日本学術会議（第二部）
冬季シンポジウム

ゲノムから見たヒトの多様性と普遍性

２００８年２月５日

日本学術会議講堂

榊　佳之

（理化学研究所ゲノム科学研究所）

ご協力をいただいた方々

- 理化学研究所ゲノム科学総合研究センター ヒトゲノム解析グループのメンバー
- 油谷　浩幸　　東京大学
- 佐々木　裕之　国立遺伝学研究所
- 伊藤　隆司　　東京大学

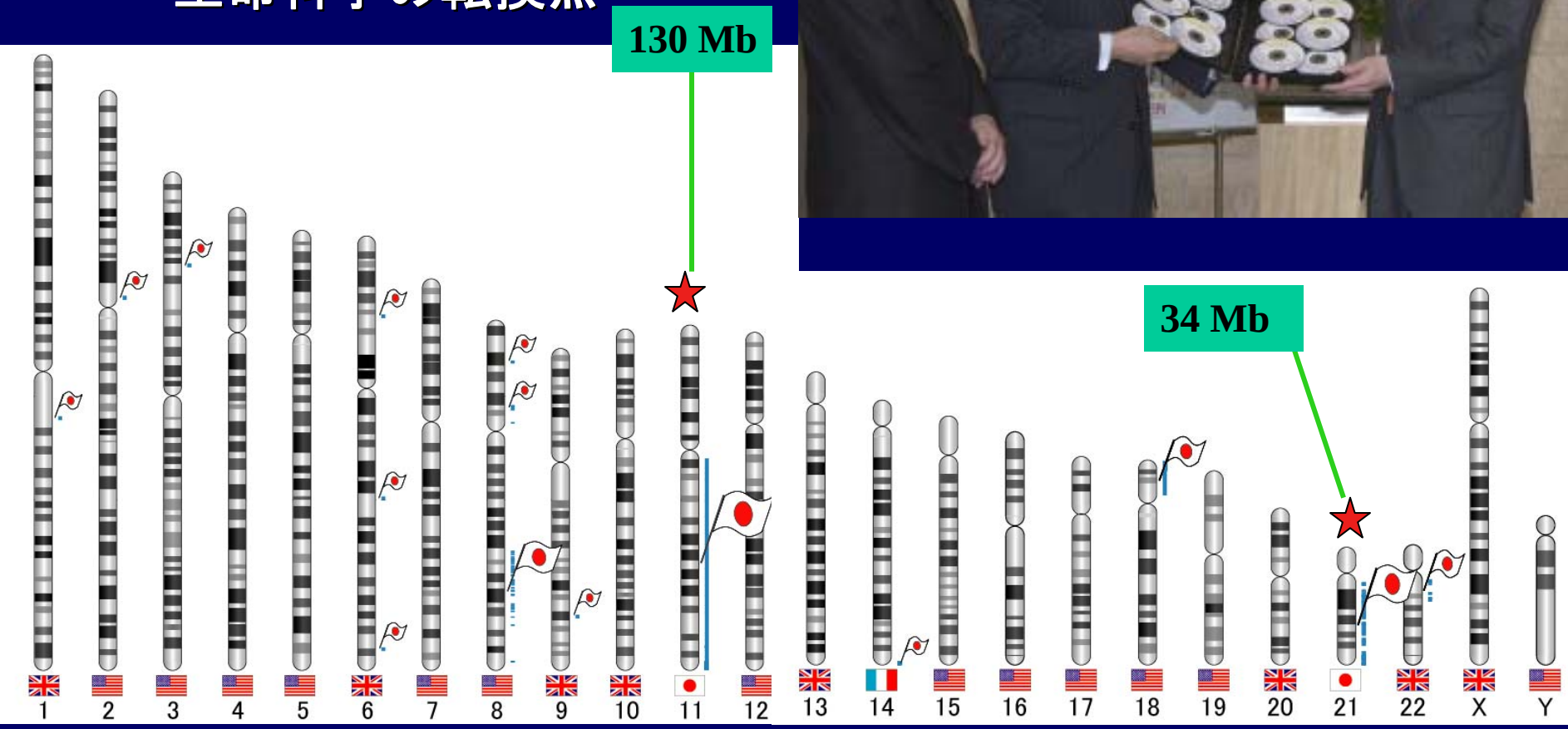
ヒトの生物学的位置付け

チンパンジーとの比較から見るヒトの特質

著しく発達した脳
高度な知的活動・情報処理能力
複雑な言語の使用
長寿
直立二足歩行
感染症への感受性 (例：エイズ，脳炎，マラリアなど)

ヒトの遺伝的特質を担う ヒトゲノムの解読完了 （2003年4月）

生命科学の転換点



チンパンジーのゲノム配列を決定した2つの論文

DNA sequence and comparative analysis of chimpanzee chromosome 22

The International Chimpanzee Chromosome 22 Consortium*

**A list of authors and their affiliations appears at the end of the paper*

塩基置換：1.44%

Human–chimpanzee comparative genome research is essential for narrowing down genetic changes involved in the acquisition of unique human features, such as highly developed cognitive functions, bipedalism or the use of complex language. Here, we report the high-quality DNA sequence of 33.3 megabases of chimpanzee chromosome 22. By comparing the whole sequence with the human counterpart, chromosome 21, we found that 1.44% of the chromosome consists of single-base substitutions in addition to nearly 68,000 insertions or deletions. These differences are sufficient to generate changes in most of the proteins. Indeed, 83% of the 231 coding sequences, including functionally important genes, show differences at the amino acid sequence level. Furthermore, we demonstrate different expansion of particular subfamilies of retrotransposons between the lineages, suggesting different impacts of retrotranspositions on human and chimpanzee evolution. The genomic changes after speciation and their biological consequences seem more complex than originally hypothesized.

Nature. Vol.429, 382-388 (2004)

Initial sequence of the chimpanzee genome and comparison with the human genome

塩基置換：1.23%

The Chimpanzee Sequencing and Analysis Consortium*

Here we present a draft genome sequence of the common chimpanzee (*Pan troglodytes*). Through comparison with the human genome, we have generated a largely complete catalogue of the genetic differences that have accumulated since the human and chimpanzee species diverged from our common ancestor, constituting approximately thirty-five million single-nucleotide changes, five million insertion/deletion events, and various chromosomal rearrangements. We use this catalogue to explore the magnitude and regional variation of mutational forces shaping these two genomes, and the strength of positive and negative selection acting on their genes. In particular, we find that the patterns of evolution in human and chimpanzee protein-coding genes are highly correlated and dominated by the fixation of neutral and slightly deleterious alleles. We also use the chimpanzee genome as an outgroup to investigate human population genetics and identify signatures of selective sweeps in recent human evolut

Vol 437|1 September 2005|**doi:10.1038/nature04072**

塩基配列の違い
1.23%

ヒト

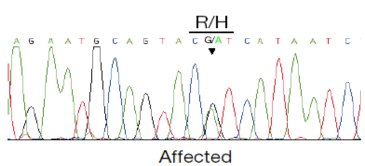
チンパンジー

言語野の発達に関わるFOXP2遺伝子にヒト特異的変化が見つかった

Molecular evolution of *FOXP2*, a gene involved in speech and language

Wolfgang Enard*, Molly Przeworski*, Simon E. Fisher†, Cecilia S. L. Lai†, Victor Wiebe*, Takashi Kitano*, Anthony P. Monaco† & Svante Pääbo*

** Max Planck Institute fo*
D-04103 Leipzig, Germa
† Wellcome Trust Centre



7q31 R553H

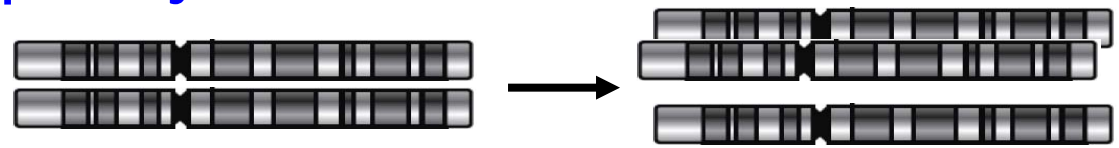
Human	TSSNTSKASP	PITHHSIVNG	QSSVLSARRD
Chimp	...T......	....	.....N....
Gorilla	...T......	....	.....N....
Orang	...T......	....	.....N....
Rhesus	...T......	....	.....N....
Mouse	...T......	....	.....N....

