

Současné možnosti hledání genetických příčin komplexních neuropsychiatrických nemocí a poruch osobnosti

Stanislav Kmoch & Jan Vevera

Ústav dědičných metabolických poruch & Psychiatrická klinika

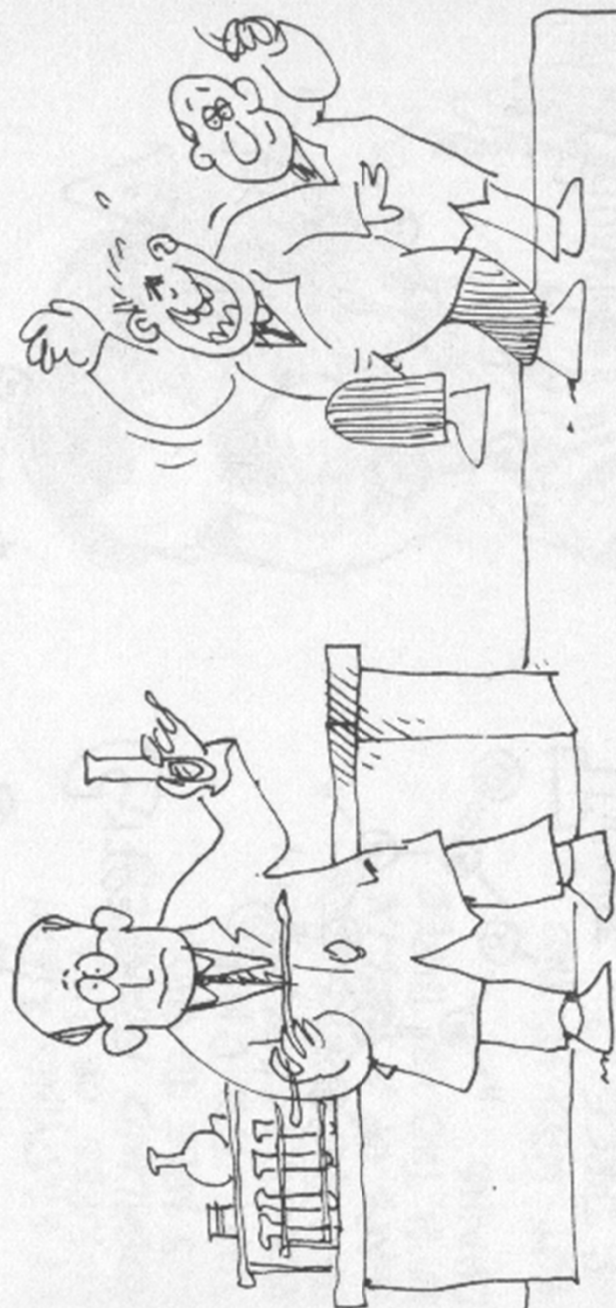
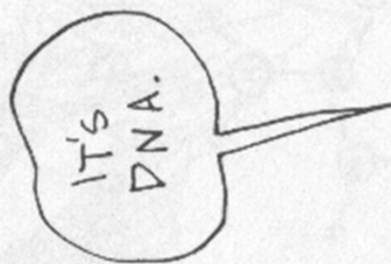
1.Lékařská fakulta, Univerzita Karlova v Praze

&

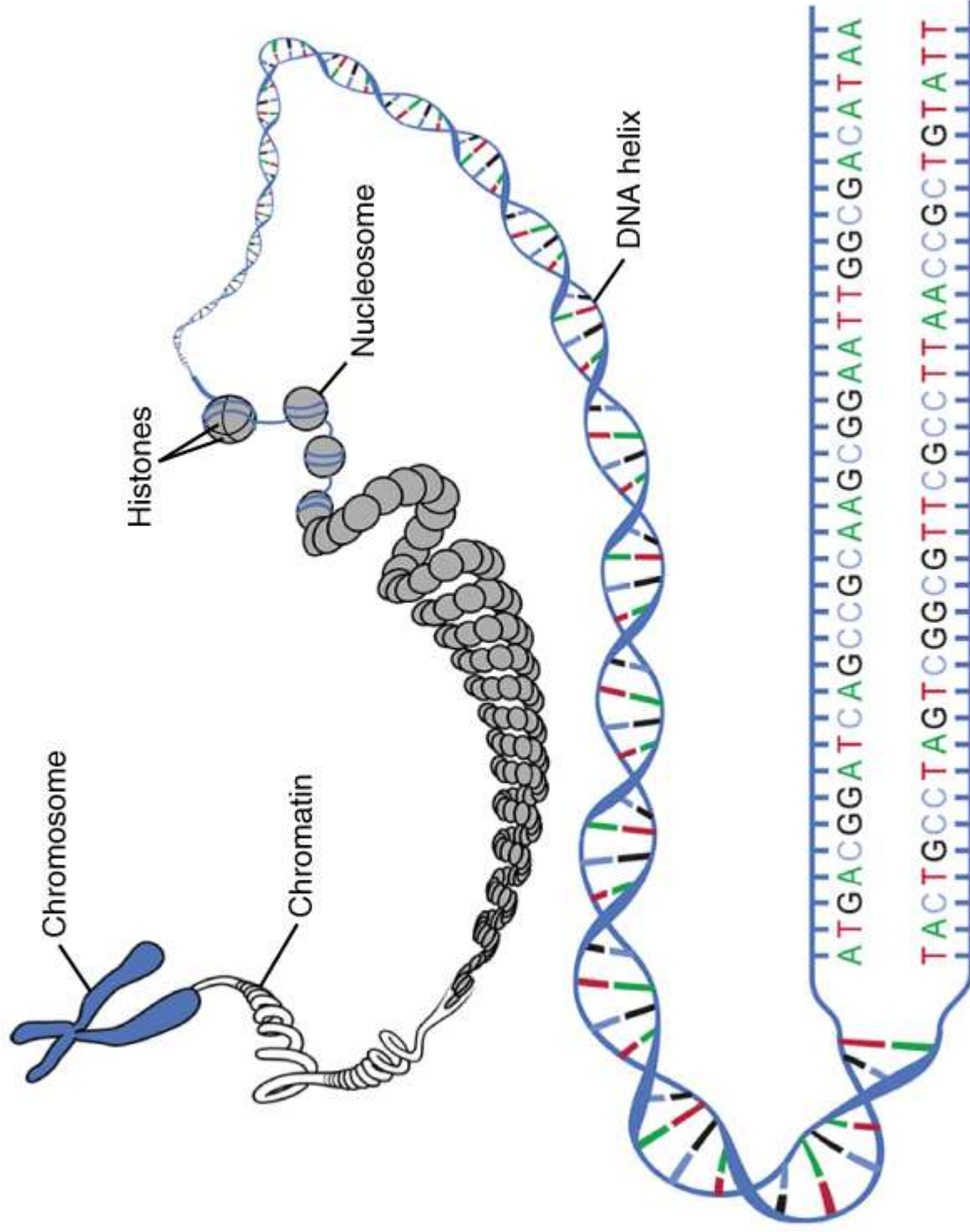
**Biotechnologické a biomedicínské centrum Akademie věd a Univerzity Karlovy
(BIOCEV)**

Genetic architecture of complex traits

- **Several key concepts of human genetics**
 - Inheritance, variability, mutation rate
- **When geneticists should get involved**
 - genetic epidemiology
- **Genetic concepts of complex traits**
 - common vs rare variants
- **Genetic dissection of complex traits**
 - linkage , association
- **Future of genetic studies in complex traits**
 - clan and personal genomics
- **Genetic architecture of impulsive violence**
 - Our own experience



WHEN AVERY ANNOUNCED HIS RESULTS IN 1940, FEW SCIENTISTS
BELIEVED HIM.¹⁹



Ideas on Protein Synthesis (Oct. 1956)

The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it.

