTTATACGTCACITTTGTTTTACTGTCTTAAGTTTATACTCTTATAGACAACATGGCCGTGAAC

Reading:2040.NOD2r27(#165) Length:409(1394) Vector:unknown Clone:unknown Chemistry:terminator Primer:forward universal

SNP-Bestimmung

Dye Terminator-Sequenzierung



InDel-Bestimmung

DyeTerminator-Sequenzierung

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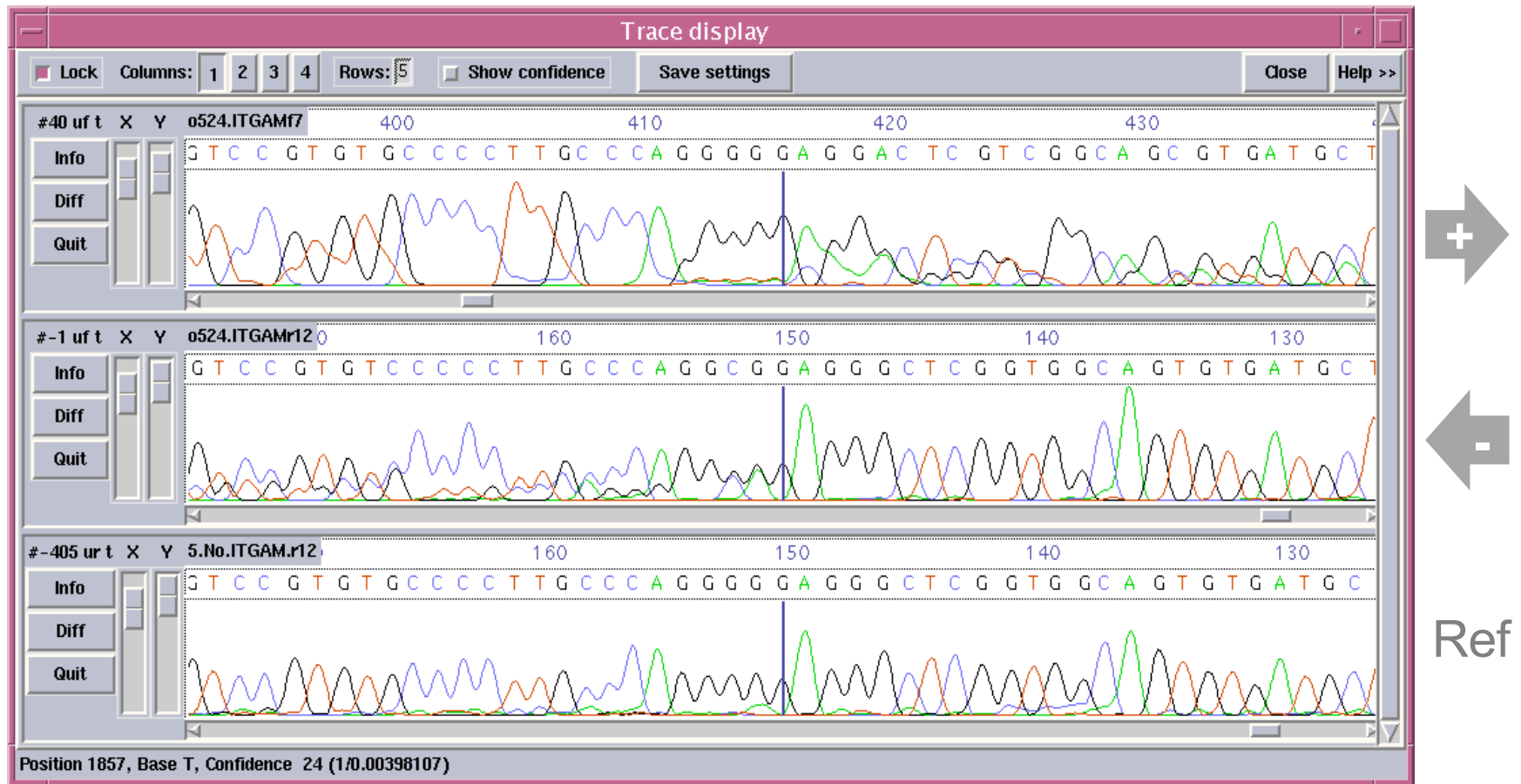
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-5 970034. ITGAMr12												
-21 o795. ITGAMr12												
-1 o524. ITGAMr12					C.		C.				T.	
-10 970280. ITGAMr12												
-310 19. c. D. ITGAM. r12	T.	G. GC.	CC.	CCAG.	GTG.	C.	CAG.	***				
-309 4. No. ITGAM. r12		C.	CA.		C.	CA.	***					
-9 970230. ITGAMr12												
-6 o726. ITGAMr12												
-20 o775. ITGAMr12												
-312 16. c. D. ITGAM. r12		C.	CC.	CCA.	C. C.	CA.	***					
-4 o659. ITGAMr12									T.	T.		
-8 2203. ITGAMr12	C. C. T.	C.	*	A.	GTG.	GT.	CC.	C.				
438 16. c. D. ITGAMf5				G.					T.			
-413 7. u. c. ITGAM. r12												
479 4. No. ITGAMf7						TC.	A. T.		A.			CT
487 7. u. c. ITGAMf7												T
482 8. u. c. ITGAMf7						A.	TC.					CT
483 11. u. c. ITGAMf7						TC.	A.					CT
485 3. No. ITGAMf7						A.	TC.	A.	A.	G.	A. G.	CT
486 6. No. ITGAMf7												TT
437 13. u. c. ITGAMf7												T
39 2203. ITGAMf7						A.	C.	A.	CT.	A.	G. A.	CC
37 o826. ITGAMf7												
38 o404. ITGAMf7												
35 o726. ITGAMf7						T.						T
44 o659. ITGAMf7												T
34 o288. ITGAMf7												T
43 o795. ITGAMf7												T
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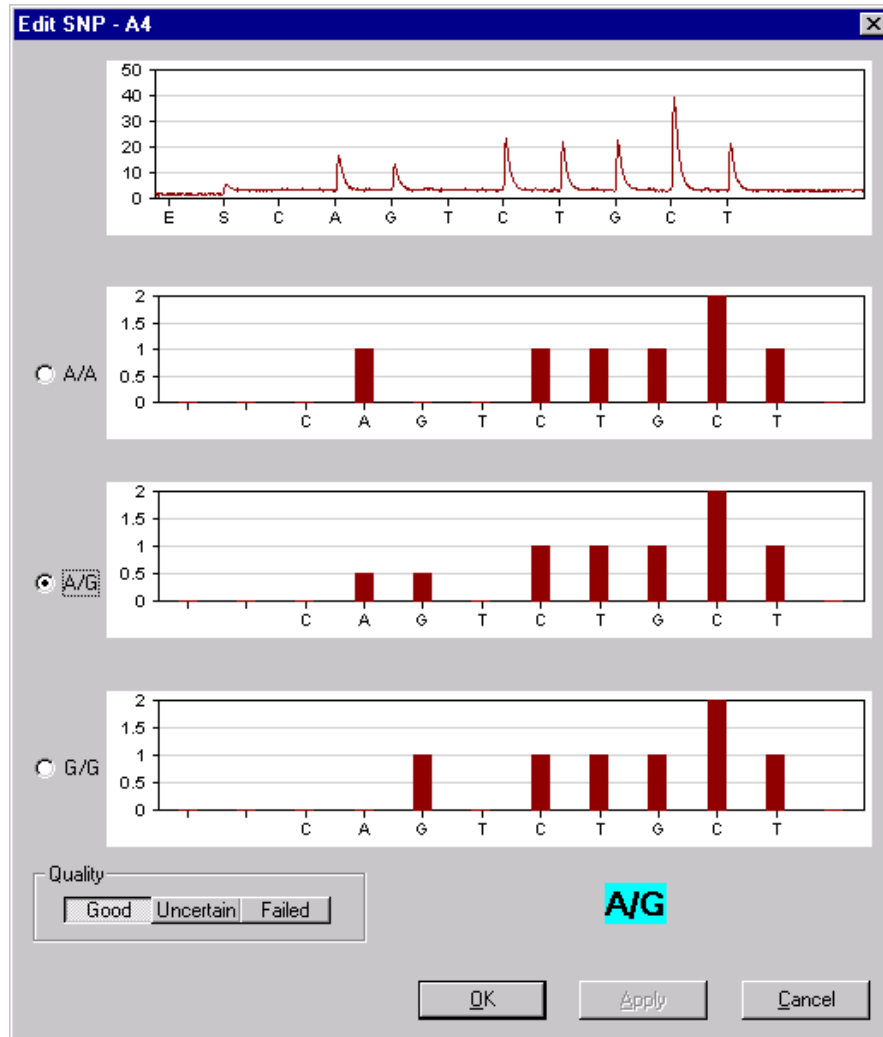
Tag type: EXON Direction: + Comment: "Exon13"

InDel-Bestimmung

DyeTerminator-Sequenzierung



Pyrosequencing



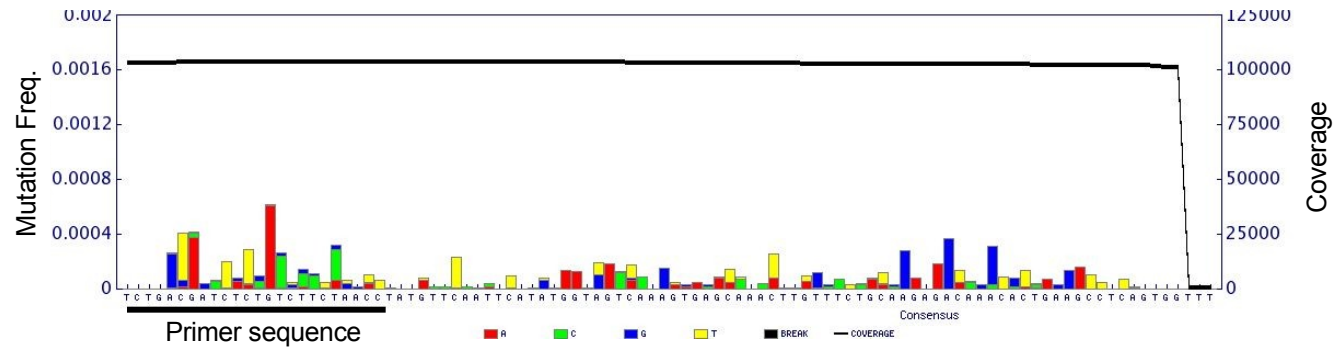
sequence to analyze:

A/GCTGCCT

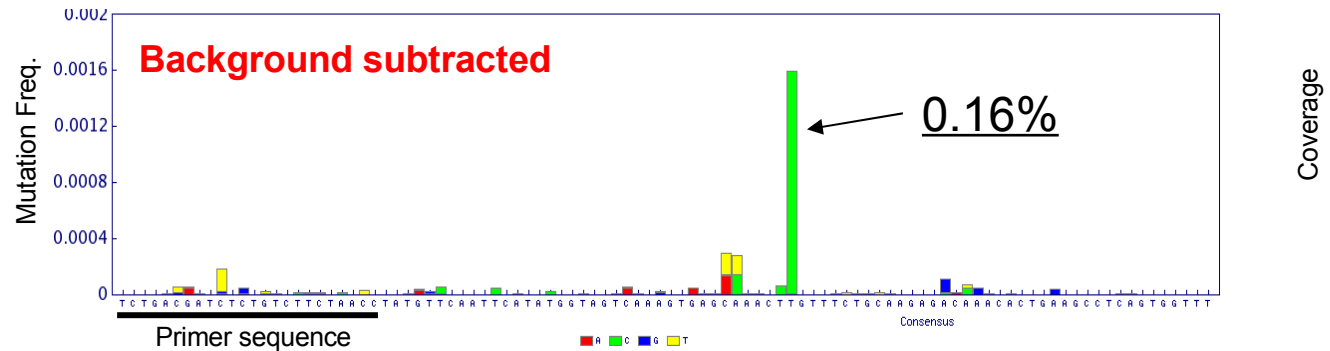
Bestimmung seltener Mutationen/Variationen