ヒト集団は遺伝的に多様である

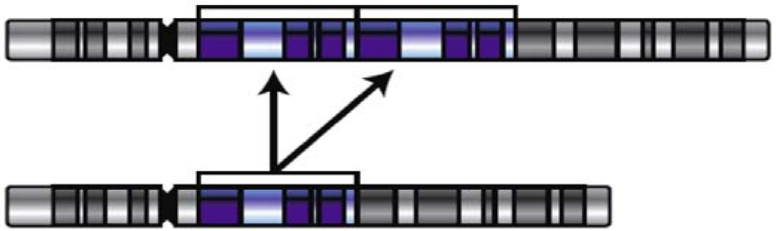
ゲノムに見られる多様性

（提供 油谷浩幸）

- Aneuploidy



- Copy number variation(CNV)
  - Insertion/Deletion
  - Segmental duplication



- Short tandem repeats

-----CACACACACACACACACA--------

- SNPs

ACCGTGCATCTCGTACTCTAT
ACCGTGCATATCGTACTCTAT

Genome diversity and human diseases

Human genome project

Candidate gene approach

SNP consortium

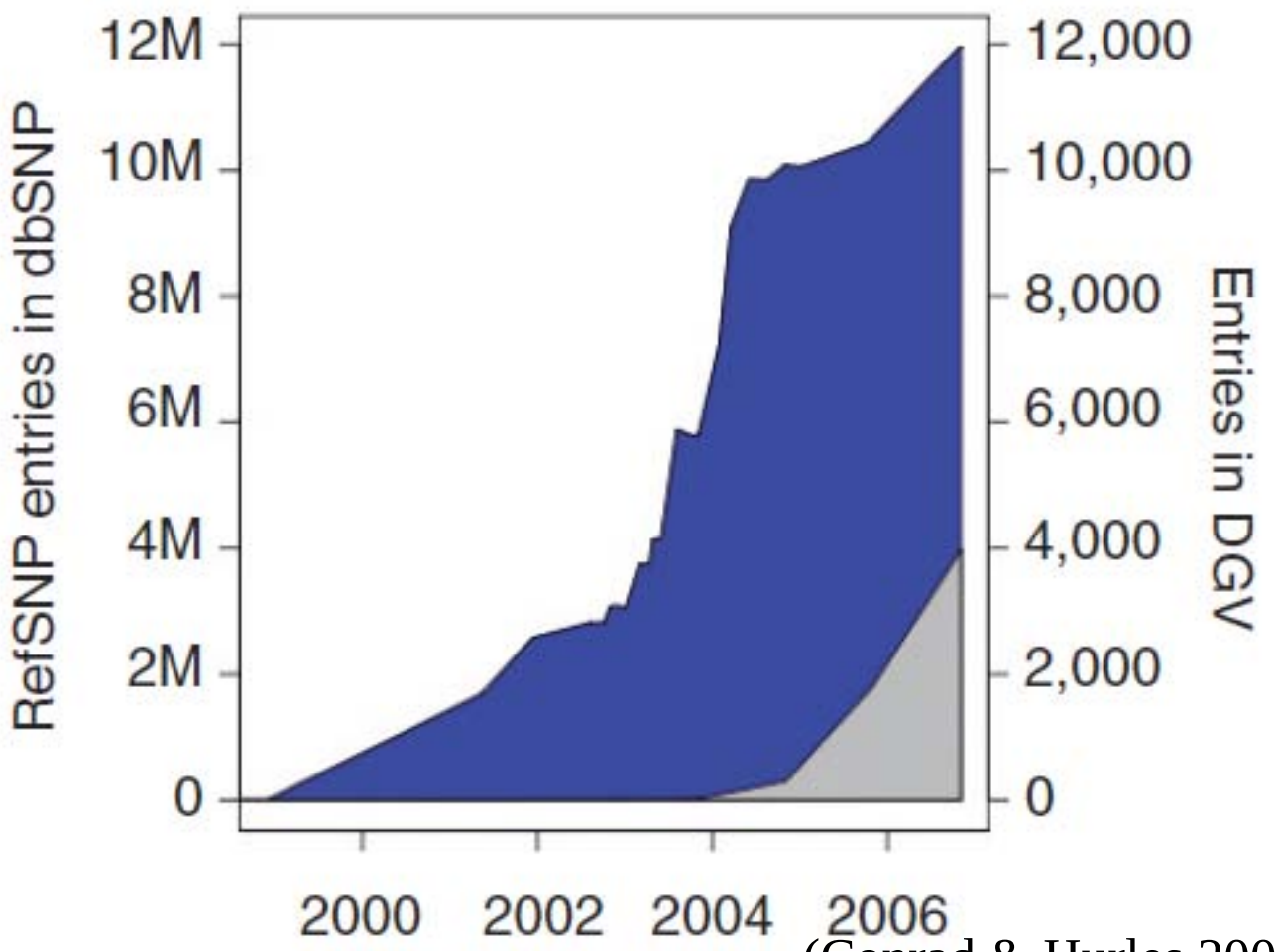
HapMap project

genome-wide association

high-resolution analysis

2001 *2003* *2005* *2007* *2009*

RefSNP entries in dbSNP
and
variant loci in the Database of Genomic Variants

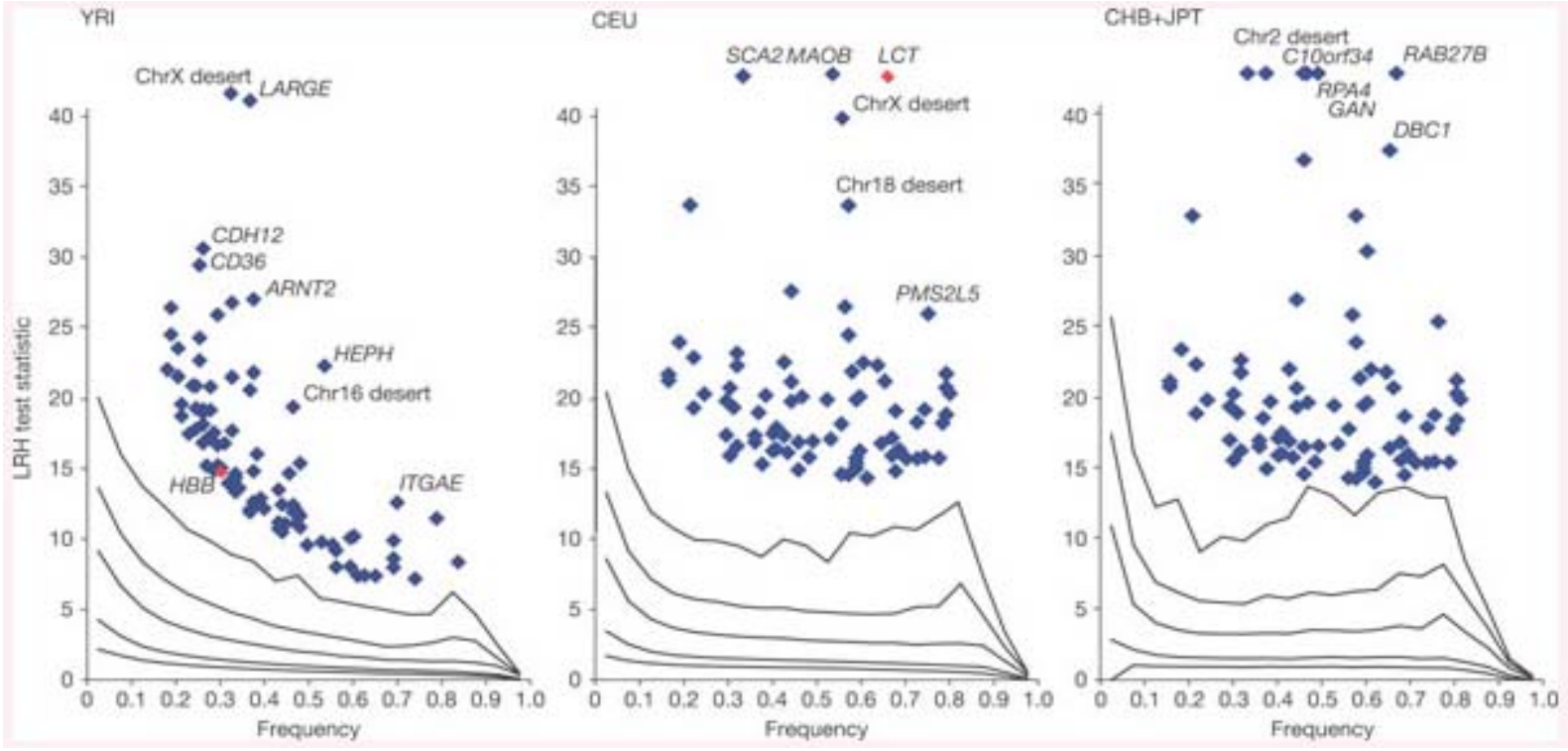


(Conrad & Hurles 2007)

A haplotype map of the human genome

The International HapMap Consortium*

Inherited genetic variation has a critical but as yet largely uncharacterized role in human disease. Here we report a public database of common variation in the human genome: more than one million single nucleotide polymorphisms (SNPs) for which accurate and complete genotypes have been obtained in 269 DNA samples from four populations, including ten 500-kilobase regions in which essentially all information about common DNA variation has been extracted. These data document the generality of recombination hotspots, a block-like structure of linkage disequilibrium and low haplotype diversity, leading to substantial correlations of SNPs with many of their neighbours. We show how the HapMap resource can guide the design and analysis of genetic association studies, shed light on structural variation and recombination, and identify loci that may have been subject to natural selection during human evolution.



The distribution of the long range haplotype (LRH92) test statistic for natural selection.