That is, we may be able to have



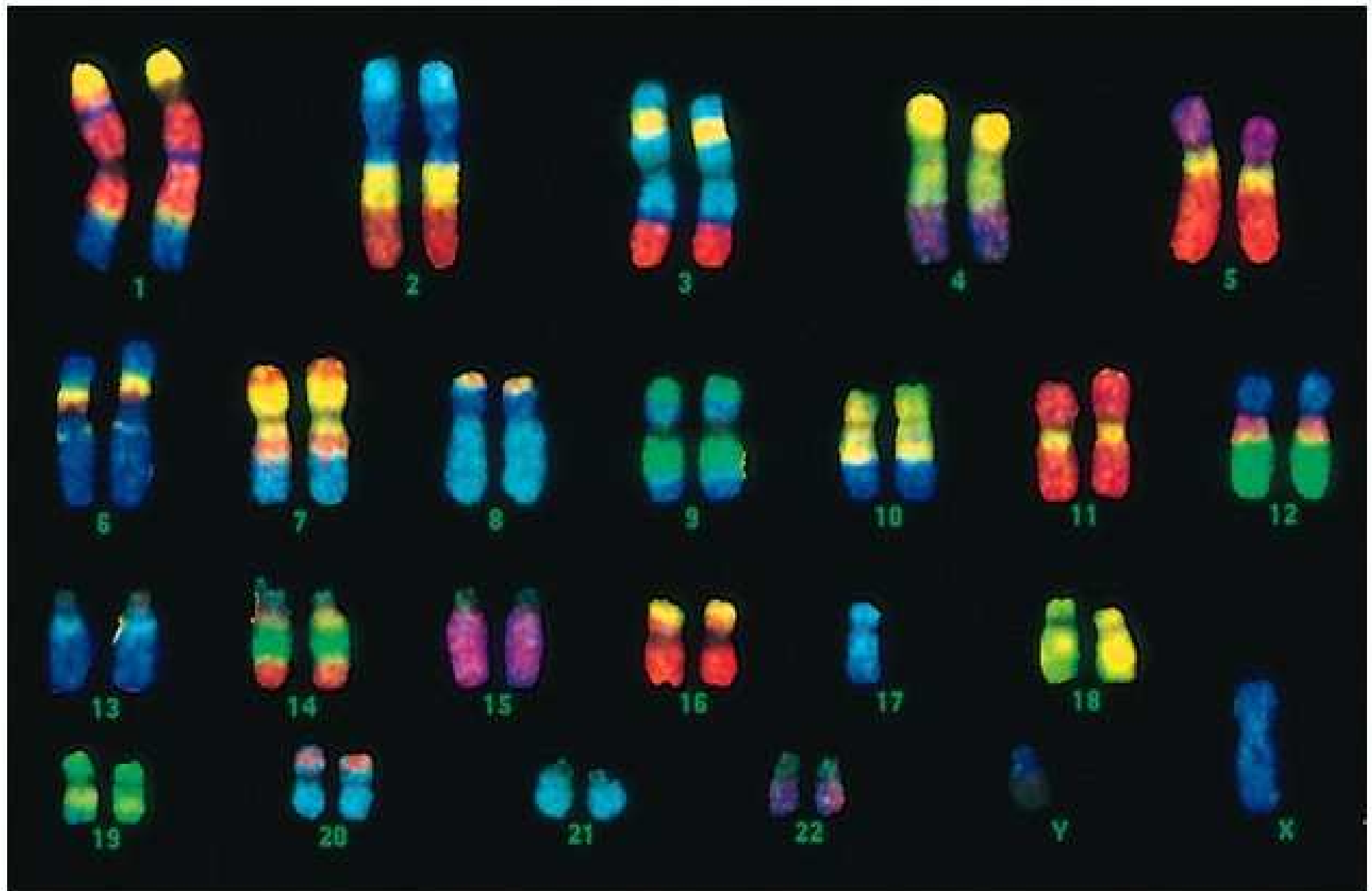
but never

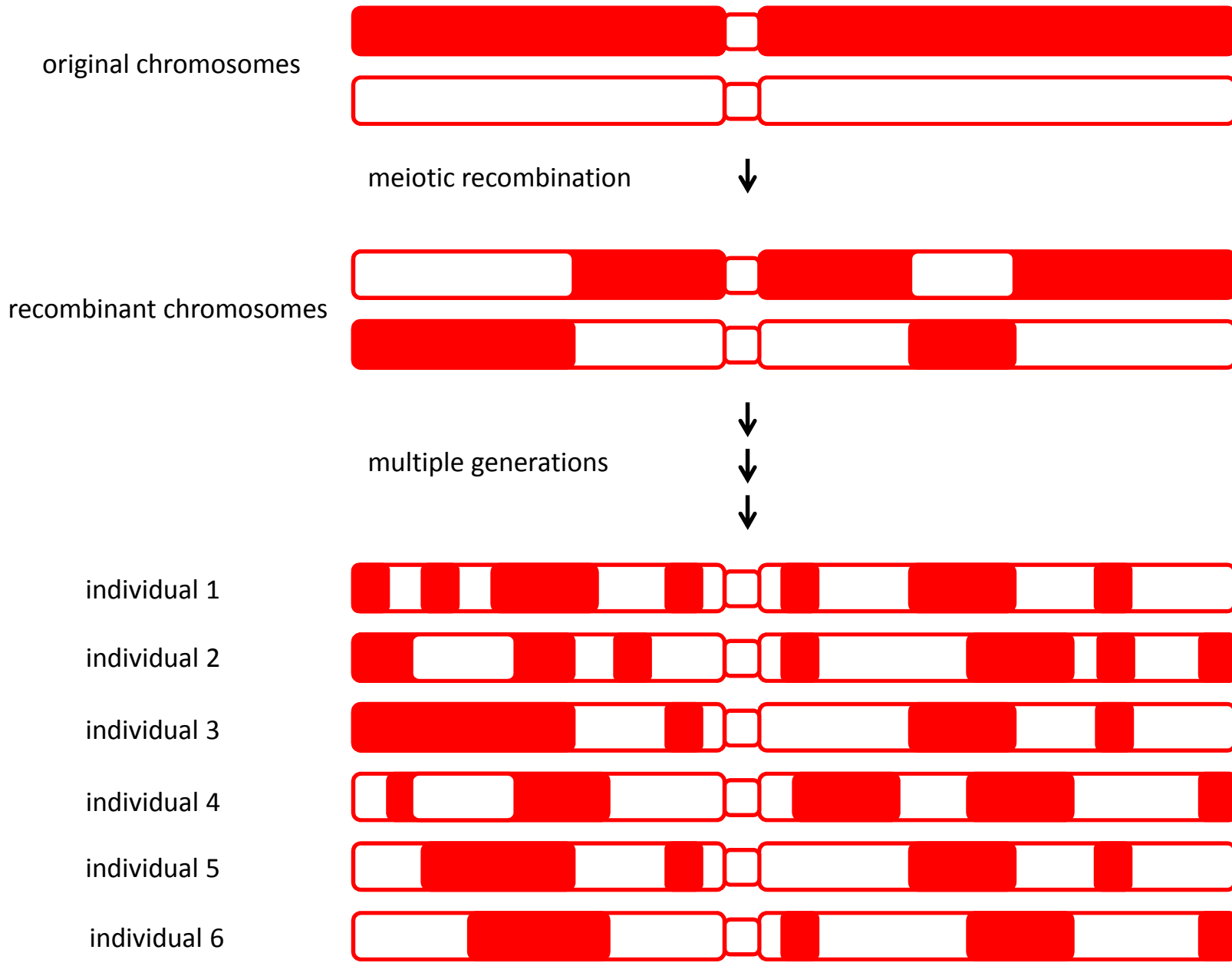


where the arrows show the transfer of information.