Ultra deep 454 sequencing

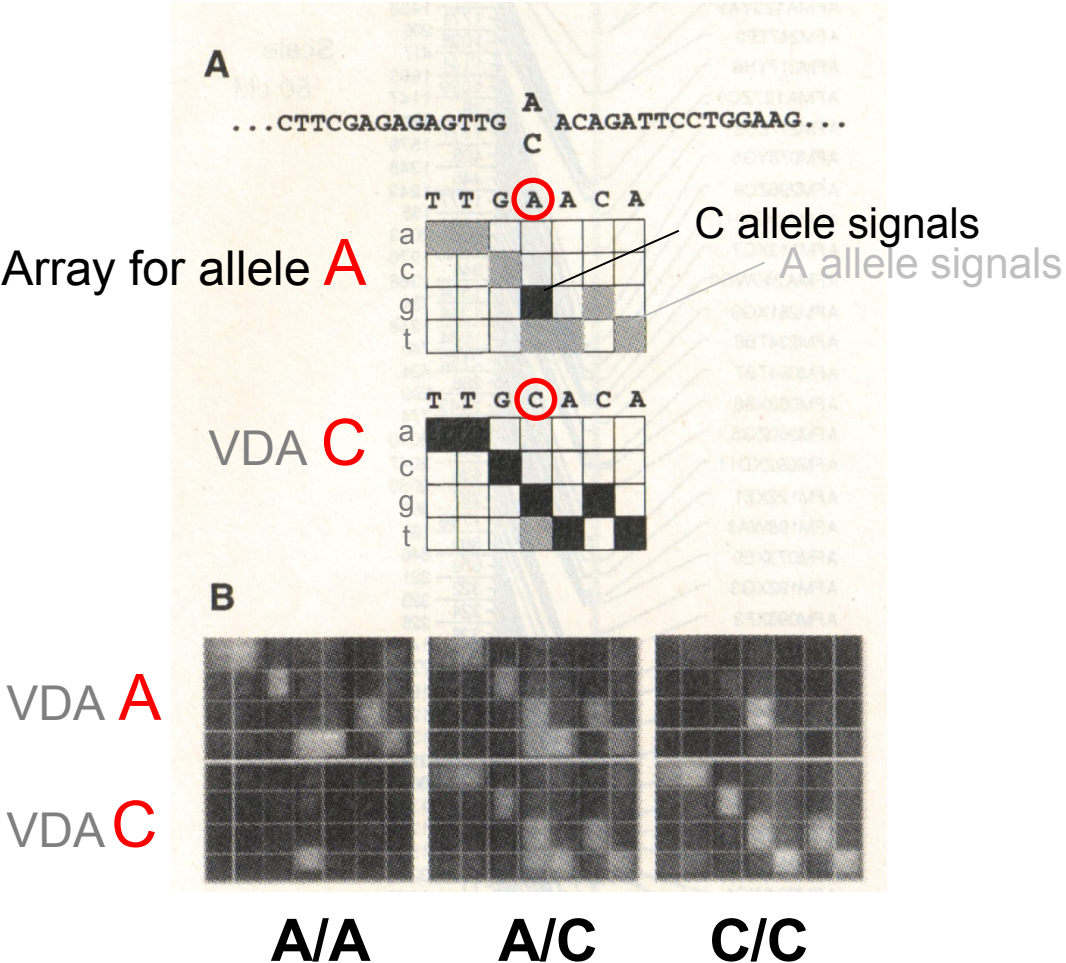
T only



C to T ratio:
1/500

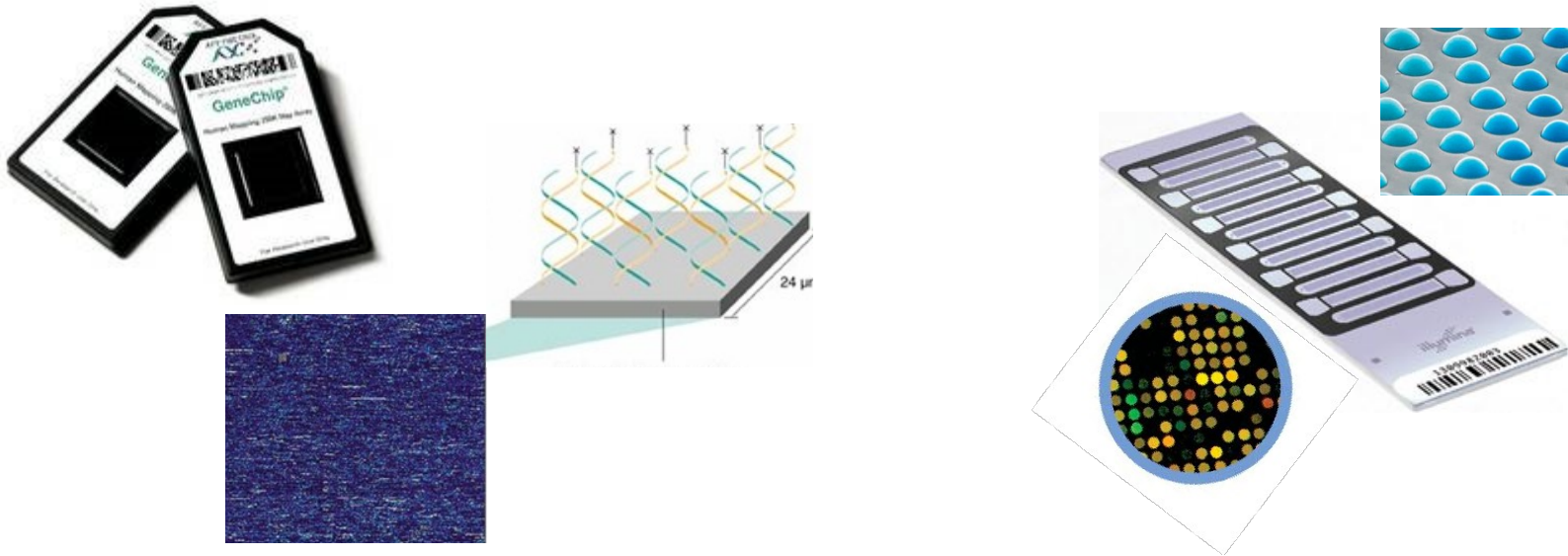


Variant Detection Array for allele A



SNP-Bestimmung

High-throughput array-based genotyping



Affymetrix

Human SNP Array 6.0

>1.8 million markers

906,600 SNPs

946,000 for CNVs

Illumina

Human 660W-Quad BeadChip

2.6 million markers / four samples

550,000 tag SNPs

100,000 for CNVs

5,000 common CNVs

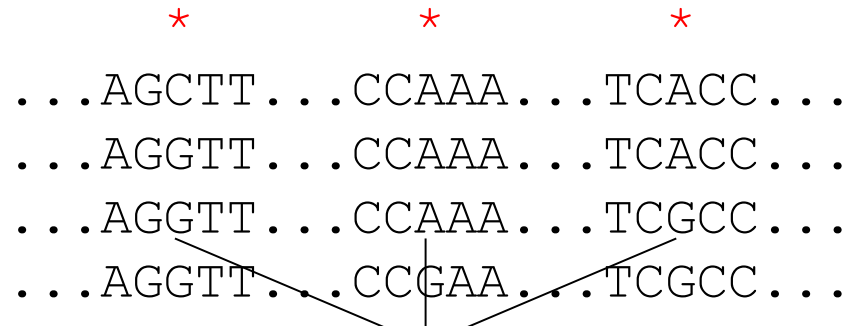
Haplotype

= **set/region** physically linked **polymorphism**

chromosomes

 * * *

...AGCTT...CCAAA...TCACC...
...AGGTT...CCAAA...TCACC...
...AGGTT...CCAAA...TCGCC...
...AGGTT...CCGAA...TCGCC...



major haplotypes

21 SNPs

10..50 kb

TGATTGTTACAACACTTTACC
AGGTCGCTCGAAAATCTAACC
AGGCTATTCGAGAGCCTAGGT
AAGTTACCCGGGAGCCCAGCC

ARTICLES

A second generation human haplotype map of over 3.1 million SNPs

The International HapMap Consortium*

We describe the Phase II HapMap, which characterizes over 3.1 million human single nucleotide polymorphisms (SNPs) genotyped in 270 individuals from four geographically diverse populations and includes 25–35% of common SNP variation in the populations surveyed. The map is estimated to capture untyped common variation with an average maximum r^2 of between 0.9 and 0.96 depending on population. We demonstrate that the current generation of commercial genome-wide genotyping products captures common Phase II SNPs with an average maximum r^2 of up to 0.8 in African and up to 0.95 in non-African populations, and that potential gains in power in association studies can be obtained through imputation. These data also reveal novel aspects of the structure of linkage disequilibrium. We show that 10–30% of pairs of individuals within a population share at least one region of extended genetic identity arising from recent ancestry and that up to 1% of all common variants are untaggable, primarily because they lie within recombination hotspots. We show that recombination rates vary systematically around genes and between genes of different function. Finally, we demonstrate increased differentiation at non-synonymous, compared to synonymous, SNPs, resulting from systematic differences in the strength or efficacy of natural selection between populations.

HapMap Projekt

Gegenstand

**270 individuals from
4 geographically diverse populations:**

YRI Africans: 30 trios (Yoruba in Ibadan, Nigeria)

CEU European: 30 trios of northern/western ancestry
(Utah, US; CEPH collection)

CHB Chinese: 45 unrelated Han individuals (Beijing, China)

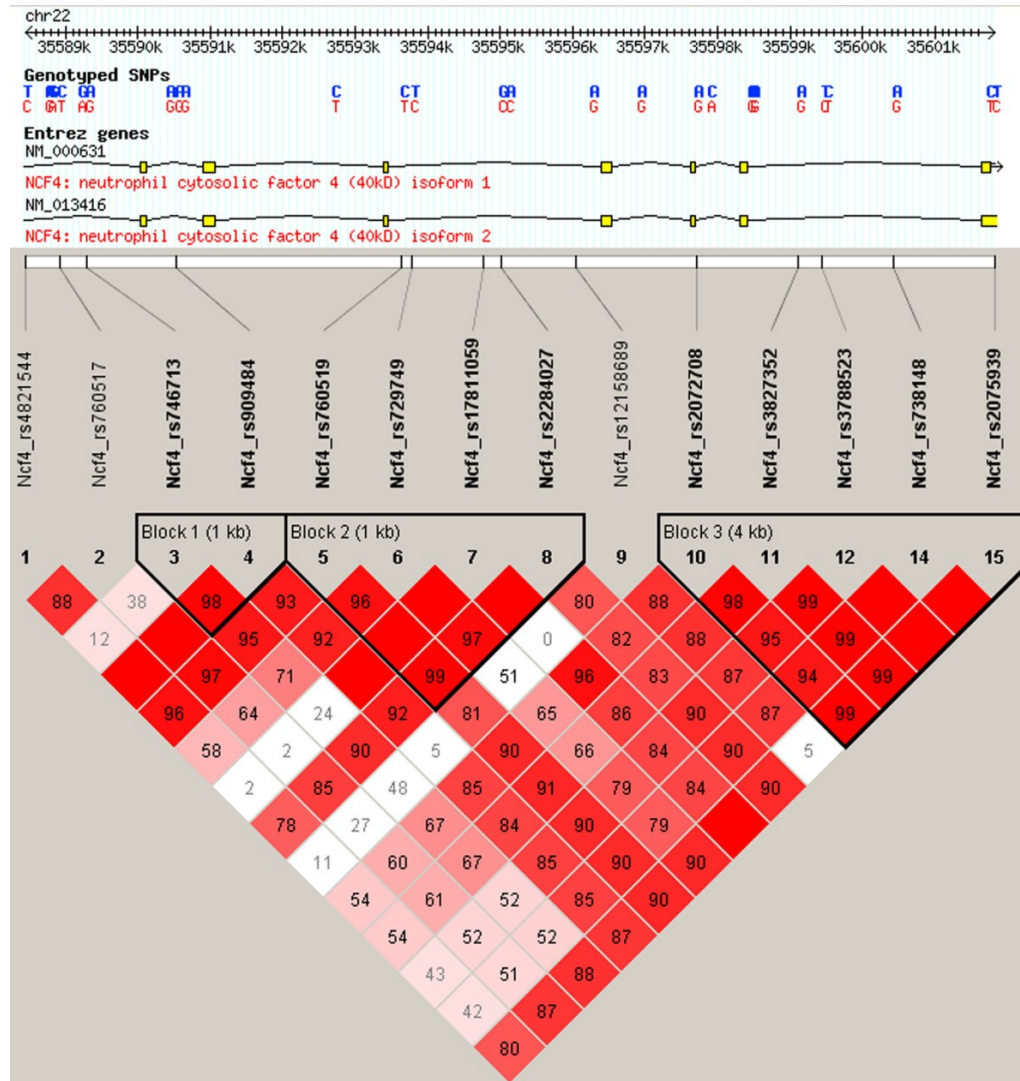
JPT Japanese: 45 unrelated individuals (Tokyo, Japan)