Nature 437, 1299 - 1320 (27 Oct 2005)

Table 10 | Candidate loci in which selection occurred

Chromosome	Position (base number) at centre	Genes in region	Population	Haplotype frequency	Empirical *P*-value
2	137,224,699	*LCT*	CEU	0.65	1.25×10^{-9}
5	22,296,347	*CDH12, PMCHL1*	YRI	0.25	5.77×10^{-8}
7	79,904,387	*CD36*	YRI	0.24	2.72×10^{-6}
7	73,747,934	*PMS2L5, WBSCR16*	CEU	0.76	3.37×10^{-6}
12	109,892,896	*CUTL2*	CEU	0.36	7.95×10^{-9}
15	78,558,508	*ARNT2*	YRI	0.32	6.92×10^{-7}
16	75,661,011	Desert	YRI	0.46	5.01×10^{-7}
17	3,945,580	*ITGAE, GSG2,* HSA277841, *CAMKK1, P2RX1*	YRI	0.70	9.26×10^{-7}
18	24,502,756	Desert	CEU	0.57	2.23×10^{-7}
22	32,459,471	*LARGE*	YRI	0.36	7.82×10^{-9}
X	20,171,291	Desert	YRI	0.33	5.02×10^{-9}
X	64,323,320	*HEPH*	YRI	0.55	3.02×10^{-8}
X	42,763,073	*MAOB*	CEU	0.53	4.21×10^{-9}
X	34,399,948	Desert	CEU	0.57	8.85×10^{-8}

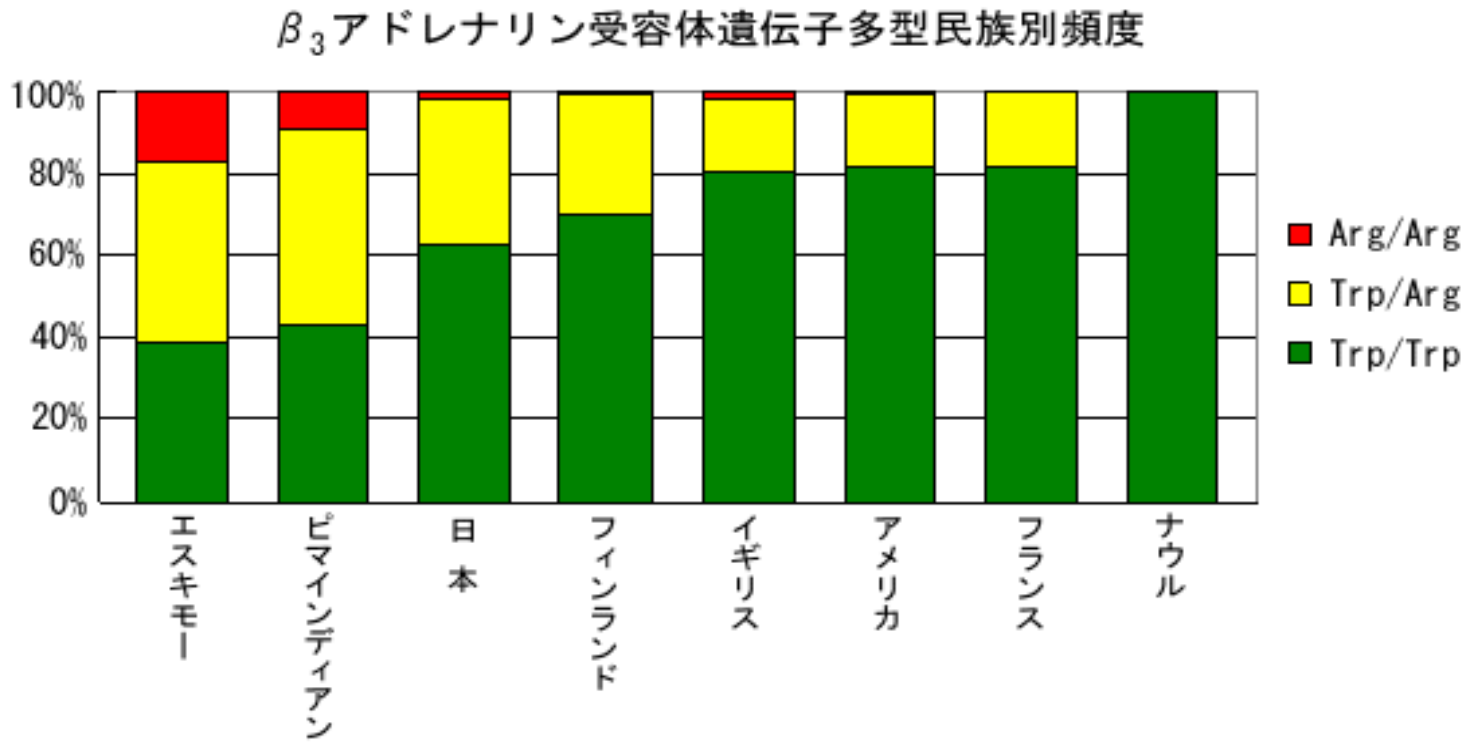
Nature 437, 1299 - 1320 (27 Oct 2005)

β３アドレナリン受容体

64番目のアミノ酸

Trp　非肥満型　ノルアドレナリン高感受性・
体脂肪分解活性が強い

Arg　肥満型・倹約型アドレナリン低感受性・
体脂肪分 解活性が弱い



福岡県久山町の集団解析から
脳梗塞になりやすい遺伝子型が見つかった

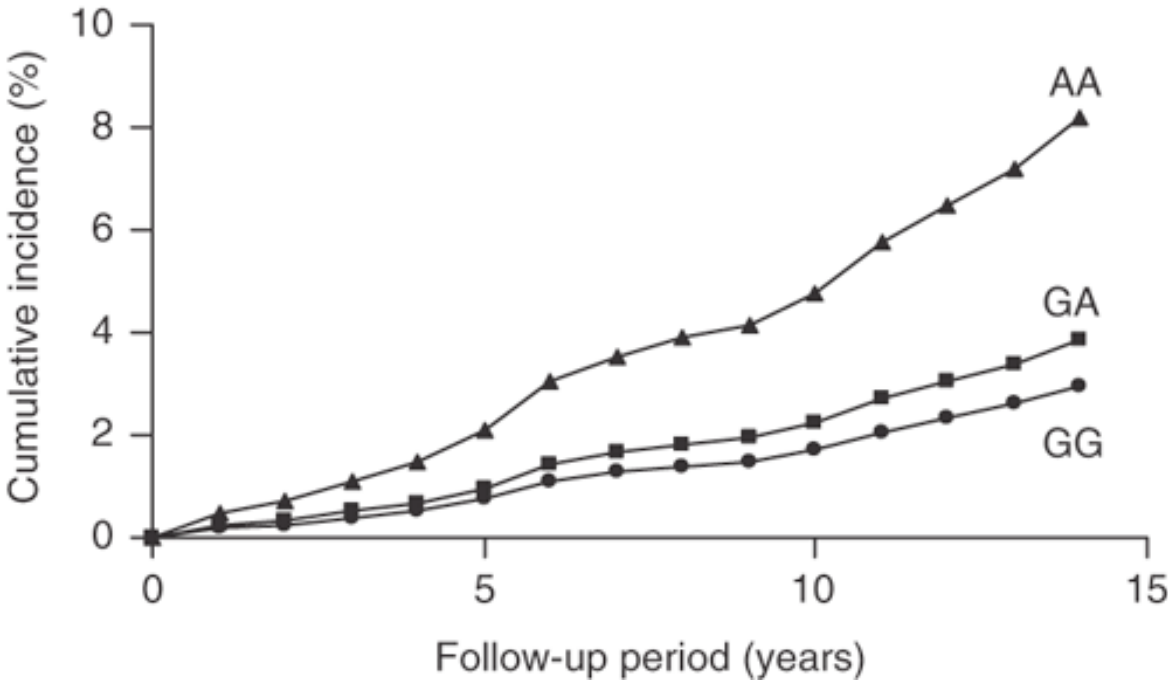
Letter
Published online: 7 January 2007; | doi:10.1038/ng1945

A nonsynonymous SNP in *PRKCH* (protein kinase Cη) increases the risk of cerebral infarction

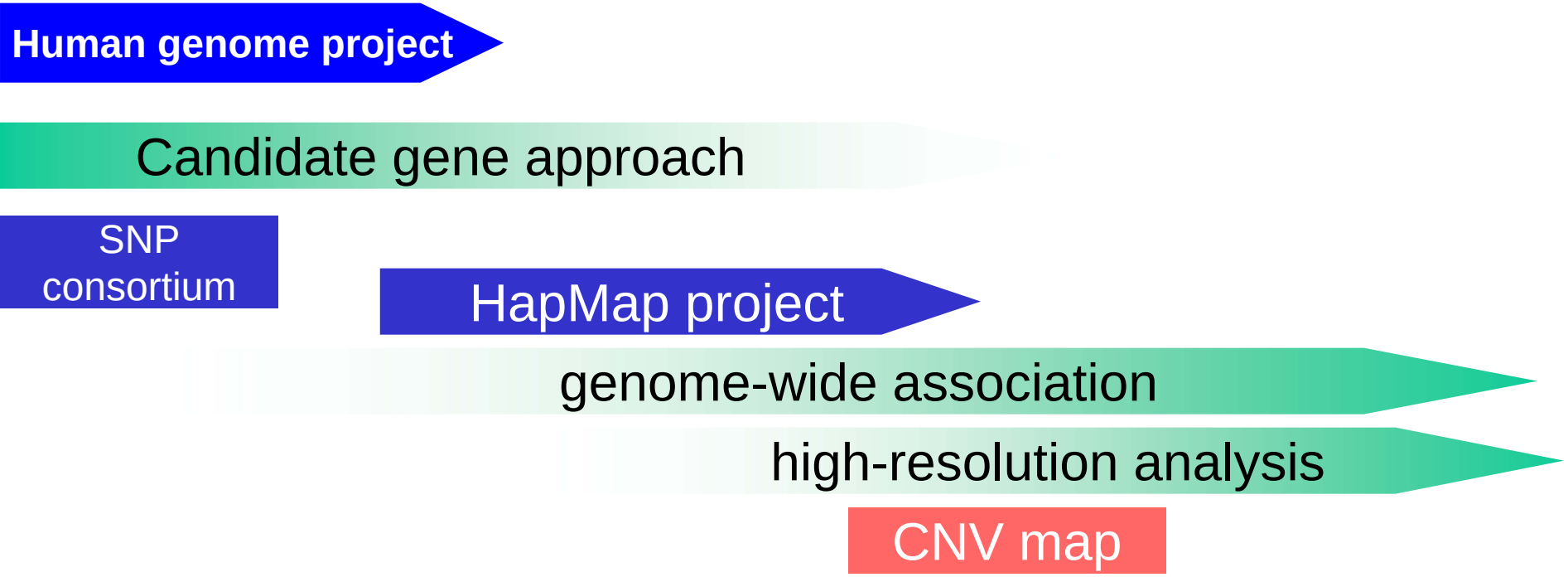
Michiaki Kubo[1, 2, 3], Jun Hata[1, 2, 3], Toshiharu Ninomiya[1, 2], Koichi Matsuda[3], Koji Yonemoto[1], Toshiaki Nakano[2, 4], Tomonaga Matsushita[2, 3], Keiko Yamazaki[3], Yozo Ohnishi[5], Susumu Saito[5], Takanari Kitazono[2], Setsuro Ibayashi[2], Katsuo Sueishi[4], Mitsuo Iida[2], Yusuke Nakamura[3] & Yutaka Kiyohara[1]