22 pairs of chromosomes + X+Y+Mt

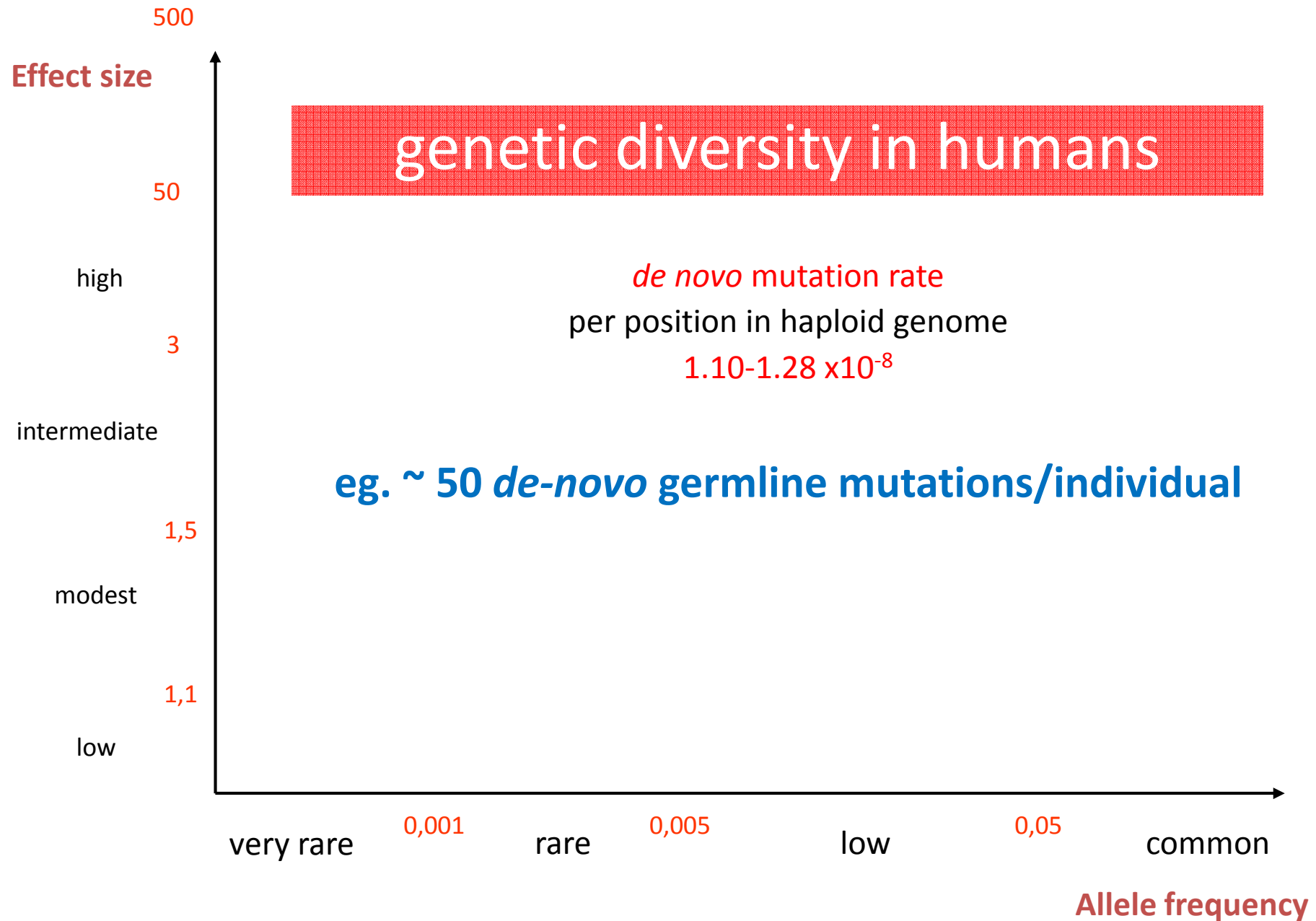


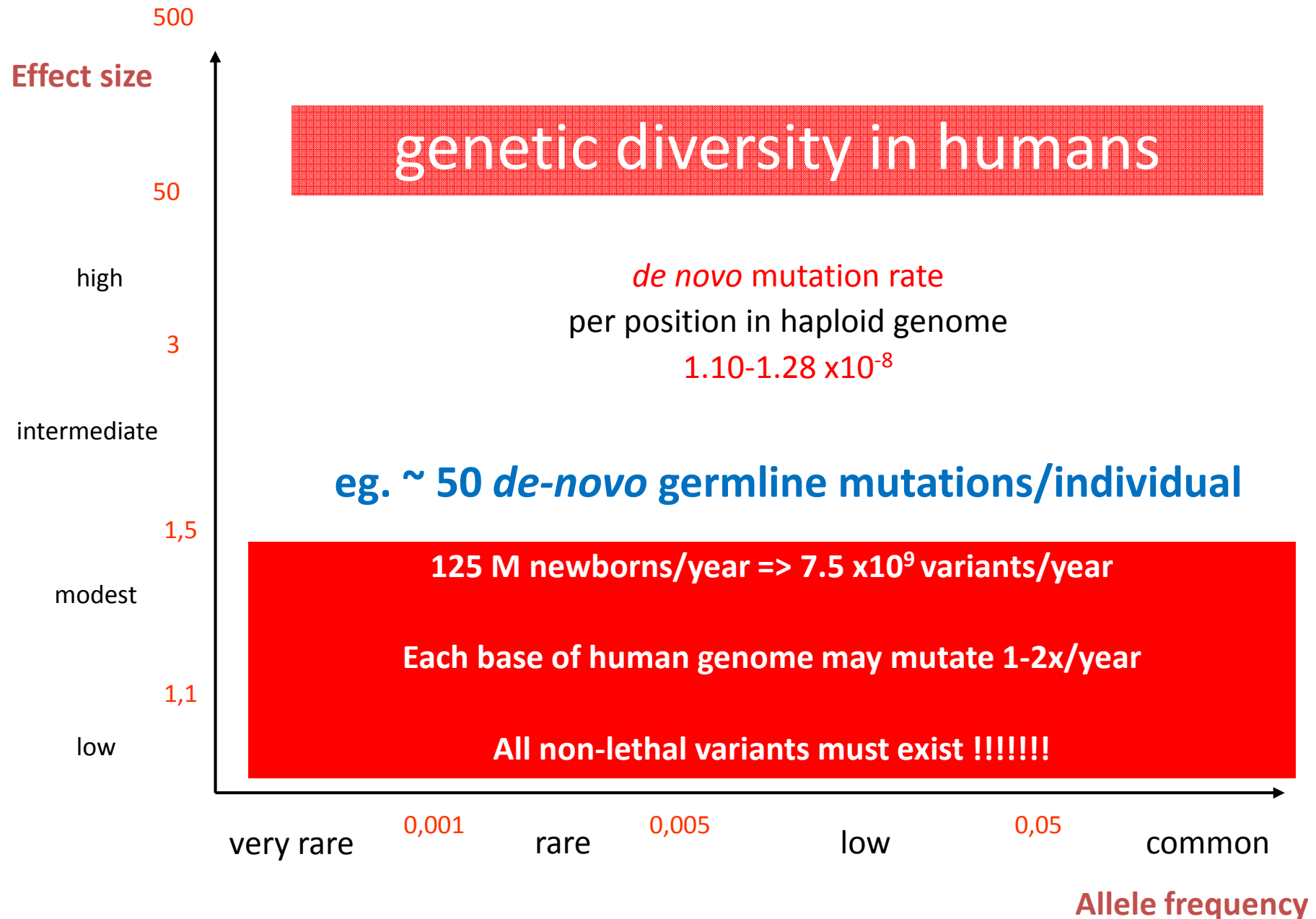


Our genomes are passed in blocks