3.1 million human SNPs genotyped

~25–35% of common SNP variation in the populations surveyed

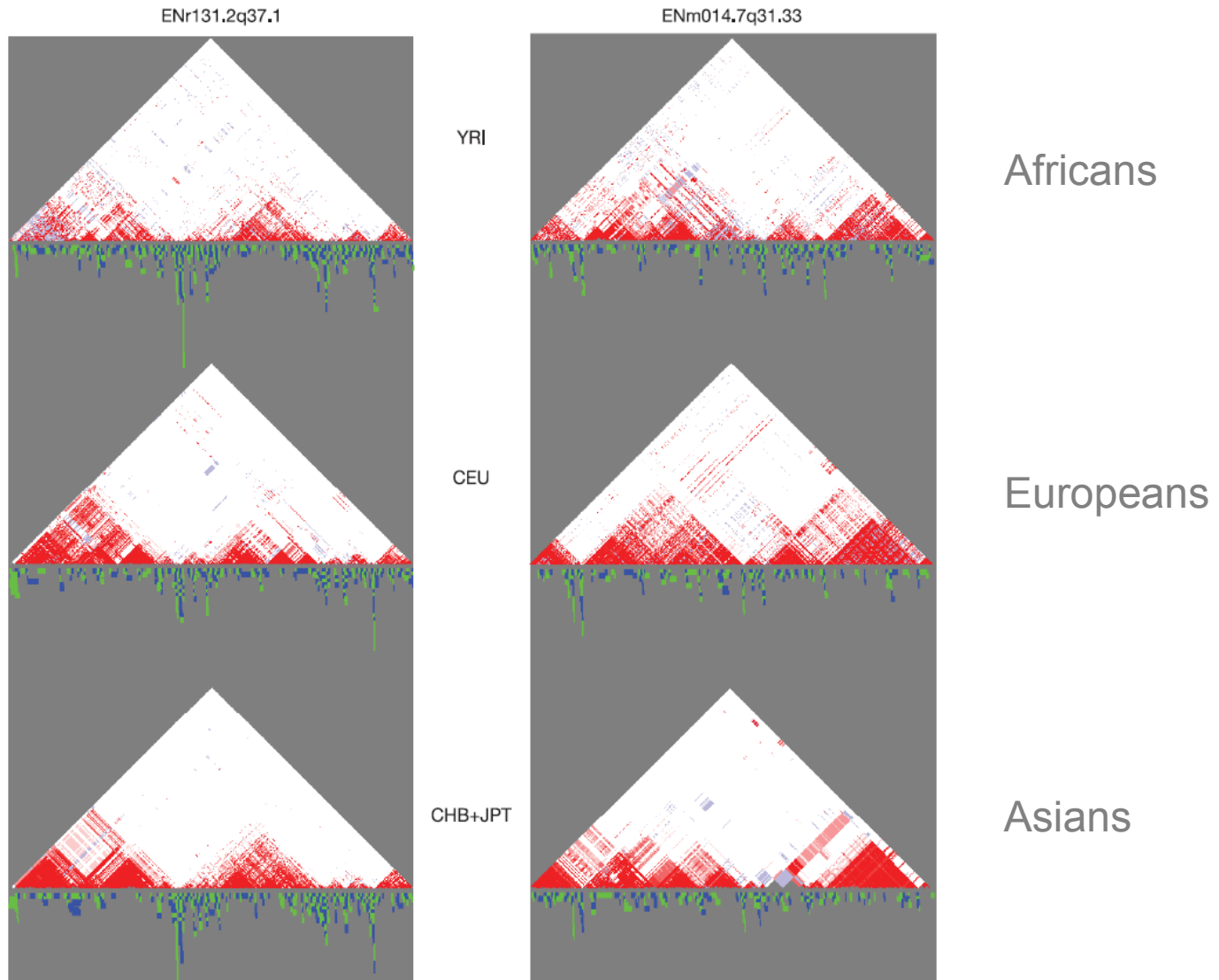
HapMap Projekt

Haplotyp-Blöcke



HapMap Projekt

Haplotyp-Blöcke

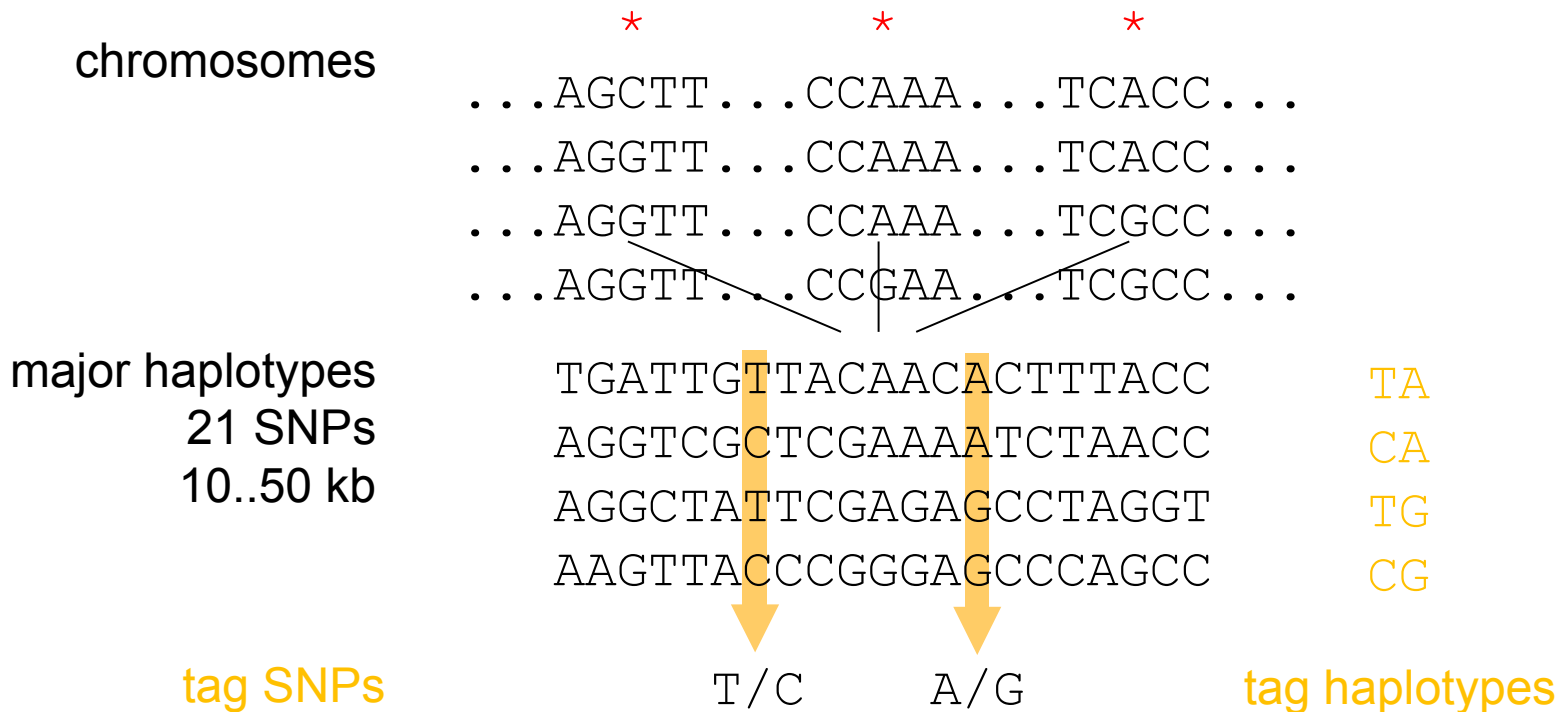


Genetische Variabilität

TagSNPs

Haplotype

= **set/region** physically linked **polymorphism**



HapMap Projekt

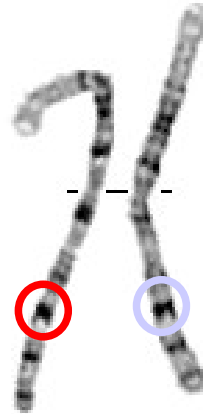
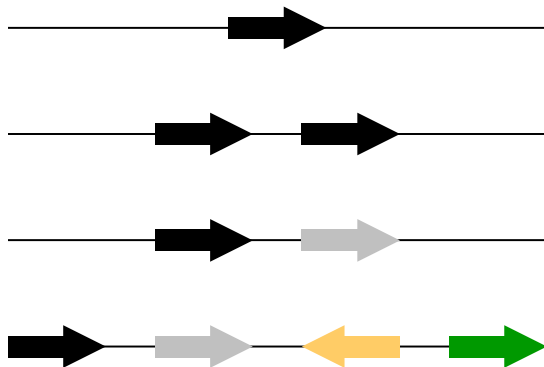
Schlussfolgerungen

- HapMap is estimated to capture the 65-75% **untyped common SNPs** with a likelihood of **90-96%** depending on population.
- Current generation of commercial genome-wide **genotyping products** captures **3.1 million** HapMap SNPs with **80%** in African and up to **95%** in non-African populations.