1 Department of Environmental Medicine, Kyushu University, Fukuoka 812-8582, Japan.
2 Department of Medicine and Clinical Science, Kyushu
3 Laboratory of Molecular Medicine, Human Genome C
4 Pathophysiological and Experimental Pathology, Grad
5 Laboratory for Genotyping, SNP Research Center, th
Correspondence should be addressed to Michiaki Kubo

**Cerebral infarction is the most common t
investigate the genetic contribution to ce
52,608 gene-based tag SNPs selected fro
SNP in a member of protein kinase C (PK
infarction in two independent Japanese s
likely to affect PKC activity. Furthermore
Japan) supported involvement of this SN
and sex-adjusted hazard ratio of 2.83). V
endothelial cells and foamy macrophages
increased as the lesion type progressed.
cerebral infarction.**



Genome diversity and human diseases



nature Vol 444|23 November 2006|doi:10.1038/nature05329

ARTICLES

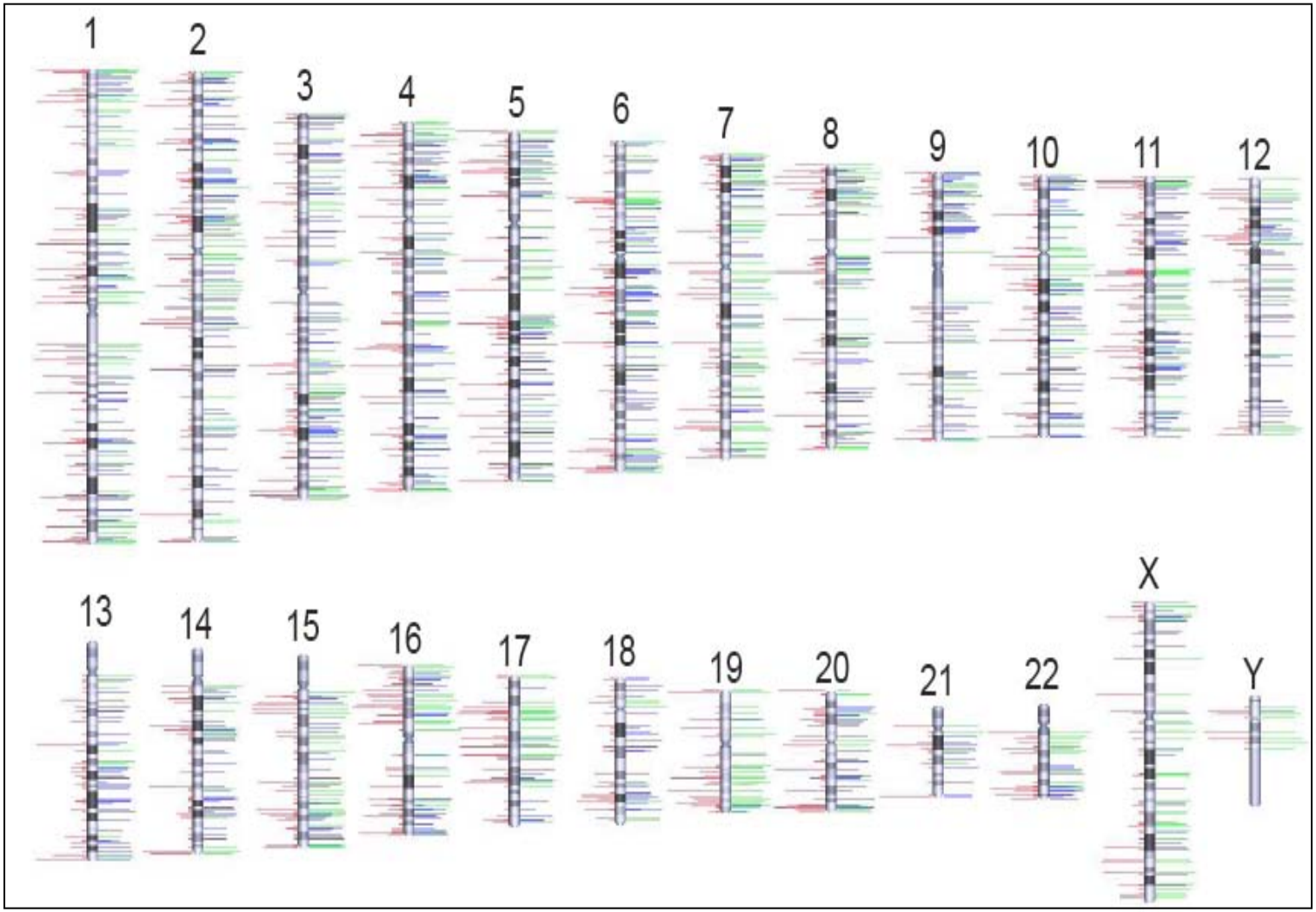
Global variation in copy number in the human genome

Richard Redon[1], Shumpei Ishikawa[2,3], Karen R. Fitch[4], Lars Feuk[5,6], George H. Perry[7], T. Daniel Andrews[1], Heike Fiegler[1], Michael H. Shapero[4], Andrew R. Carson[5,6], Wenwei Chen[4], Eun Kyung Cho[7], Stephanie Dallaire[7], Jennifer L. Freeman[7], Juan R. González[8], Mònica Gratacòs[8], Jing Huang[4], Dimitrios Kalaitzopoulos[1], Daisuke Komura[3], Jeffrey R. MacDonald[5], Christian R. Marshall[5,6], Rui Mei[4], Lyndal Montgomery[1], Kunihiro Nishimura[2], Kohji Okamura[5,6], Fan Shen[4], Martin J. Somerville[9], Joelle Tchinda[7], Armand Valsesia[1], Cara Woodwark[1], Fengtang Yang[1], Junjun Zhang[5], Tatiana Zerjal[1], Jane Zhang[4], Lluis Armengol[8], Donald F. Conrad[10], Xavier Estivill[8,11], Chris Tyler-Smith[1], Nigel P. Carter[1], Hiroyuki Aburatani[2,12], Charles Lee[7,13], Keith W. Jones[4], Stephen W. Scherer[5,6] & Matthew E. Hurles[1]

- HapMap 270 individuals
  - EBV-transformed lymphoblastoid cell lines
    - CEPH 90 (30 trios)
    - Yoruba 90 (30 trios)
    - Japanese/Chinese 90 (45/45)

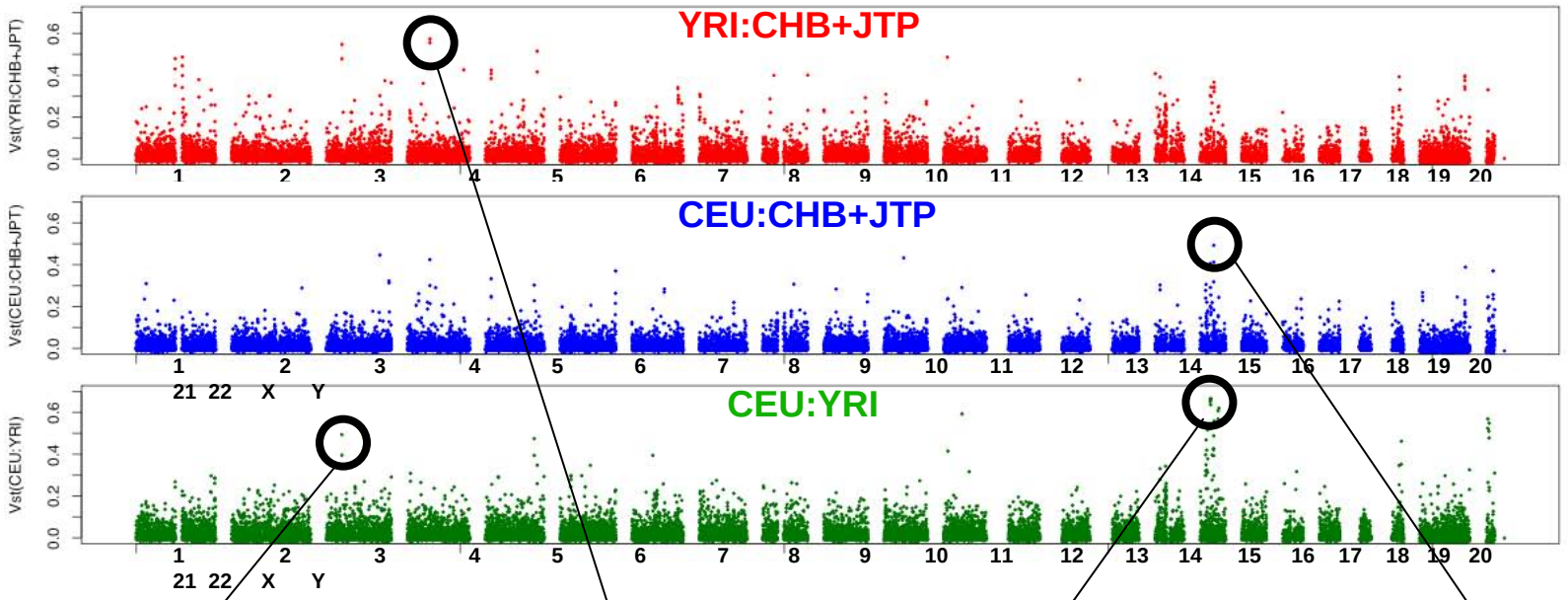
(Redon, Ishikawa, Fitch, Falk, Nature 2006)