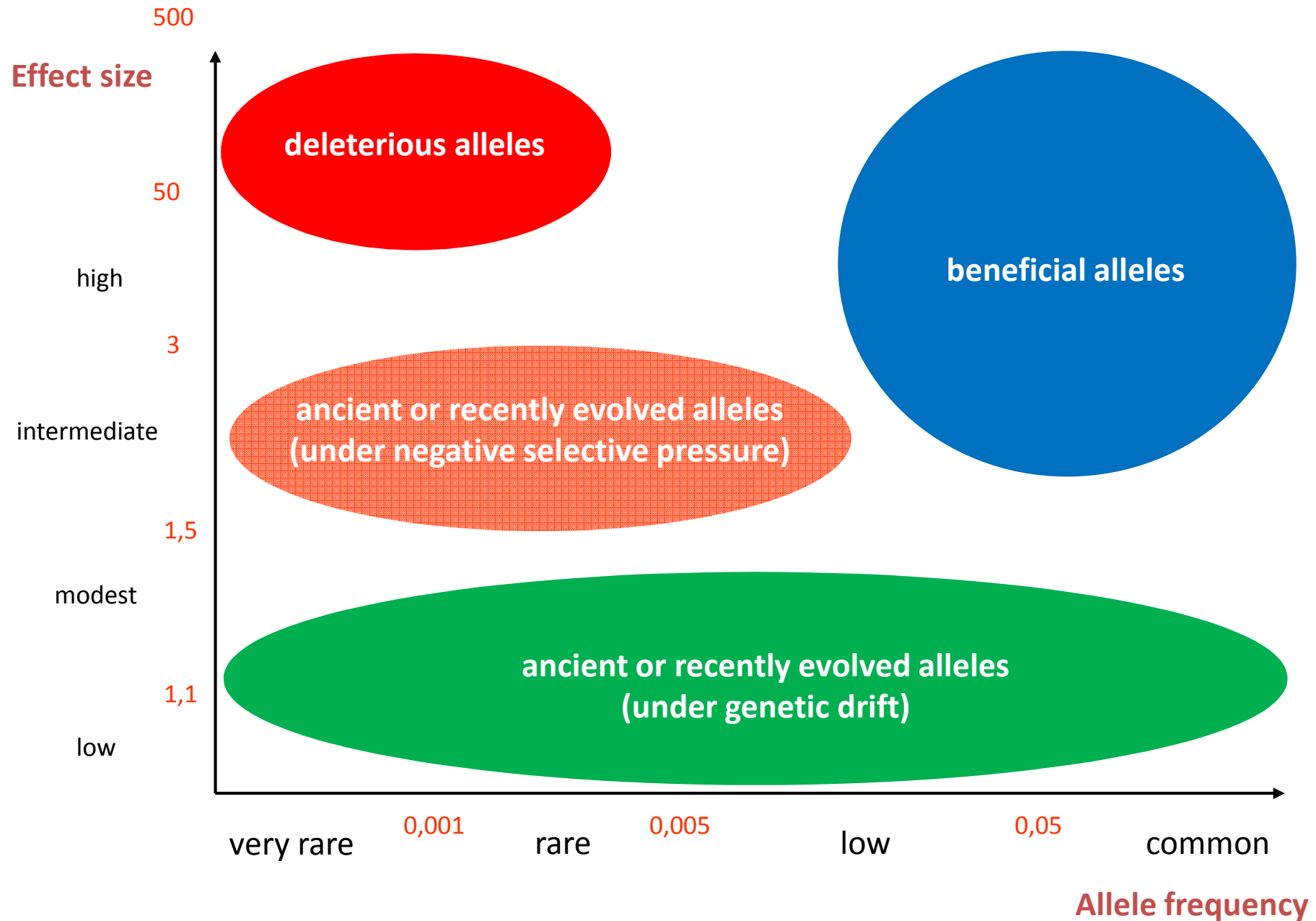


Mutations are source of variability

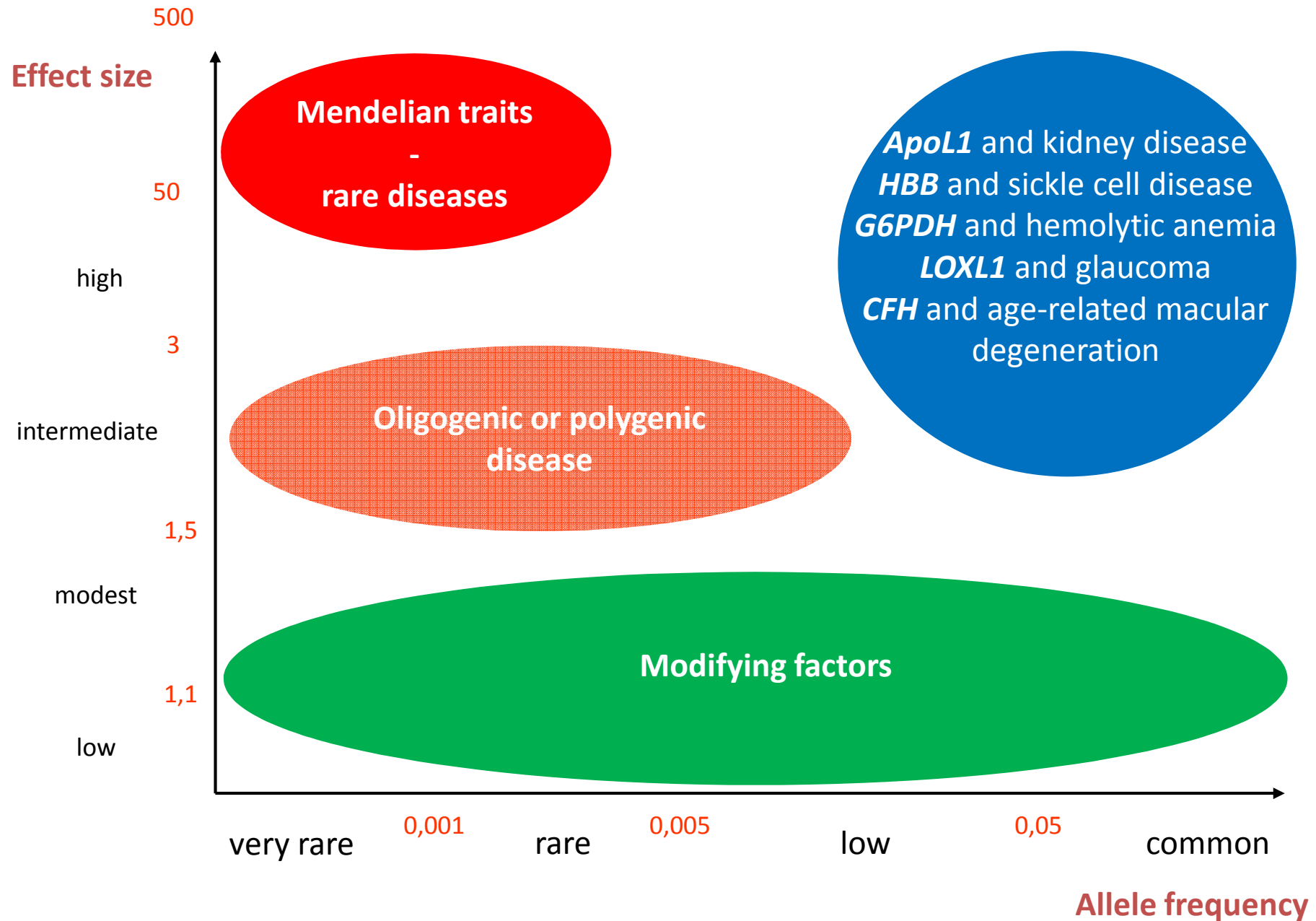




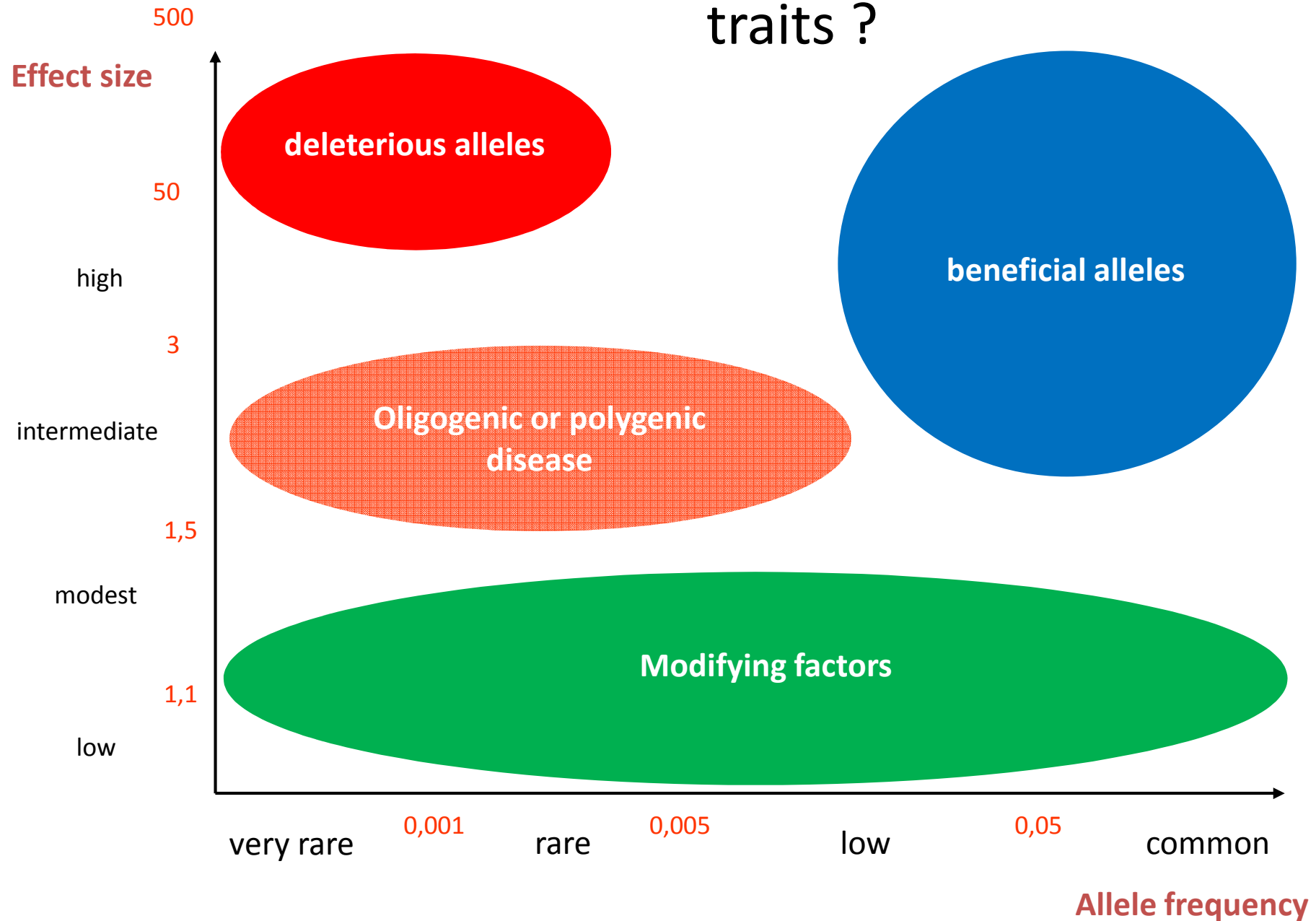