Genetische Variabilität

Strukturelle Variationen

Chromosom A



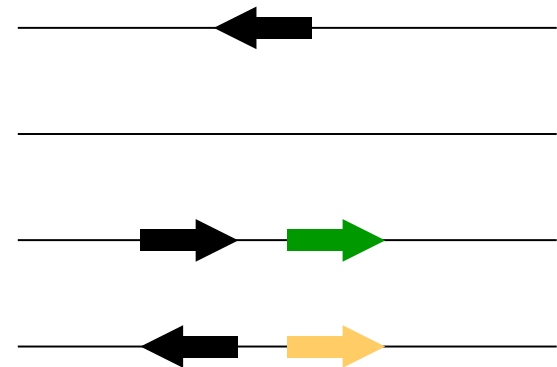
Inversion

InDel

Allel-Variation

Kombination

Chromosom B



Segmentale Duplikation

Definition

genomic regions **>1kb**
with nt identity **>90%**

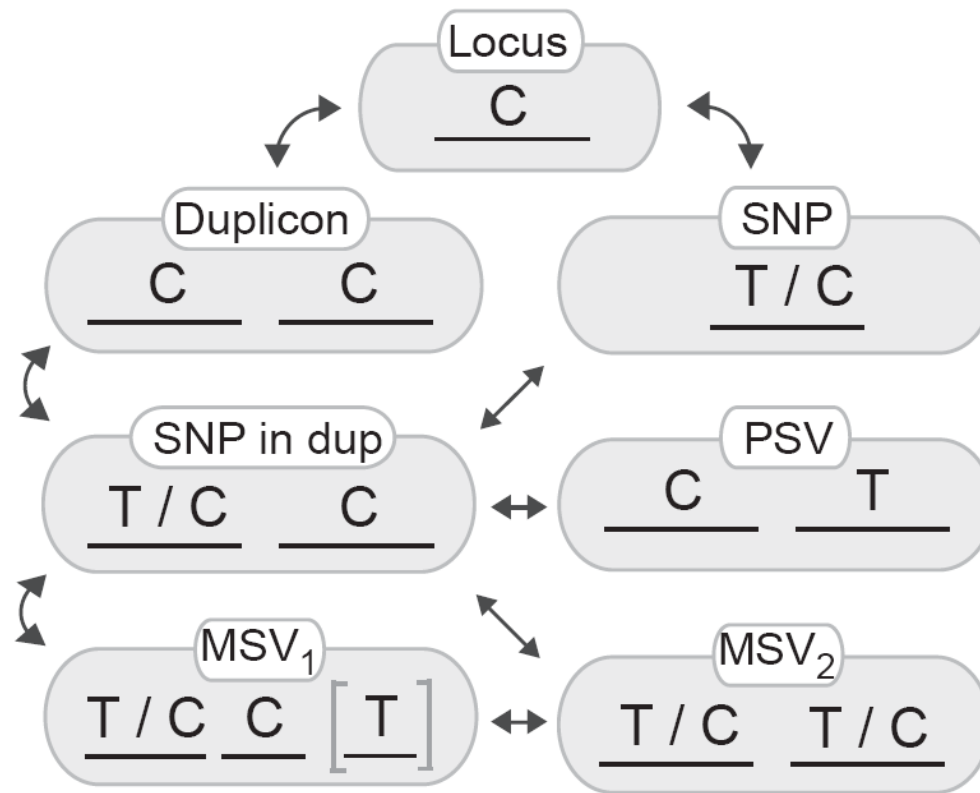
Human genome

5.3% segmentally duplicated

87% of all segmental duplications **>50 kb**

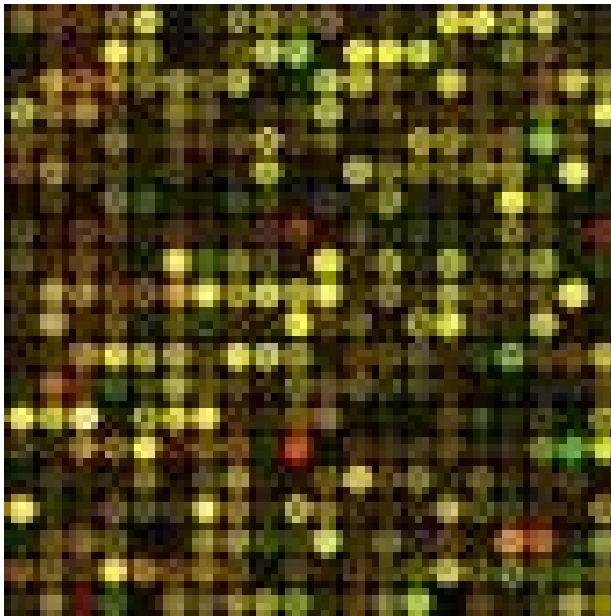
Segmentale Duplikation

SNVs

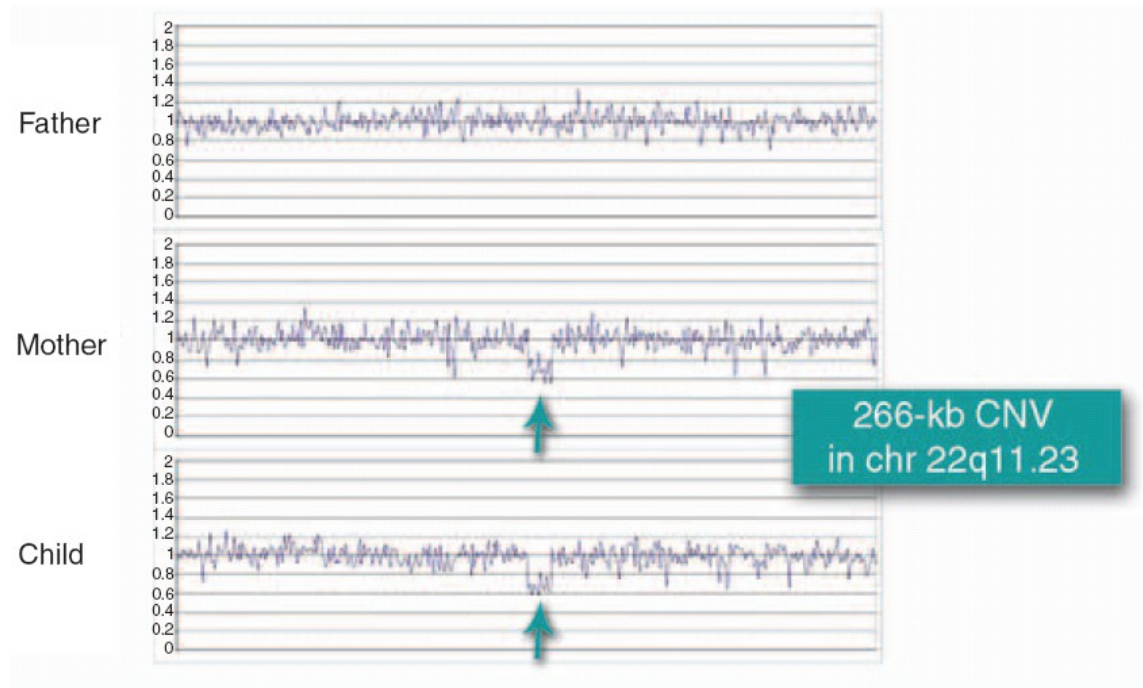


Copy number variation (CNV)

Detection by DNA microarrays

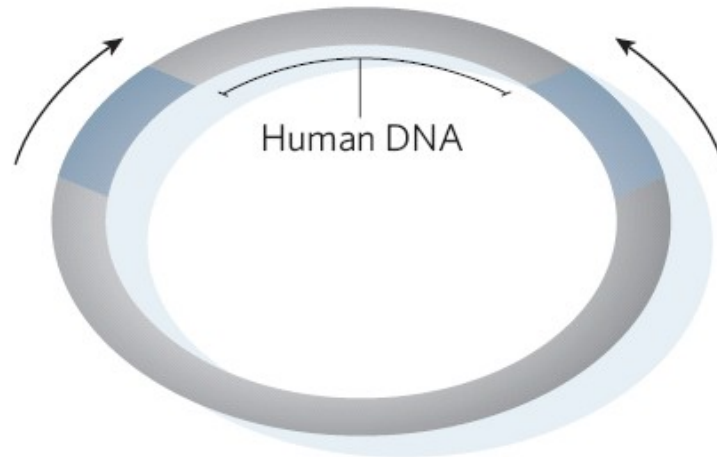


- 0.5-2 Mio data points
 - comparative hybridization vs. a reference



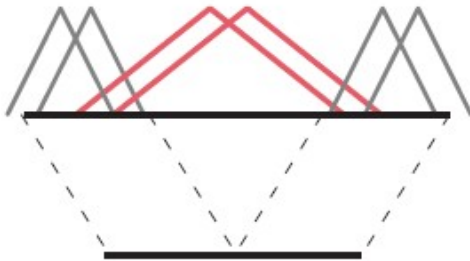
Strukturelle Variationen

Kartierung



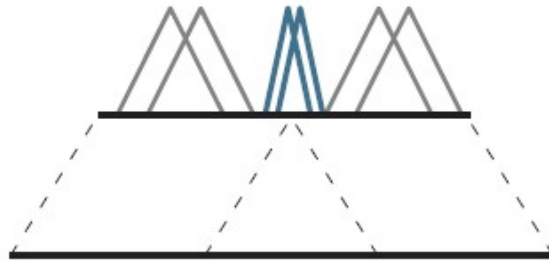
BAC/Fosmid vector

Span > mean +3 s.d.



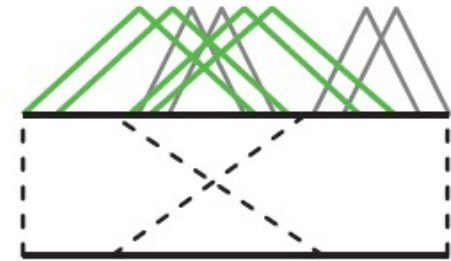
Deletion

Span > mean -3 s.d.

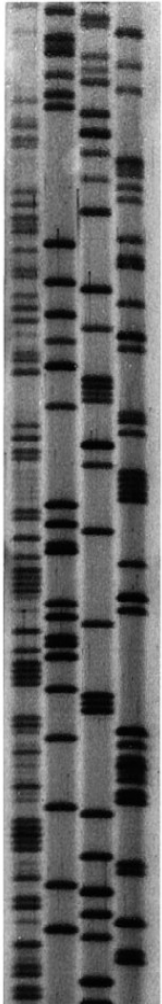


Insertion

Inverted orientation



Inversion



A C G T

DNA-Analytik

epigenetische Modifikationen

METHYL MAGiC

**Maximum Health
Through Methylation**

METHYLATION

Prevents Heart Disease and Stroke
Boosts Brain Power
Cures Depression
Treats Arthritis and Many Other Diseases
Prevents Cancer
Slows Down Aging

Craig Cooney, Ph.D.

with Bill Lawren

Foreword by Kilmer S. McCully, M.D.

Kenntnisstand

- in den meisten Organismen sind ~5% aller Cytosine in Position 5 des Pyrimidinringes methyliert
- Cytosinmethylierung ist kodierungsneutral und dient als Markierung der DNA
- diese Markierung der DNA erfüllt in unterschiedlichen Organismengruppen unterschiedliche Aufgaben
- in Säugern führt die *in-vitro* Methylierung von Promotorbereichen zur transkriptionellen Inaktivierung des betreffenden Gens *in-vivo*
- die mit aktiven Genen assoziierten *CpG islands* sind unmethyliert
- der 5-Methylcytosingehalt von DNA ist gewebespezifisch

Methylierung in unterschiedlichen Organismen



Bakterien

- Restriktions-/Modifikationssystem
- Reparatursystem
- Markierung des Replikationsorigins



Pilze

- Erkennung von Duplikationen
- *host-defence-mechanism (?)*



Pflanzen

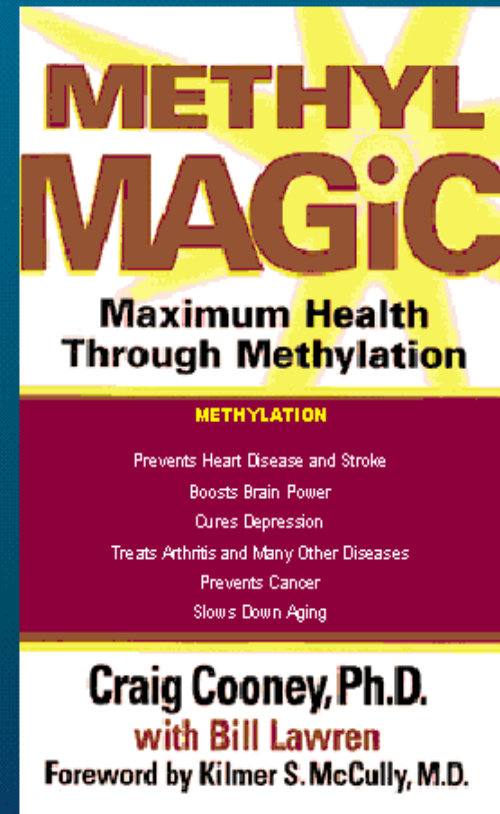
- *host-defence-mechanism (?)*
- Geninaktivierung
- Hemmung des Elongationsschrittes der Transkription



Tiere

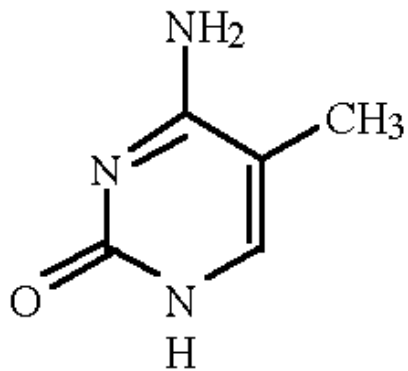
- *host-defence-mechanism (?)*
- Geninaktivierung, Heterochromatisierung
- Hemmung des Initiationsionsschrittes der Transkription

Mensch:

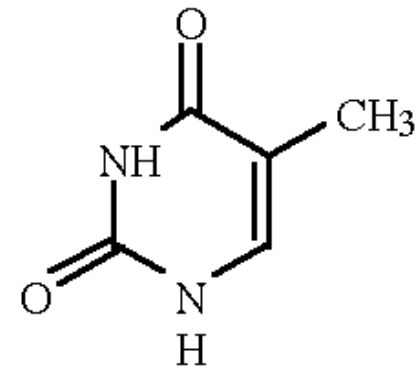


Methylierung

spontane Desaminierung



5-Methyl-cytosin



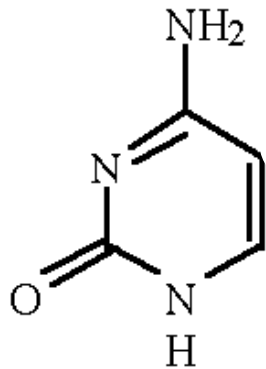
Thymin

Was sind *CpG islands*?