Location and frequency of 1,447 CNVs



Population differentiation

$V_{ST}=(V_T-V_S)/V_T$

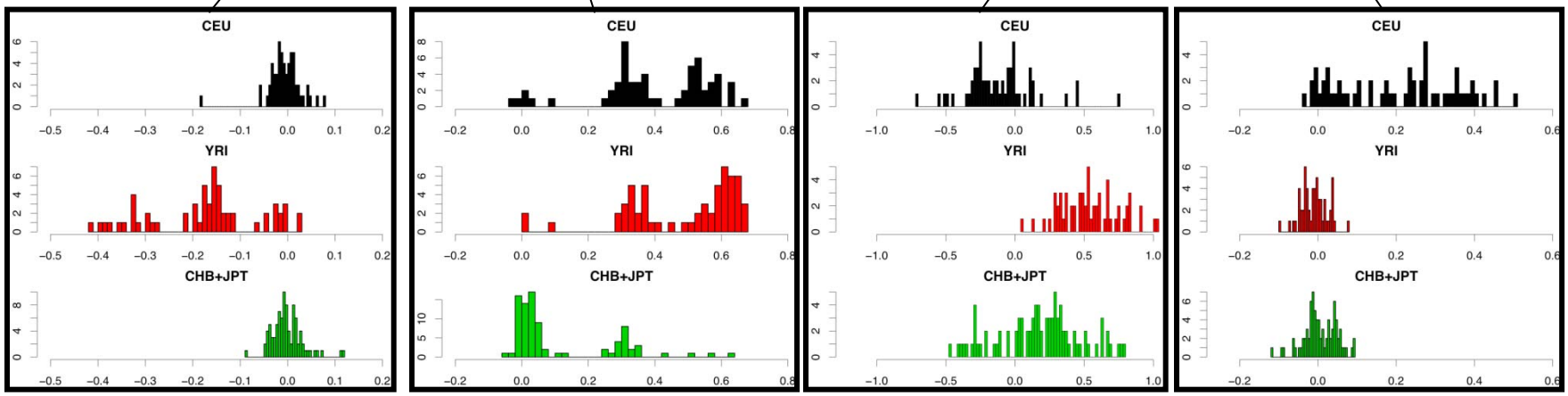


CEU

YRI

CHB

JTP



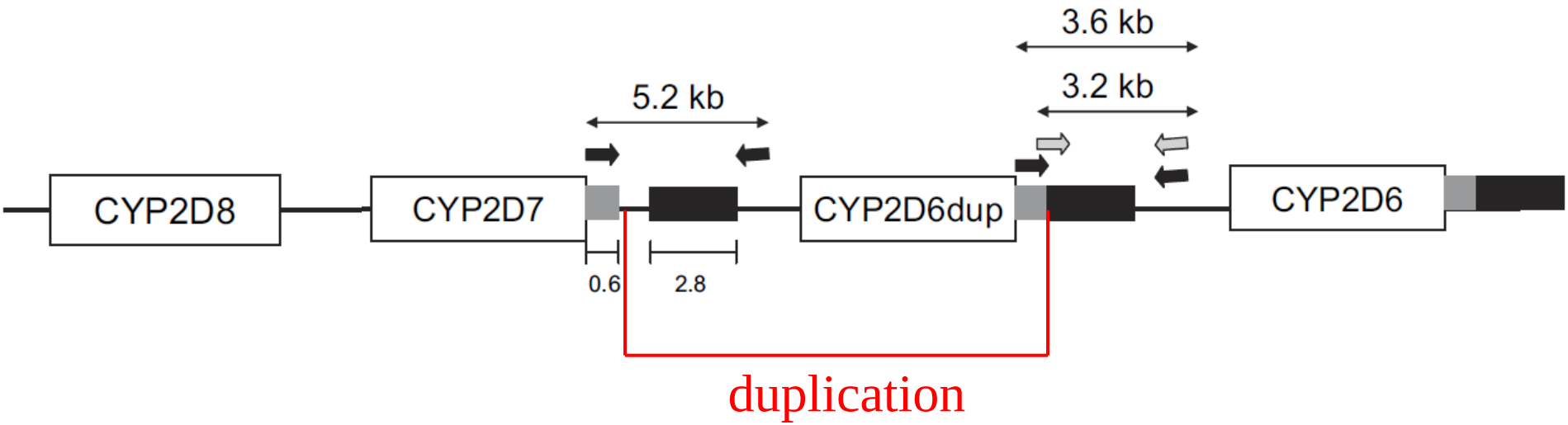
Chr3tp-10A3 UGT2B17 CCL3L1 MAPT

The Pharmacogenomics Journal (2007) 7, 257–265

www.nature.com/tpj

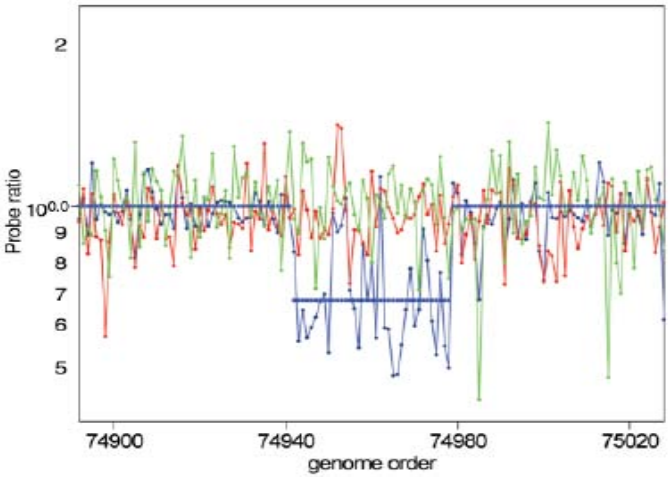
ORIGINAL ARTICLE

Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to *CYP2D6* duplication



Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat,[1*] B. Lakshmi,[1] Dheeraj Malhotra,[1*] Jenni
Tom Walsh,[3] Boris Yamrom,[1] Seungtai Yoon,[1] Alex Krasni
Deepa Pai,[1] Ray Zhang,[1] Yoon-Ha Lee,[1] James Hicks,[1] Sa
Kaija Puura,[6] Terho Lehtimäki,[7] David Ledbetter,[2] Peter
James S. Sutcliffe,[9] Vaidehi Jobanputra,[10] Wendy Chung,
Mary-Claire King,[3] David Skuse,[11] Daniel H. Geschwind,[12]
Kenny Ye,[14] Michael Wigler[1]†



- Such CNVs were identified in 12 out of 118 (10%) of patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls.
- Most de novo CNVs were smaller than microscopic resolution.

Science 20 April 2007:Vol. 316. no. 5823, pp. 445 – 449

Copy Number Variants Involved in Human Disease

DISEASE	GENE	PHENOTYPE
Charcot-Marie-Tooth type 1A	*PMP22*	Demyelination, peripheral neuropathy
X-linked hypopituitarism	*SOX3*	In males, short stature, mild mental retardation
Autosomal dominant leukodystrophy	*LMNB1*	Demyelination, white brain matter abnormalities
Parkinson's	*SNCA*	Neuron degeneration, rigidity, tremor
Alzheimer's	*APP*	Amyloid β precursor protein buildup
Altered drug metabolism	*CYP2D6*	Increased side effects, increased or decreased efficacy
HIV/AIDS	*CCL3L1*	Increased susceptibility to infection and disease
Lupus	*FCGR3B*	Increased susceptibility to kidney failure
Smith-Magenis syndrome	*RAI1*	Mental retardation
Pelizaeus-Merzbacher	*PLP1*	Demyelination, paralysis of legs, involuntary jerking of head
Spinal muscular atrophy	*SMN1*	Spinal deterioration, milder disease w/later onset
Rett-like syndrome	*MECP2*	Mental retardation, spasticity, language/speech problems
Miller-Dieker syndrome	*LIS1*	Brain malformation, mental retardation, epilepsy
Neurofibromatosis type 1	*NF1*	Tumors, cognitive deficits