evolutionary perspective



disease perspective



Neuropsychiatric and behavioral traits ?

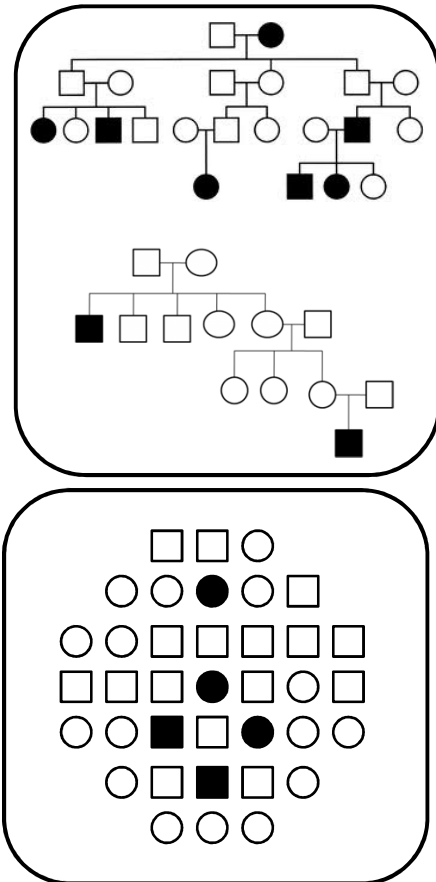


When geneticists should get involved ?