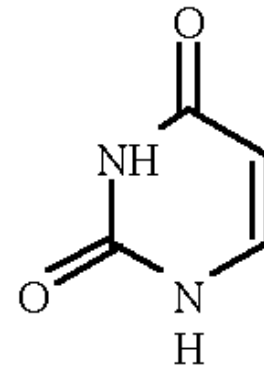
- CpG = Cytosin, in 5'-Richtung gefolgt von einem Guanin
- CpG-Paare sind im Genom der Eukaryoten etwa 5fach unterrepräsentiert.
- Bereiche in denen CpG-Paare mit der statistisch zu erwartenden Häufigkeit auftreten, werden *CpG islands* genannt.
- C+G-Dichte und CpG/GpC Verhältnis zur *in-silico* Identifizierung genutzt
(observed/expected > 0,8; G+C > 60%)
- 5'-Bereiche von 60% aller Gene sind mit *CpG islands* assoziiert.
- In Vertebraten sind nur Cytosine in CpG-Paaren methyliert.
- *CpG islands* sind i.d.R. unmethyliert.

Bisulfit Sequenzierung

chemische Desaminierung



Cytosin

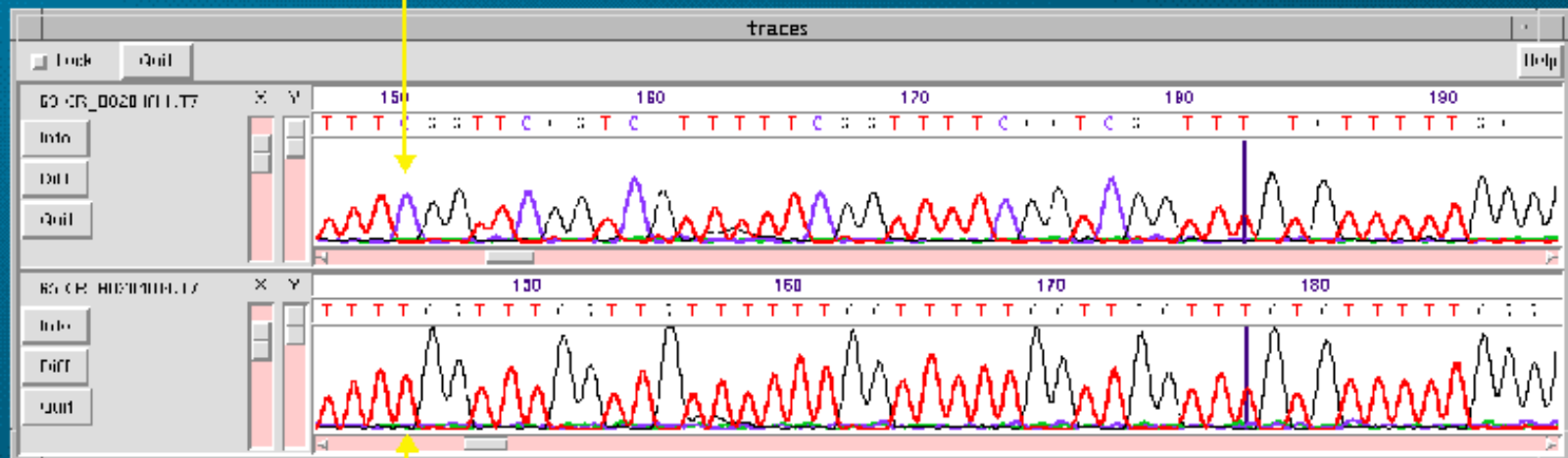


Uracil

Bisulfit Sequenzierung

Nachweis mit DyeTerminatoren

5-Methylcytosin erscheint als Cytosin



unmethyliertes Cytosin erscheint als Thymin

Bisulfit Sequenzierung

Genomweite Analyse

Vol 462 | 19 November 2009 | doi:10.1038/nature08514

nature

ARTICLES

Human DNA methylomes at base resolution show widespread epigenomic differences

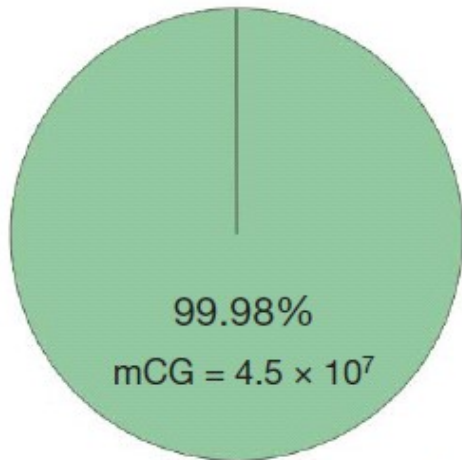
Ryan Lister^{1*}, Mattia Pelizzola^{1*}, Robert H. Downen¹, R. David Hawkins², Gary Hon², Julian Tonti-Filippini⁴, Joseph R. Nery¹, Leonard Lee², Zhen Ye², Que-Minh Ngo², Lee Edsall², Jessica Antosiewicz-Bourget^{5,6}, Ron Stewart^{5,6}, Victor Ruotti^{5,6}, A. Harvey Millar⁴, James A. Thomson^{5,6,7,8}, Bing Ren^{2,3} & Joseph R. Ecker¹

DNA cytosine methylation is a central epigenetic modification that has essential roles in cellular processes including genome regulation, development and disease. Here we present the first genome-wide, single-base-resolution maps of methylated cytosines in a mammalian genome, from both human embryonic stem cells and fetal fibroblasts, along with comparative analysis of messenger RNA and small RNA components of the transcriptome, several histone modifications, and sites of DNA–protein interaction for several key regulatory factors. Widespread differences were identified in the composition and patterning of cytosine methylation between the two genomes. Nearly one-quarter of all methylation identified in embryonic stem cells was in a non-CG context, suggesting that embryonic stem cells may use different methylation mechanisms to affect gene regulation. Methylation in non-CG contexts showed enrichment in gene bodies and depletion in protein binding sites and enhancers. Non-CG methylation disappeared upon induced differentiation of the embryonic stem cells, and was restored in induced pluripotent stem cells. We identified hundreds of differentially methylated regions proximal to genes involved in pluripotency and differentiation, and widespread reduced methylation levels in fibroblasts associated with lower transcriptional activity. These reference epigenomes provide a foundation for future studies exploring this key epigenetic modification in human disease and development.