Summary: copy number variation

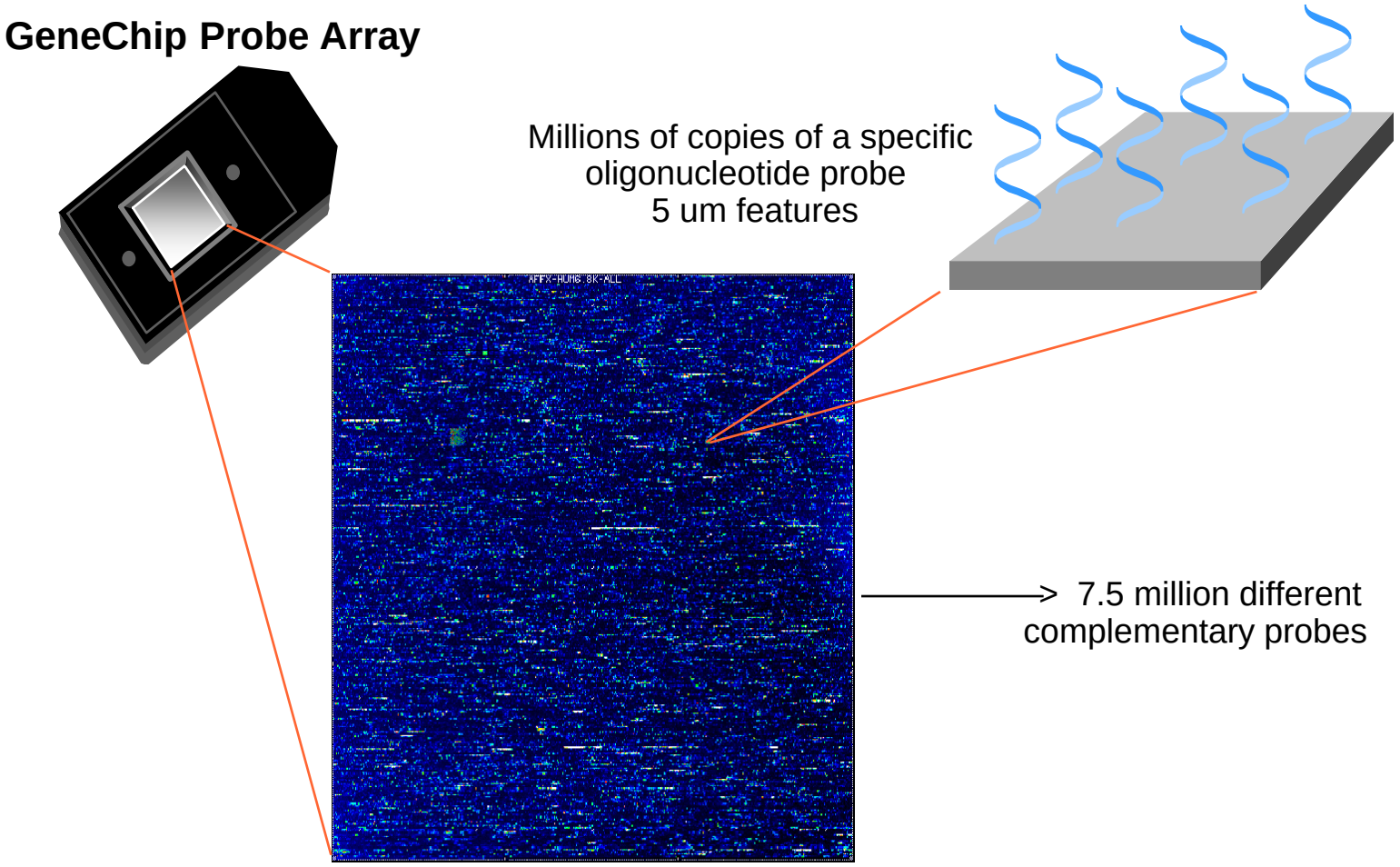
- **CNVs are extensive, genome-wide, complex and likely to have functional impact**:

  - covering ~12%(360Mbp) of the human genome
  - including about 2909 genes(11.8%), 286 genes in OMIM
  - will be examined in large scale association studies

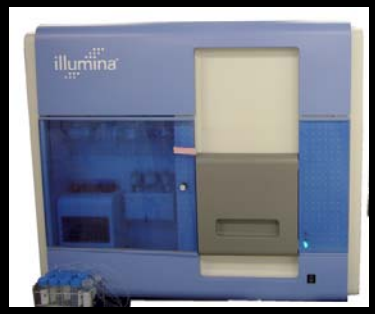
- **Many CNVs are difficult to be 'tagged'**

  - needs platform for direct CNV detection,
  - needs higher density genotyping in complex region.

GeneChip® Probe Arrays



Next Generation Sequencers



454 Life Sciences
Genome Sequencer
20 System (GS20)

100 Mb/ run
200 bp/ read

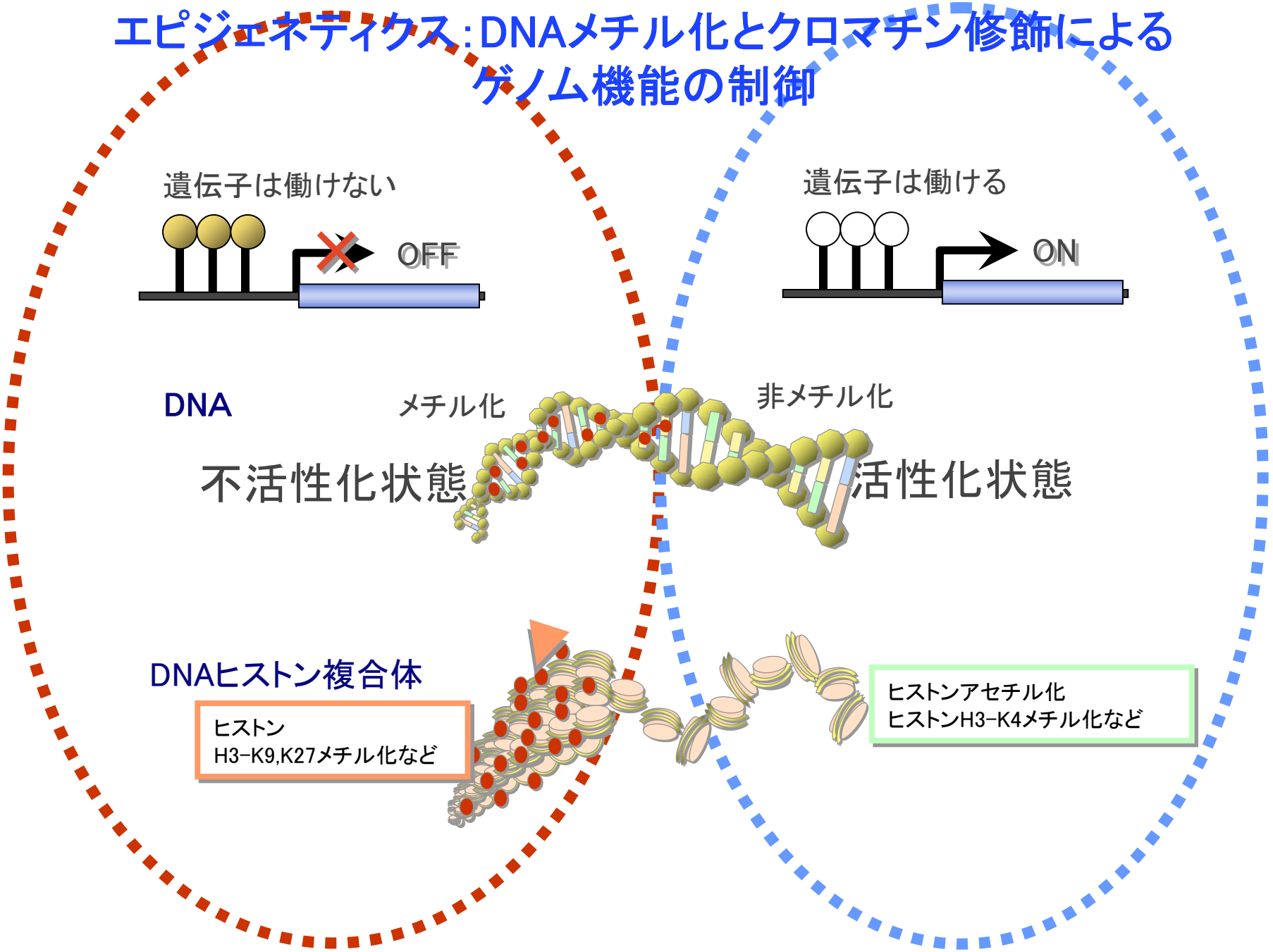
Illumina / Solexa
1G Genome Analyzer

1,000 Mb/ run
25-36 bp/ read

Applied Biosystems
SOLiD System

3,000 Mb/ run
35 bp/ read
25 bp x 2 (paired-end)

エピジェネティクス：DNAメチル化とクロマチン修飾による遺伝子機能の制御



ヒストンコード
Histone Code

Strahl, D. and Allis, C.D. Nature 403, 41-45 (2000)