Key questions and answers of genetic epidemiology

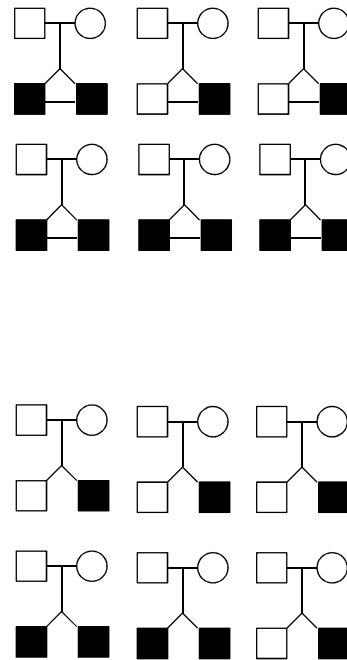
Familial clustering ?

Family aggregation studies



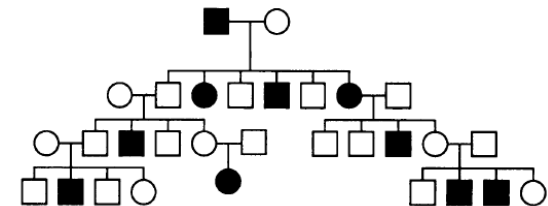
Evidence for a genetic effect ?

Twins heritability studies

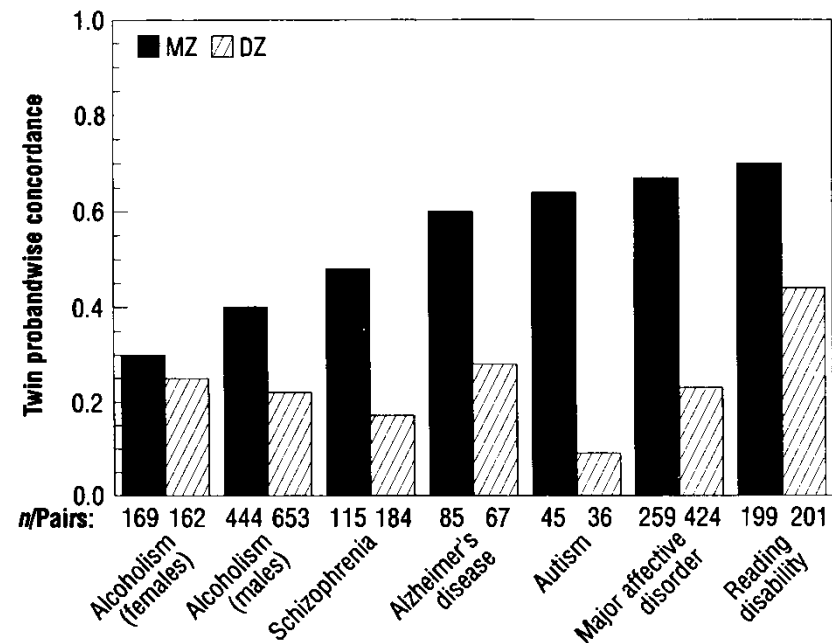
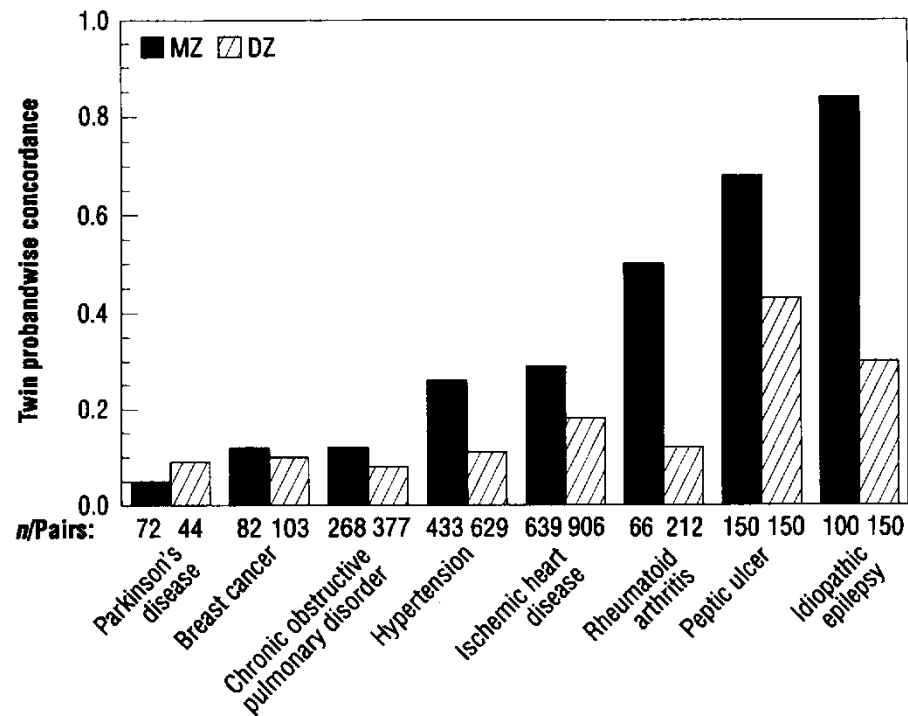


Particular genetic models?