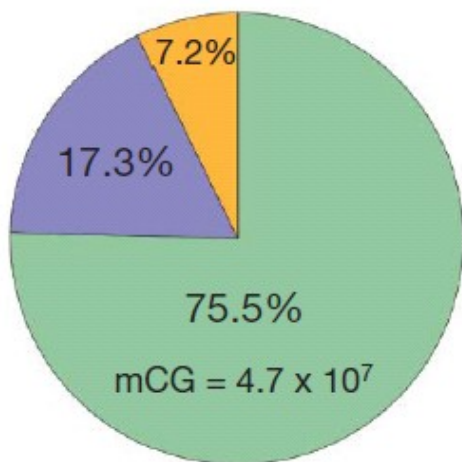
DNA Methylierung

Fibroblasten vs. ES

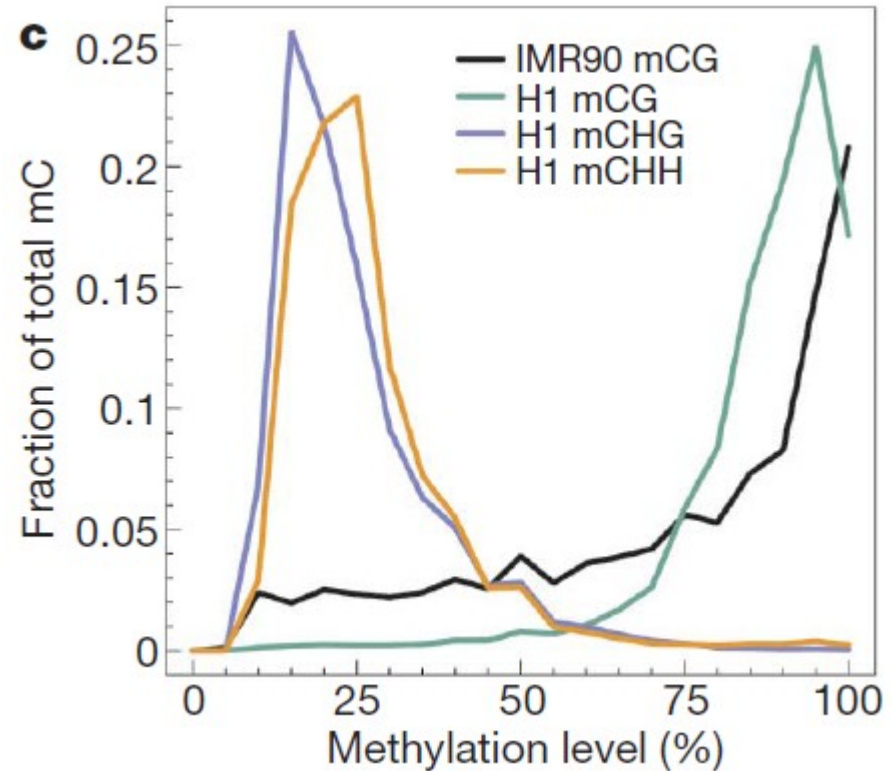
■ mCG ■ mCHG ■ mCHH



IMR90 mC = 4.5×10^7

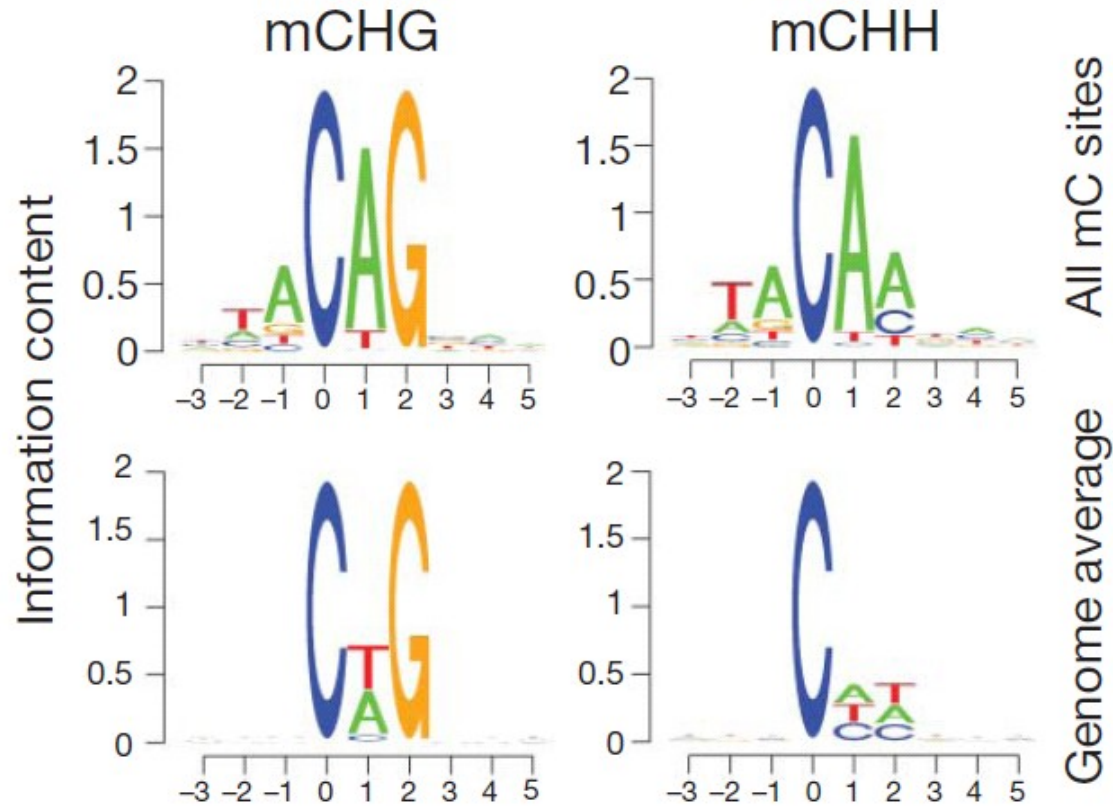


H1 mC = 6.2×10^7



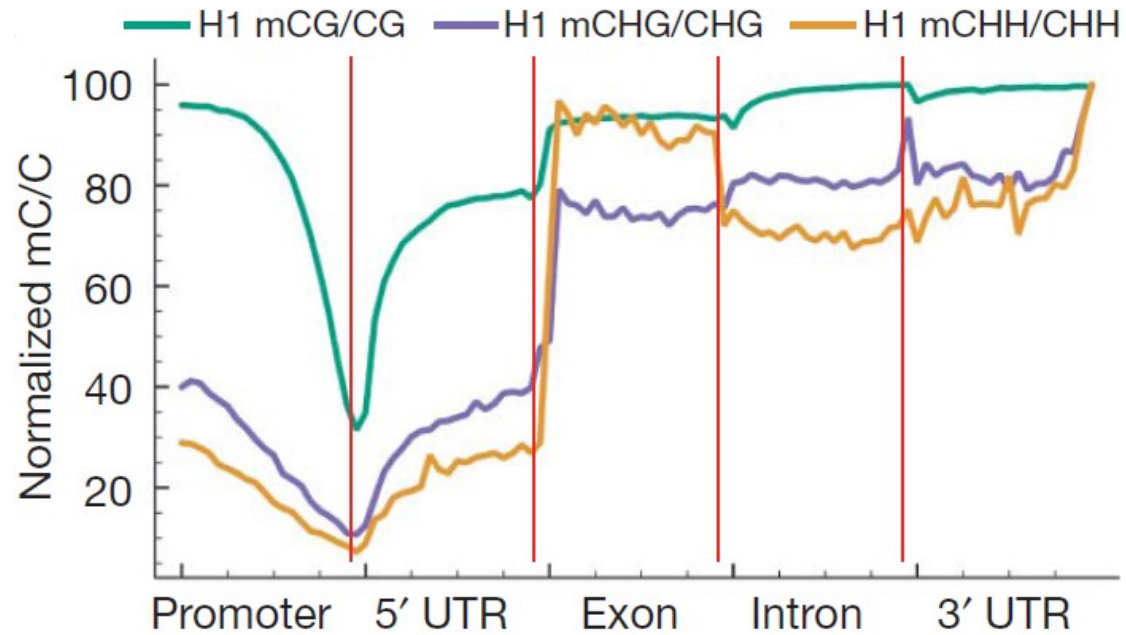
DNA Methylierung

ES



DNA Methylierung

ES

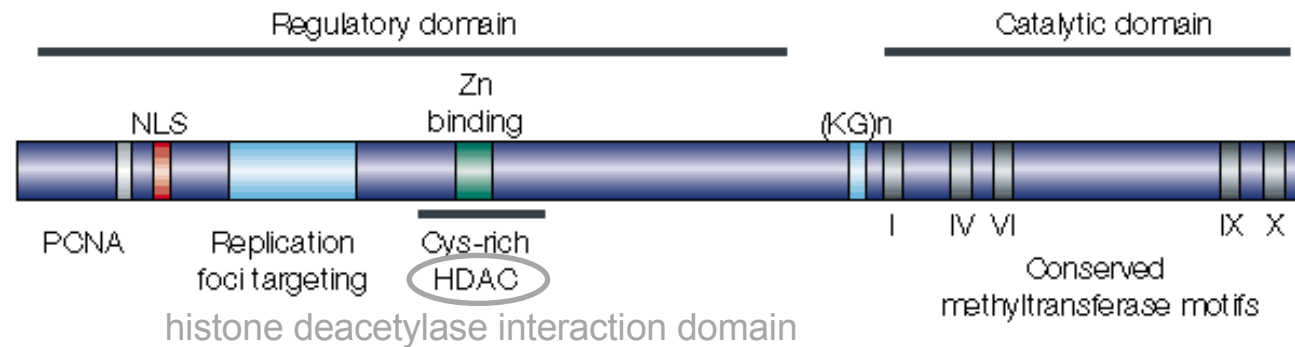


DNA Methylierung

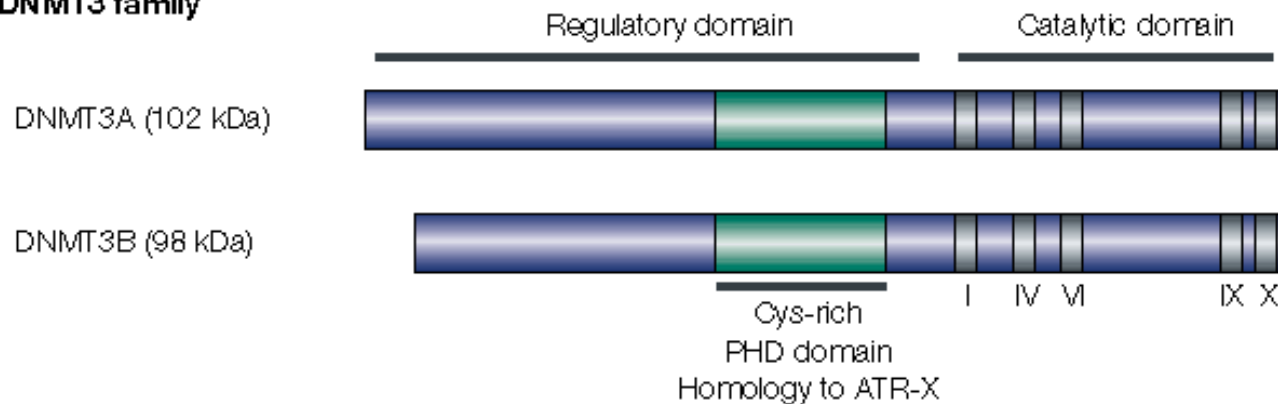
DNA-Methyl-Transferase

Aufrecht-
erhaltung

DNMT1 (193.5 kDa)



DNMT3 family

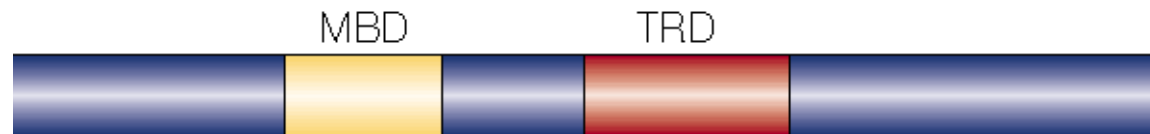


de novo

DNA Methylierung

Methyl-C bindende Proteine

MeCP2 (Xq28)

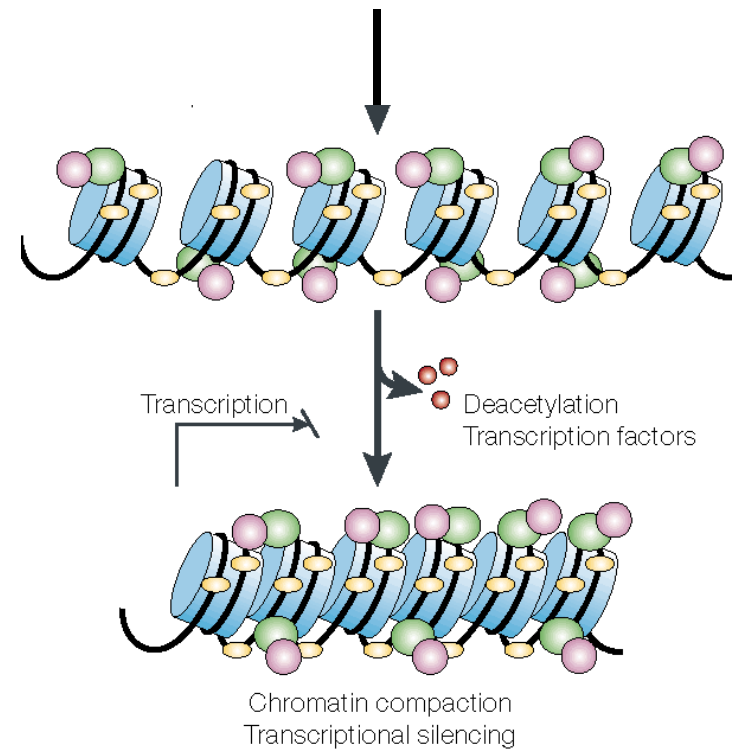
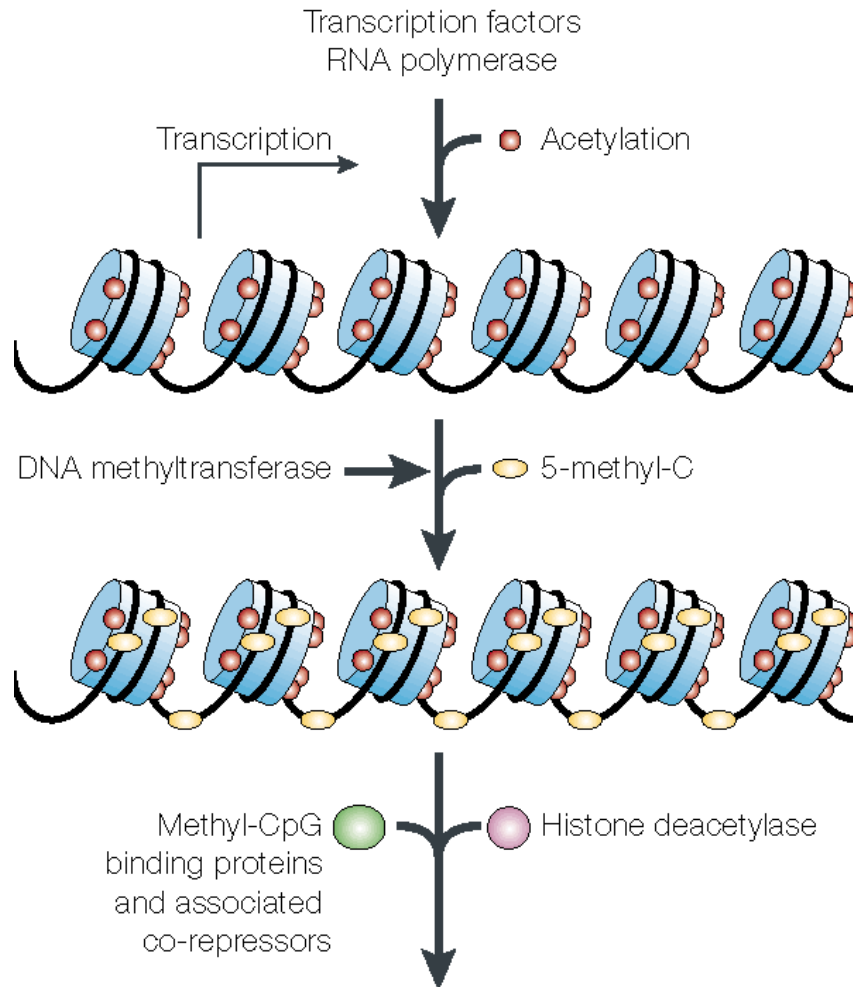