A: アセチル化　M:メチル化　P: リン酸化

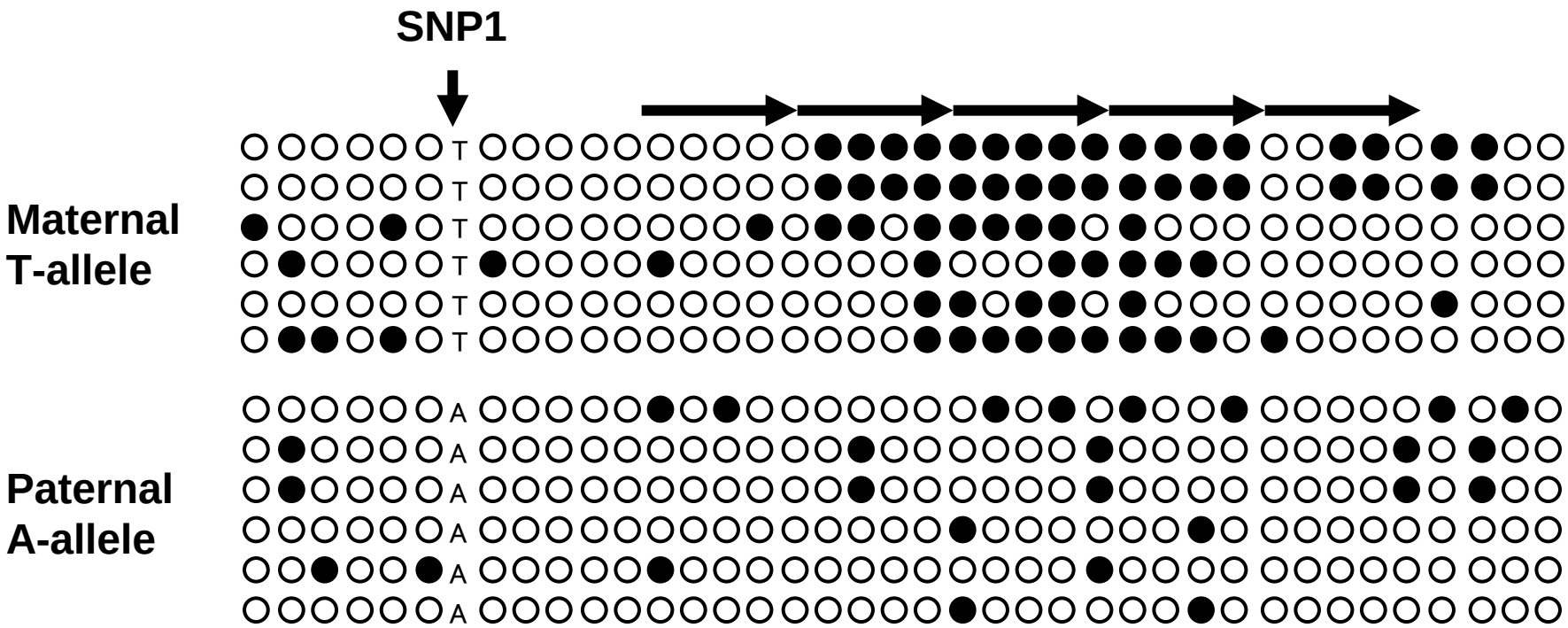
・ヒストンH3だけでなく、H4、H2A、H2Bにも修飾がある

・特定の修飾・またはその組み合わせがコードとして働く

・様々なヒストン修飾酵素・脱修飾酵素（HAT、HDAC、HMT等）

・コードの読みとり装置（HP1等）

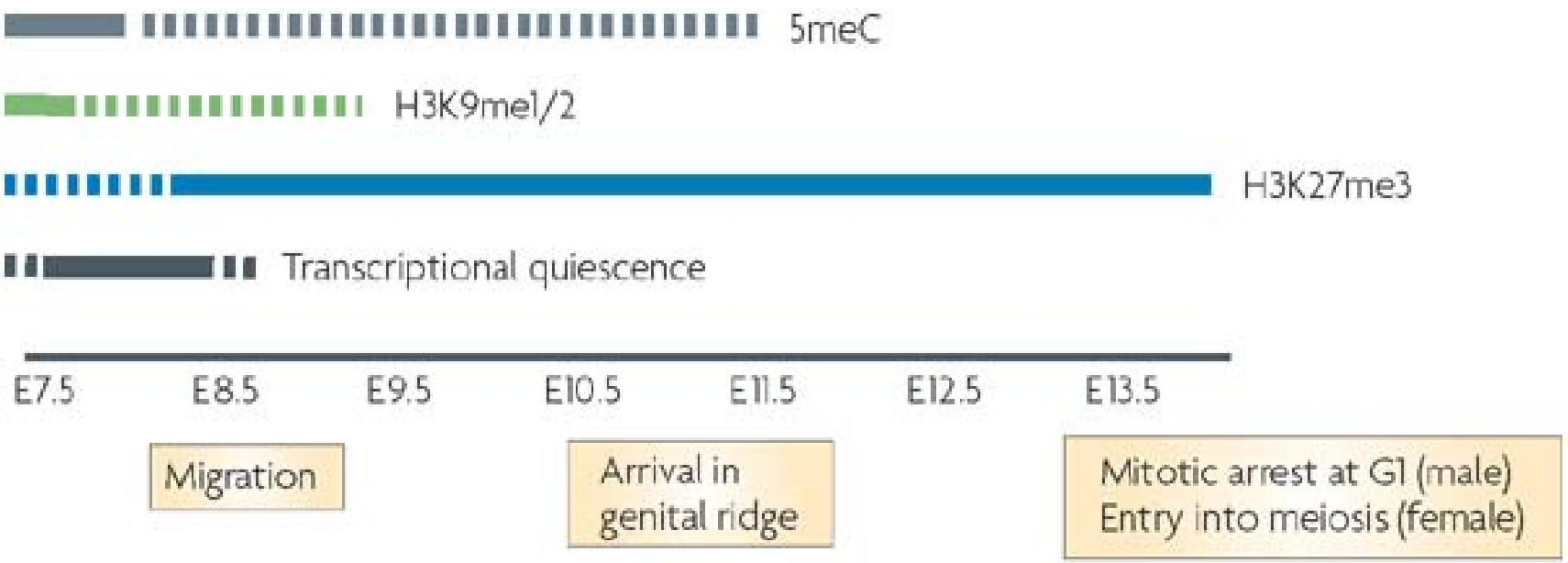
メチル化の個体差インプリント



提供：伊藤隆司

Epigenetic events in mammalian germ-cell development: reprogramming and beyond

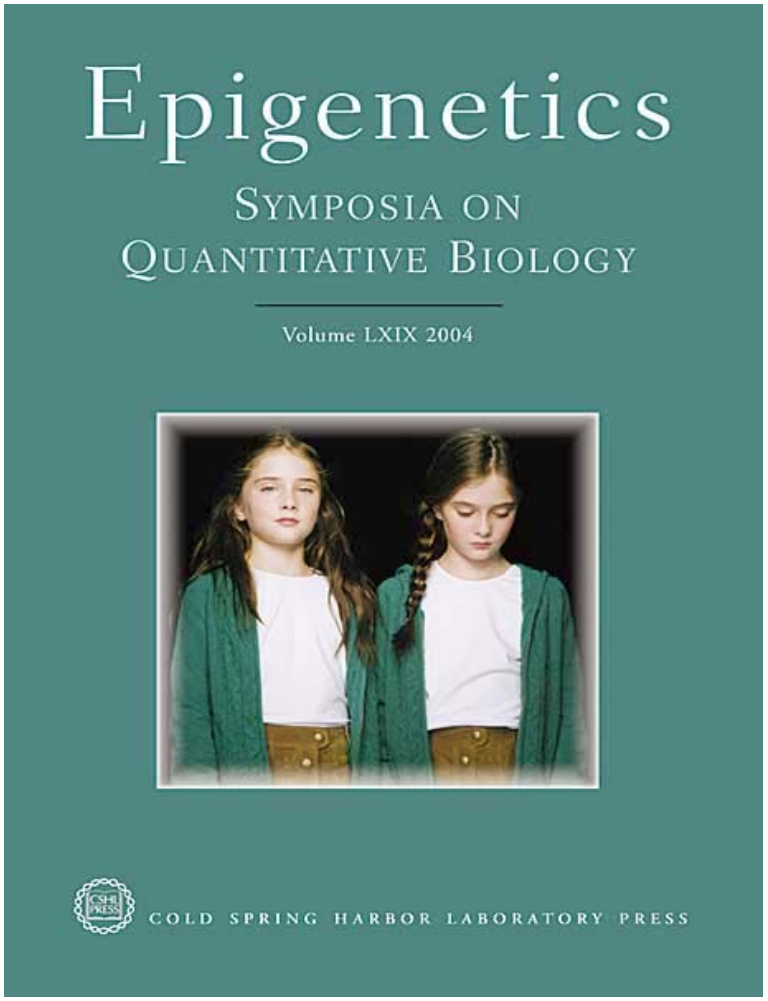
Hiroyuki Sasaki and Yasuhisa Matsui‡*



Nature Reviews | Genetics

Nature Reviews Genetics 9, 129-140 (February 2008) | doi:10.1038/nrg2295

エピジェネティクスと多様性
Epigenetics and Variation



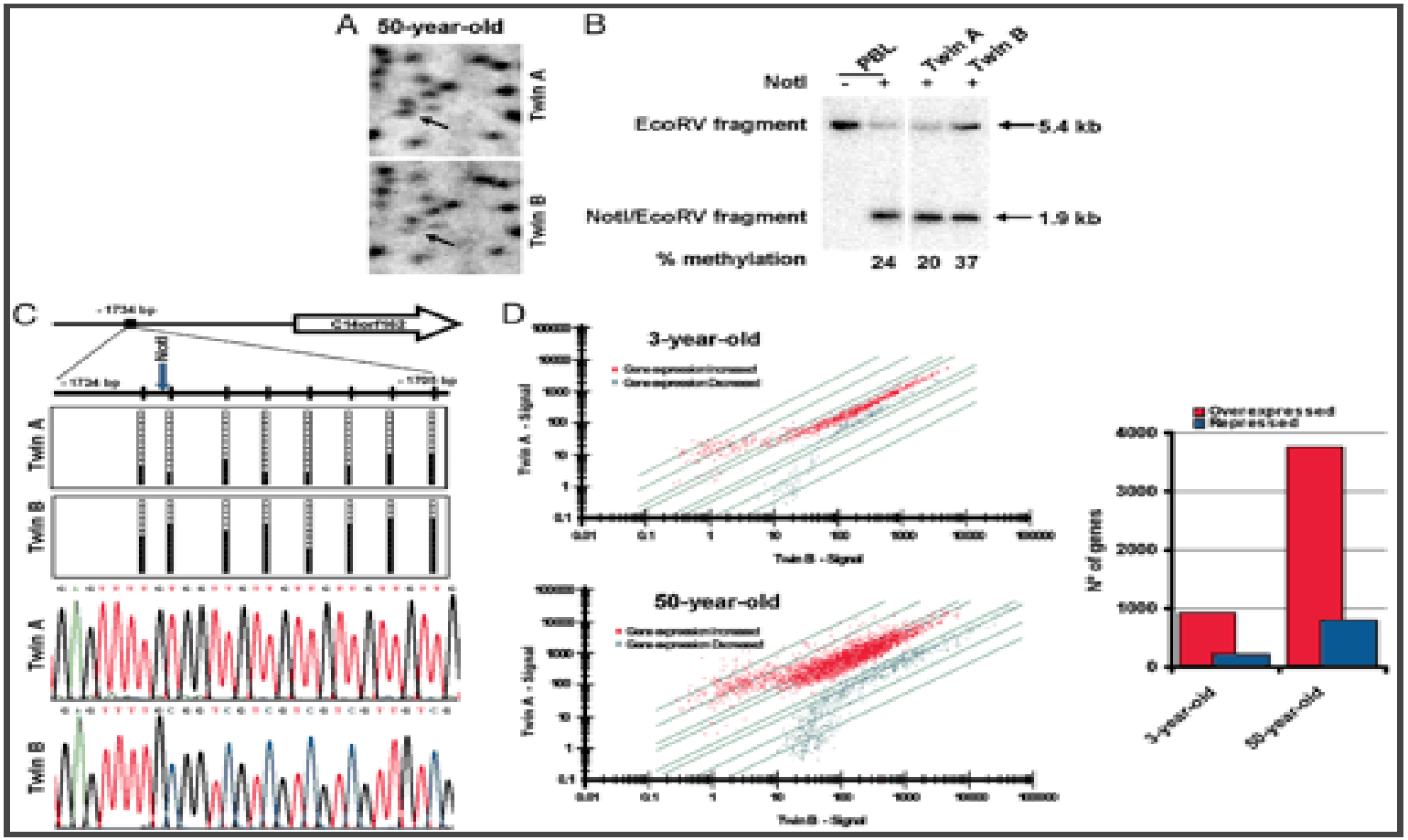
Cold Spring Harbor Symposia on Quantitative Biology 2004

氏か育ちか？
Nature or Nurture?

一卵性双生児の個性

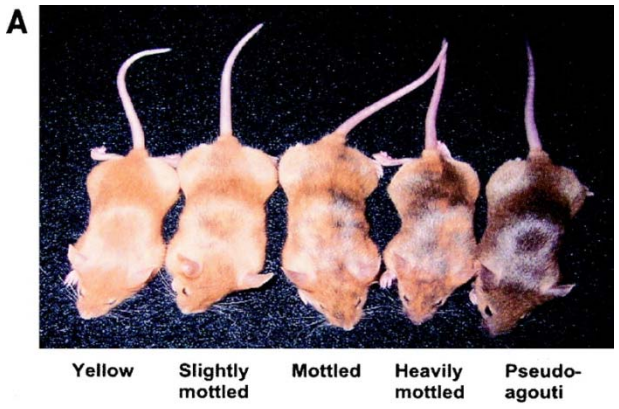