Pedigree analysis

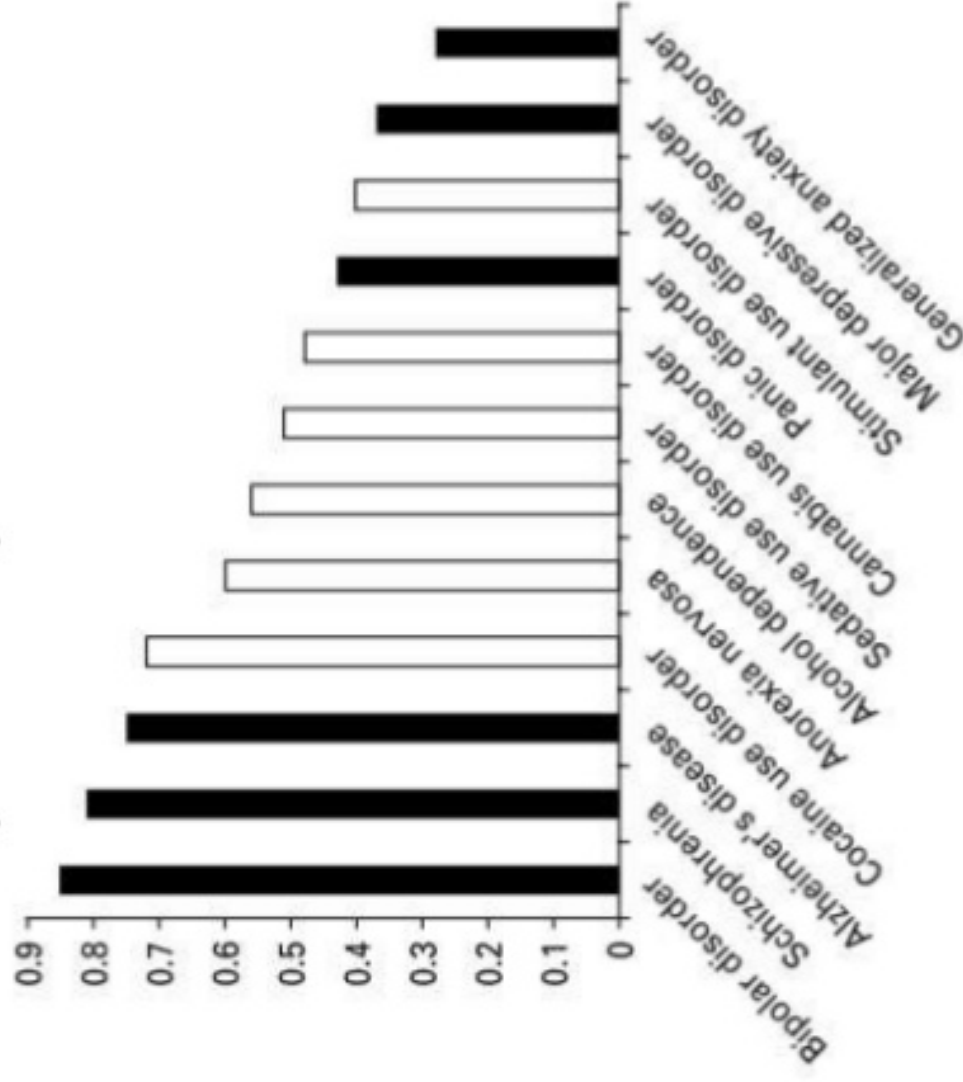


Twin concordance rates



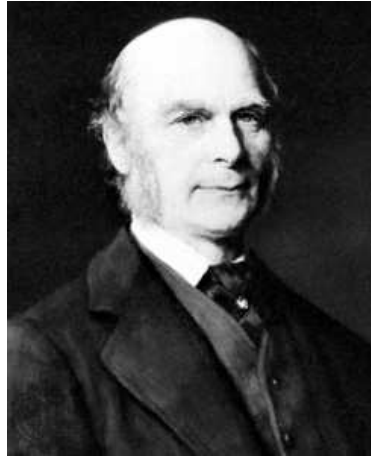
Plomin et al. 1994, Science 264: 1733-9)

Heritability of Psychiatric Disorders



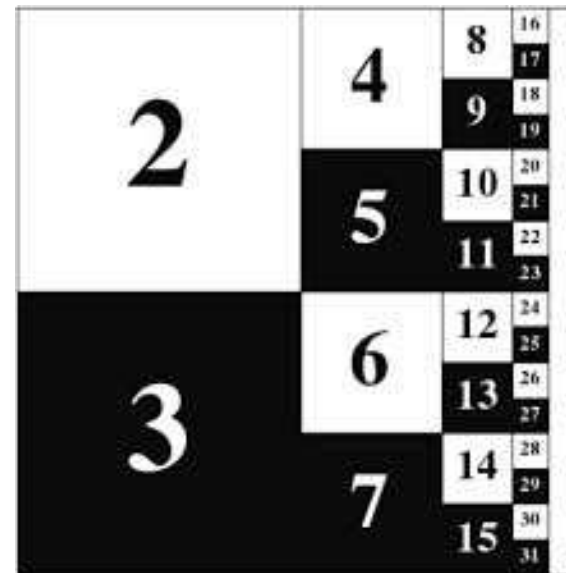
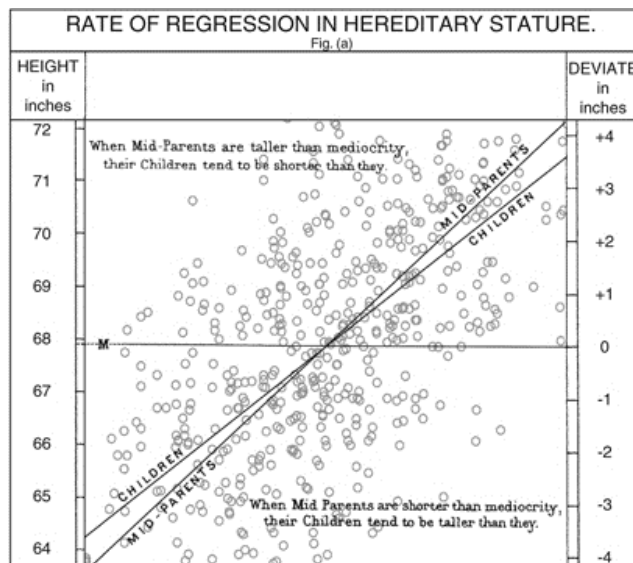
Bienvenu et al. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence.
Psychological Medicine 2011;41:33–40.

Genetic concepts of complex traits



Francis Galton

Determination of the heritability of phenotypic traits by the regression method



haploblocs

Particular individual can be thought of as having inherited ancestral contributions from generations in an exponentially decreasing fashion

Biometric Mendelian debate : how to explain genetics of complex traits



Walter Weldon



Karl Pearson



William Bateson

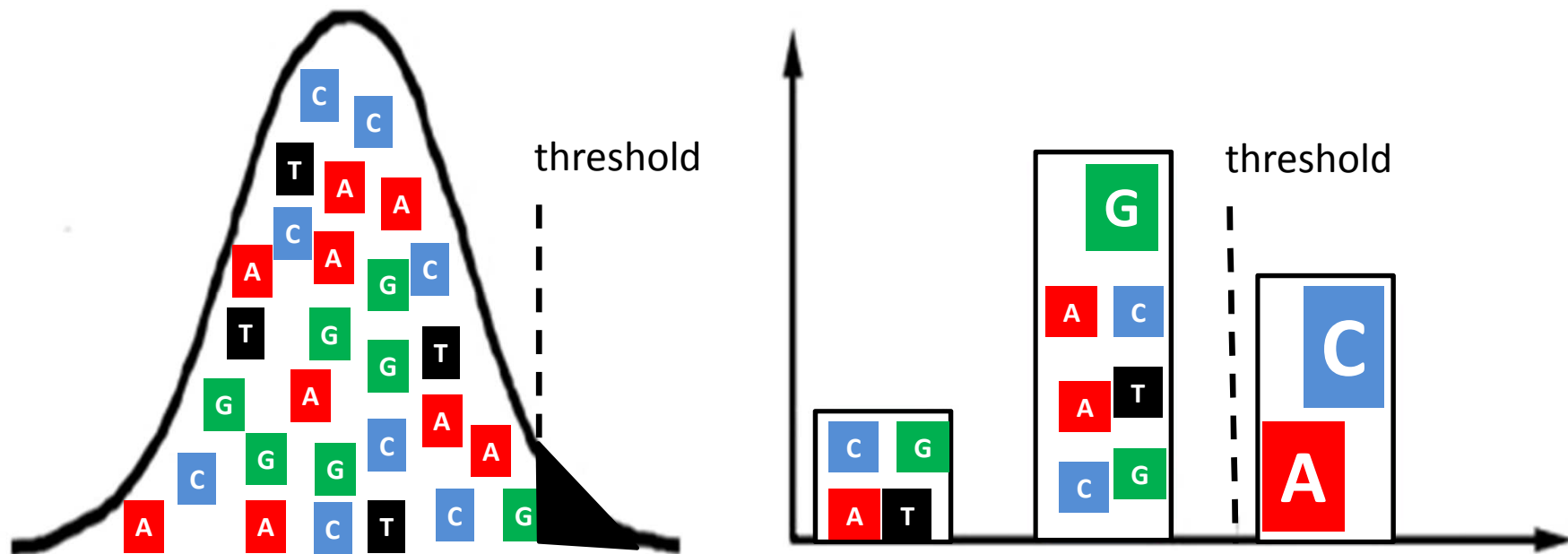
Mendel's principles might be, at best, only a special case of the more general ancestral law.