Methyl-CpG
Binding
Domain

Transcriptional
Repression
Domain

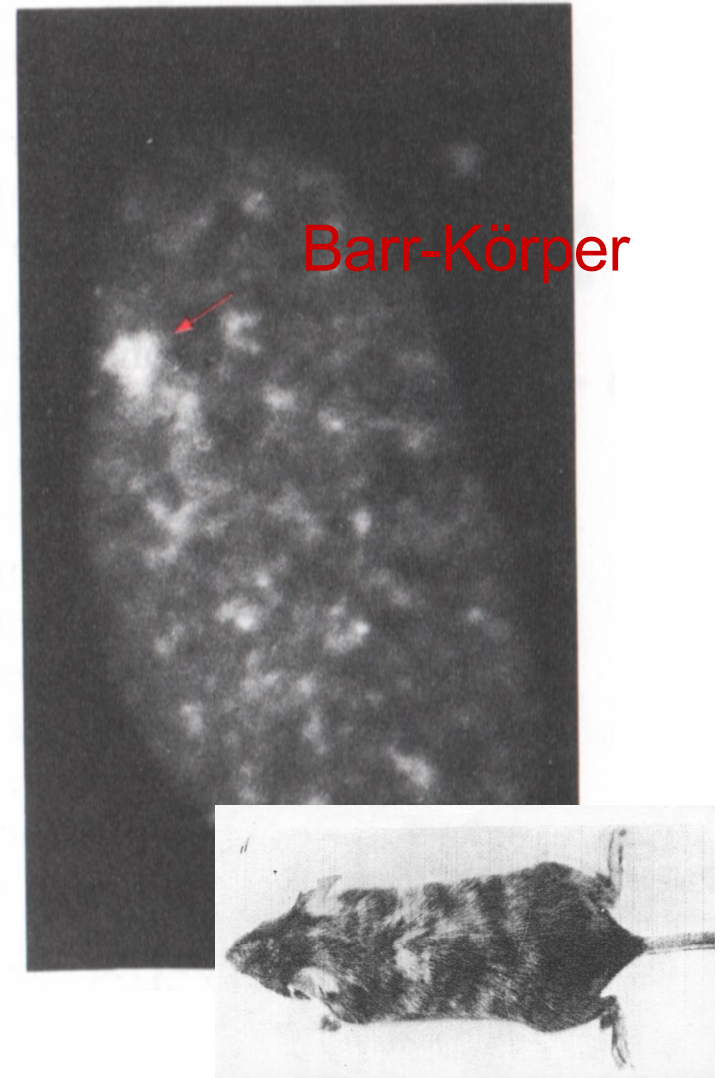
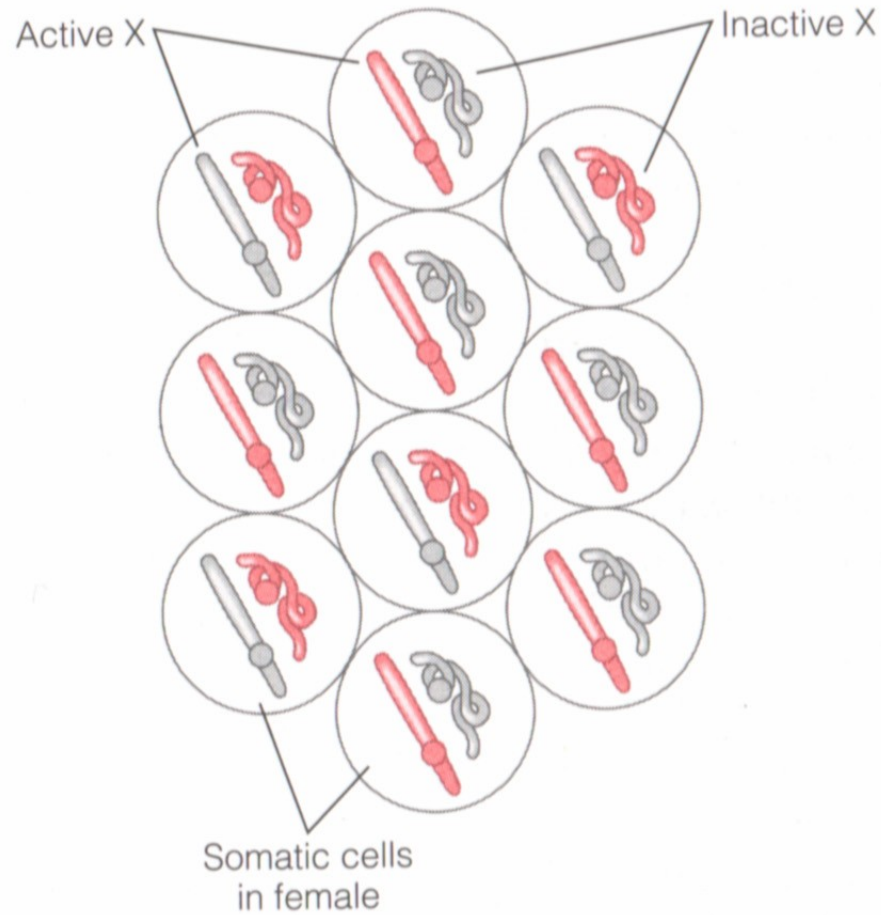
DNA Methylierung

Geninaktivierung & Heterochromatisierung



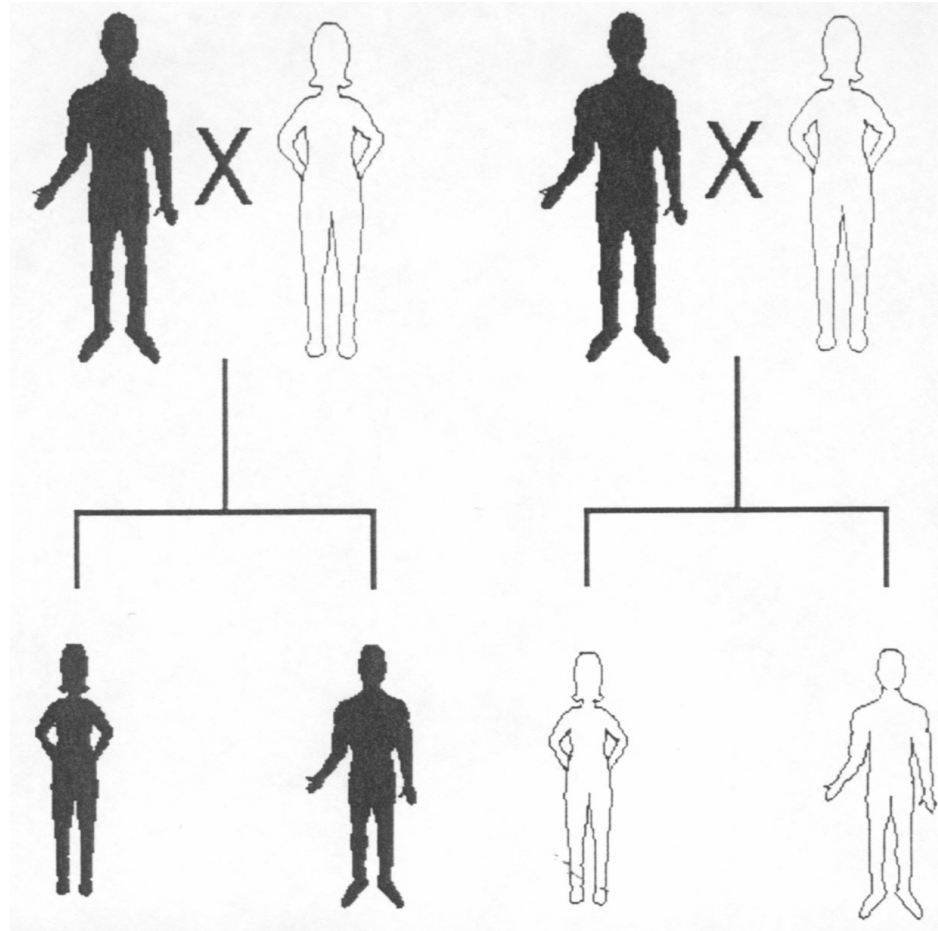
DNA Methylierung

X-Inaktivierung



DNA Methylierung

Imprinting / Prägung



mütterliche
maternales

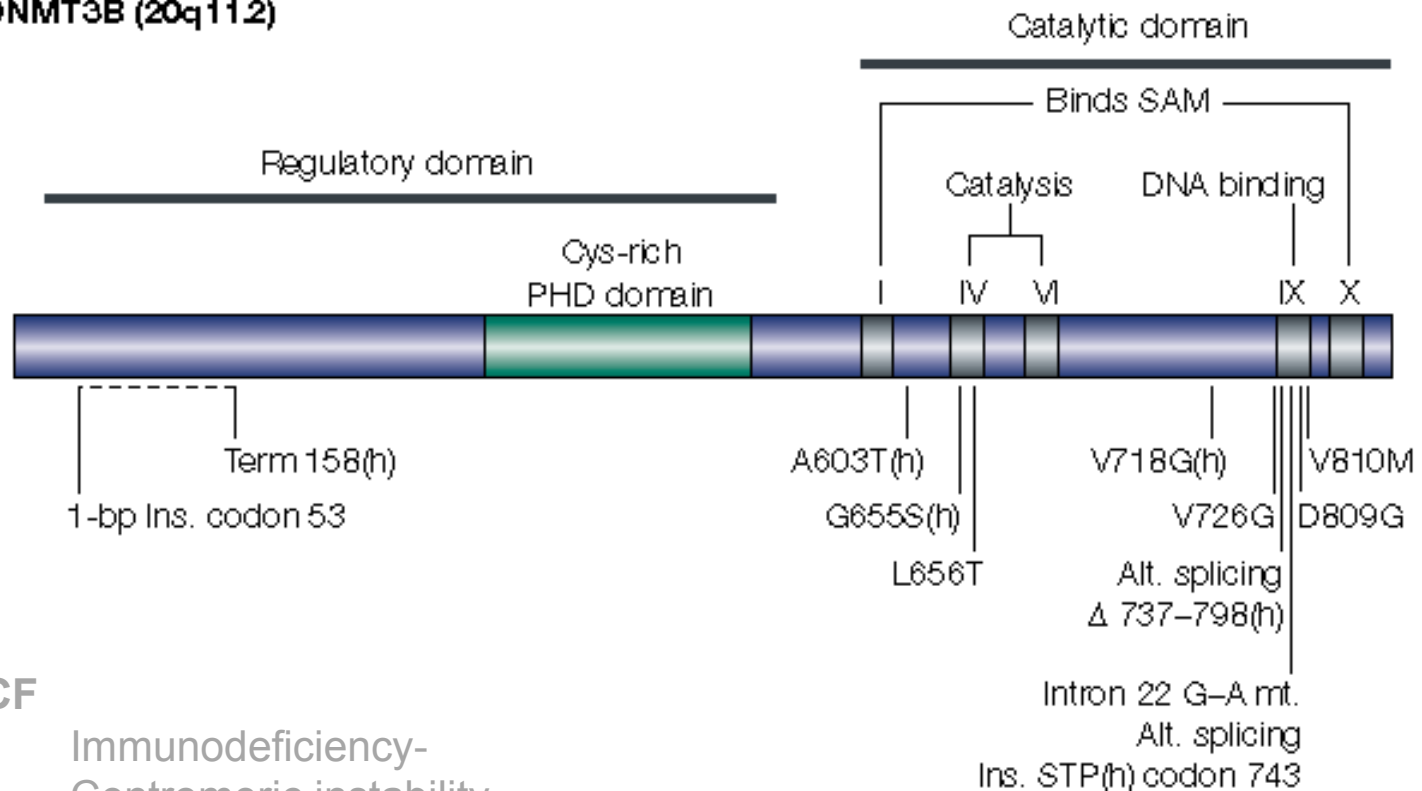
väterliche
paternales

Gen unterliegt der Prägung / Inaktivierung
Imprinting

DNA Methylierung & Krankheit

ICF-Syndrom

DNMT3B (20q11.2)