Epigenetic differences arise during the lifetime of monozygotic twins

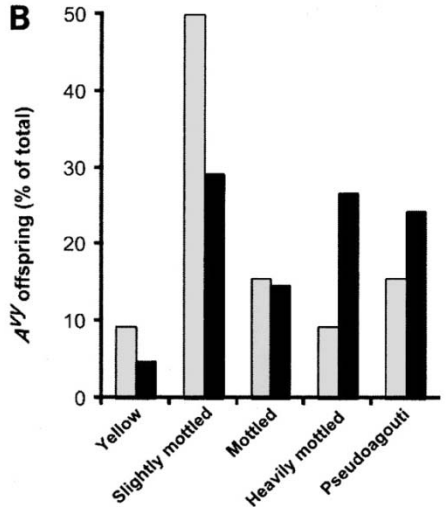
Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‖, Emma Carlsson‖, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§



食餌とエピジェネティクス
Diet and Epigenetics

A^{vy}マウスの毛色





妊娠中・授乳中の母マウスに高メチル基質食を与える（高ビタミンB12、葉酸、コリン、ベタイン食）

↓

A（アグーチ）遺伝子座上流のトランスポゾンのメチル化レベル上昇

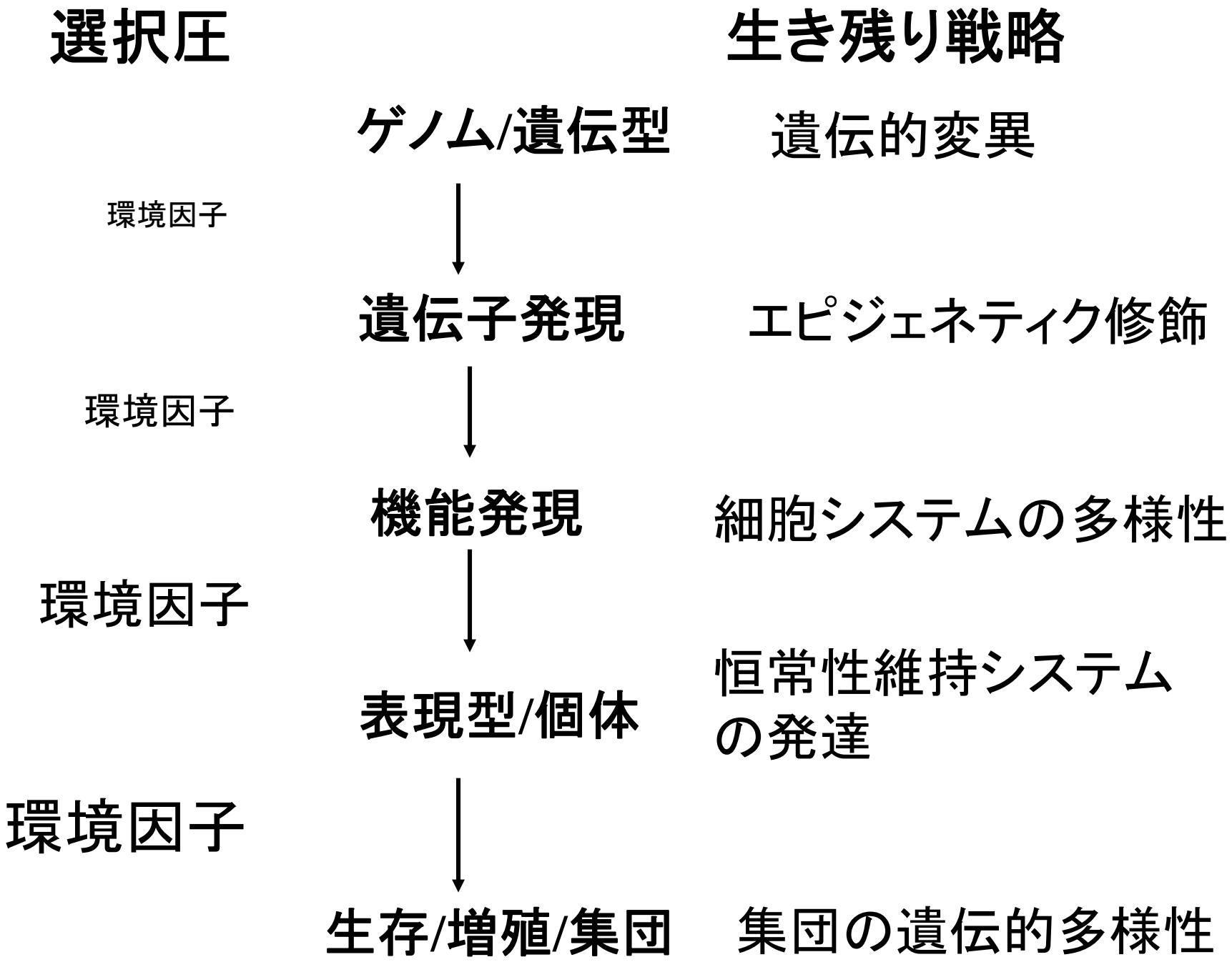
↓

A遺伝子座本来のプロモーターから転写

↓

野生色マウスの数＞黄色マウスの数

Waterland RA and Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. **Mol. Cell. Biol.** 23, 5293–5300 (2003).


選択圧
生き残り戦略
ゲノム/遺伝型
遺伝的変異
環境因子
遺伝子発現
エピジェネティク修飾
環境因子
機能発現
細胞システムの多様性
環境因子
表現型/個体
恒常性維持システム
の発達
環境因子
生存/増殖/集団
集団の遺伝的多様性