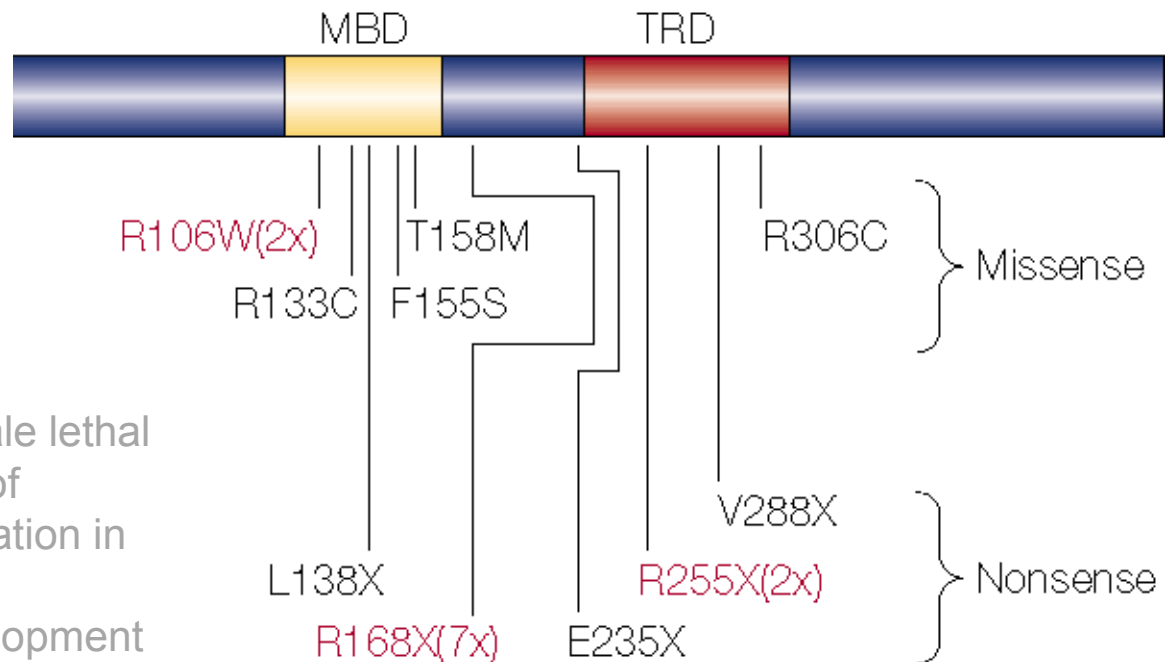
ICF

- Immunodeficiency-
- Centromeric instability
- Facial anomalies

DNA Methylierung & Krankheit

Rett-Syndrom

MeCP2 (Xq28)

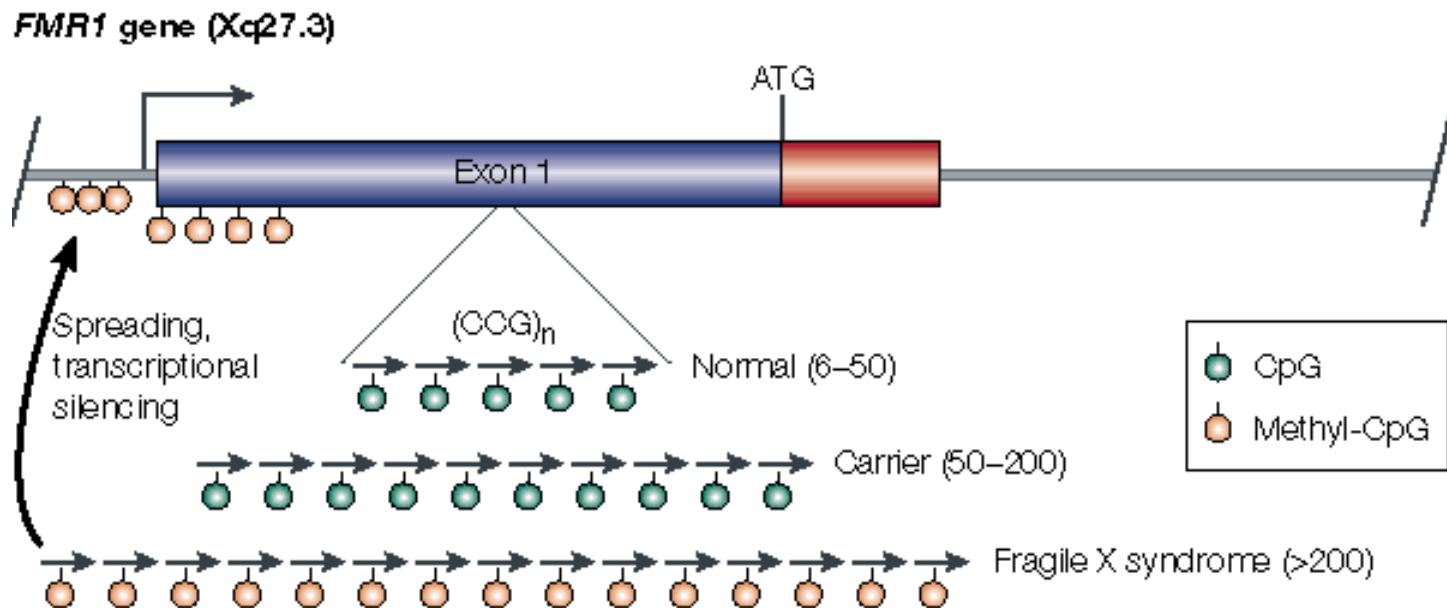


RETT

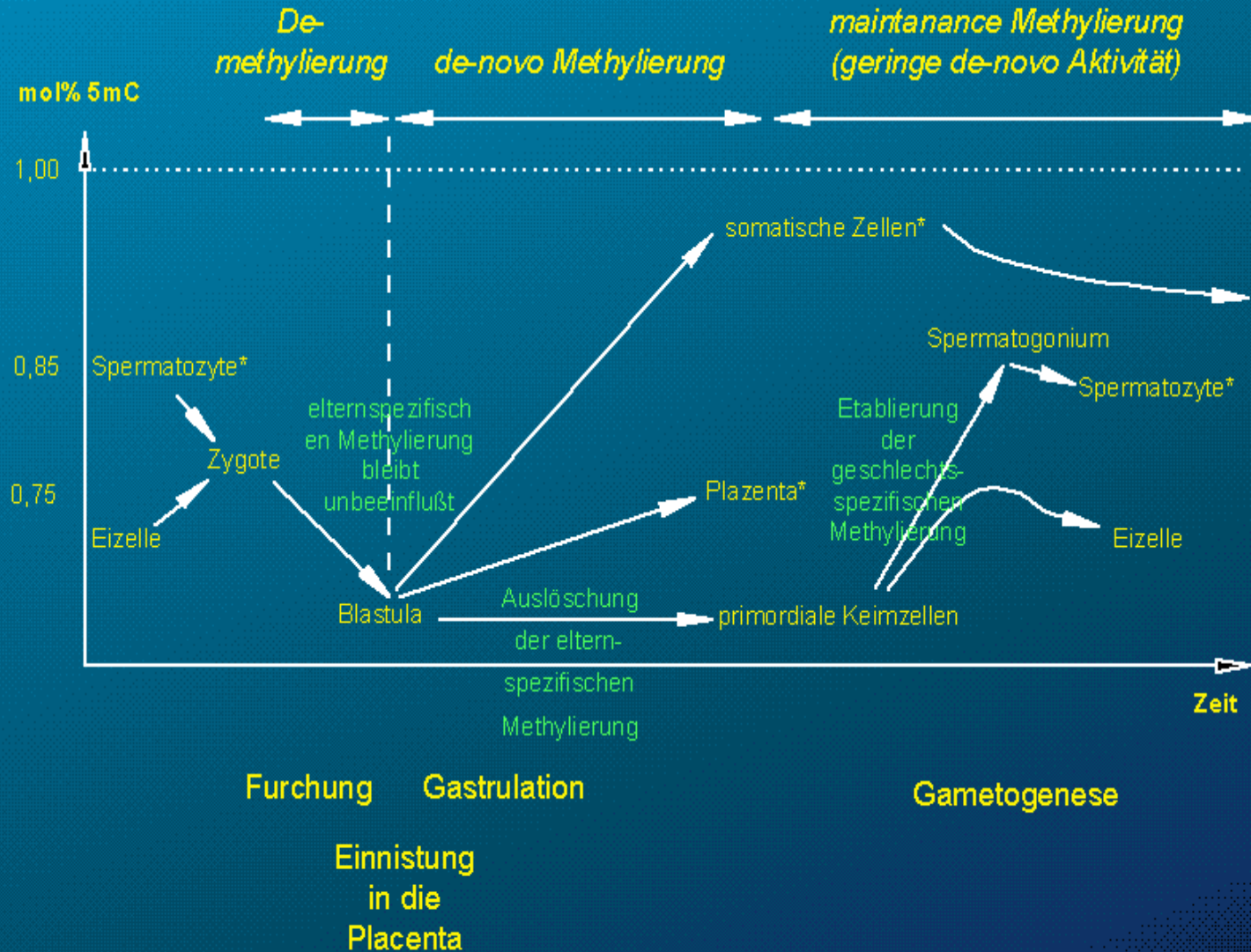
- X-linked dominant, male lethal
- most common cause of sporadic mental retardation in females
- period of normal development followed by
 - progressive degeneration in speech and motor skills,
 - seizures, autism,
 - stereotypical, repetitive hand movements

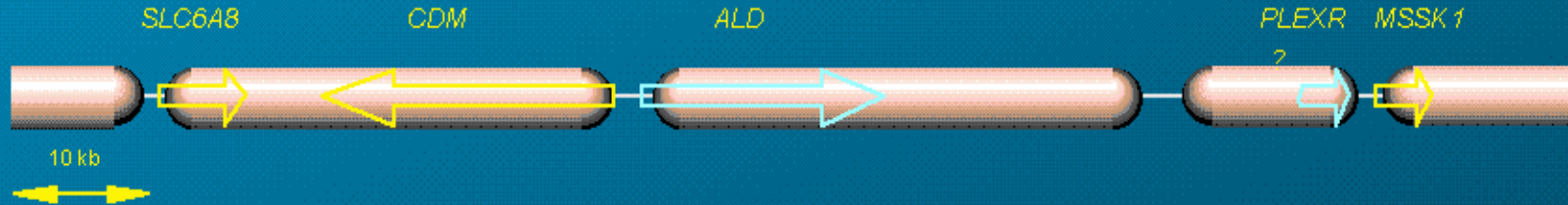
DNA Methylierung & Krankheit

Fragiles X-Syndrom

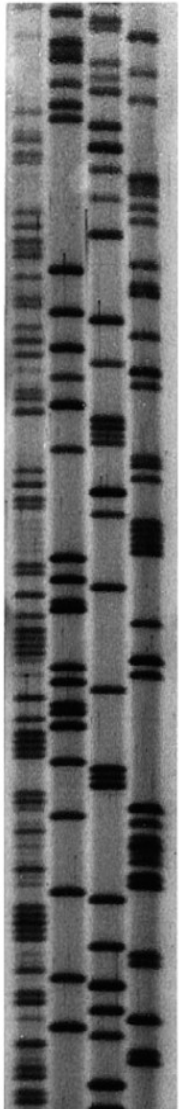


5mC-Gehalt während der frühen Embryogenese





Mittel zur Reduzierung genomischer Komplexität ?



A C G T

genome.fli-leibniz.de
Teaching