Variation is continuous, due to mutations of small effects

Mendel's heritable factors could be utilized to justify the theory of discontinuous variation.

Variation in discrete characters is due to mutations with large effects

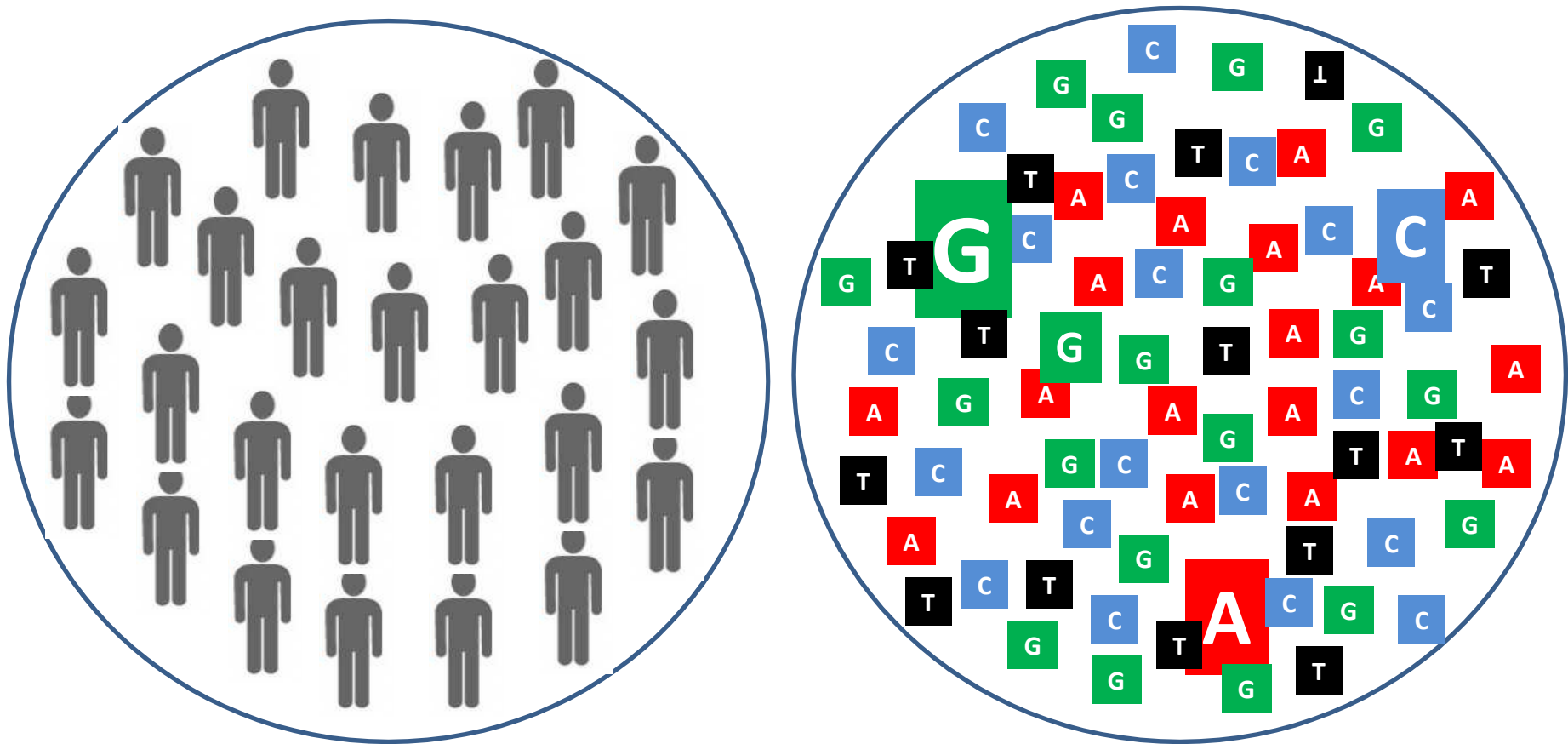
Threshold model of the complex disease, disease liability



Is the variance continuous or discontinuous ?

Common or rare variants ?

genetic variance of the trait



Do we need to explain genetic variation of particular trait at the population level ?

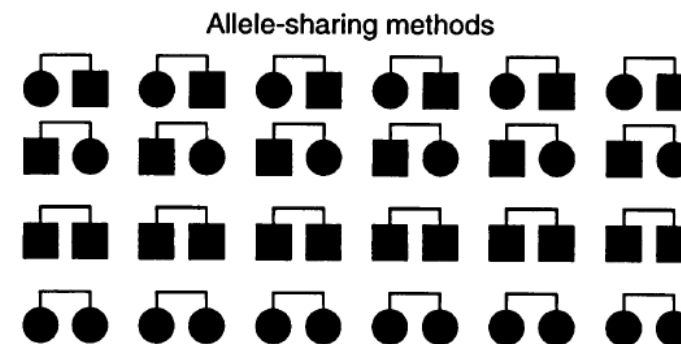
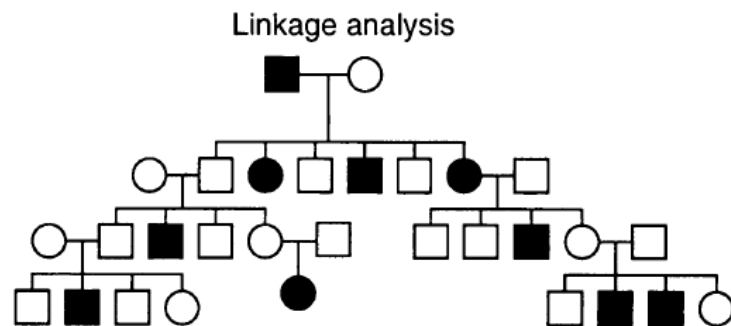
Yes, it defines genes, pathways, mechanisms and therapeutic targets.

Genetic Dissection of Complex Traits

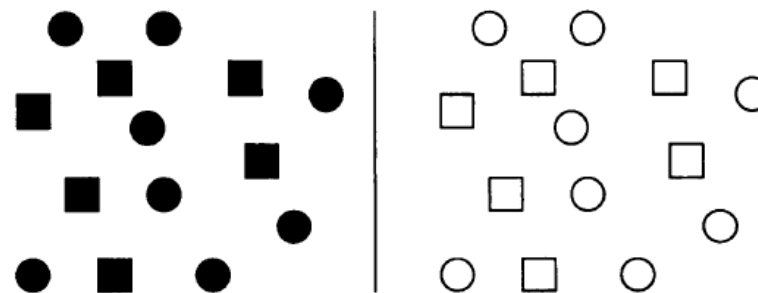
Eric S. Lander* and Nicholas J. Schork

SCIENCE • VOL. 265 • 30 SEPTEMBER 1994

Family studies



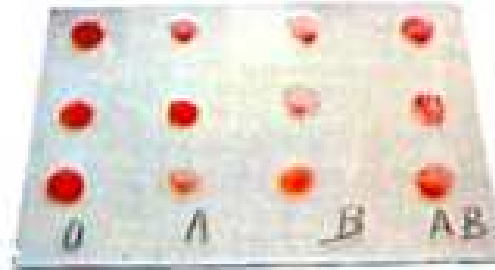
Association studies



Population

Hematologic studies in psychotics

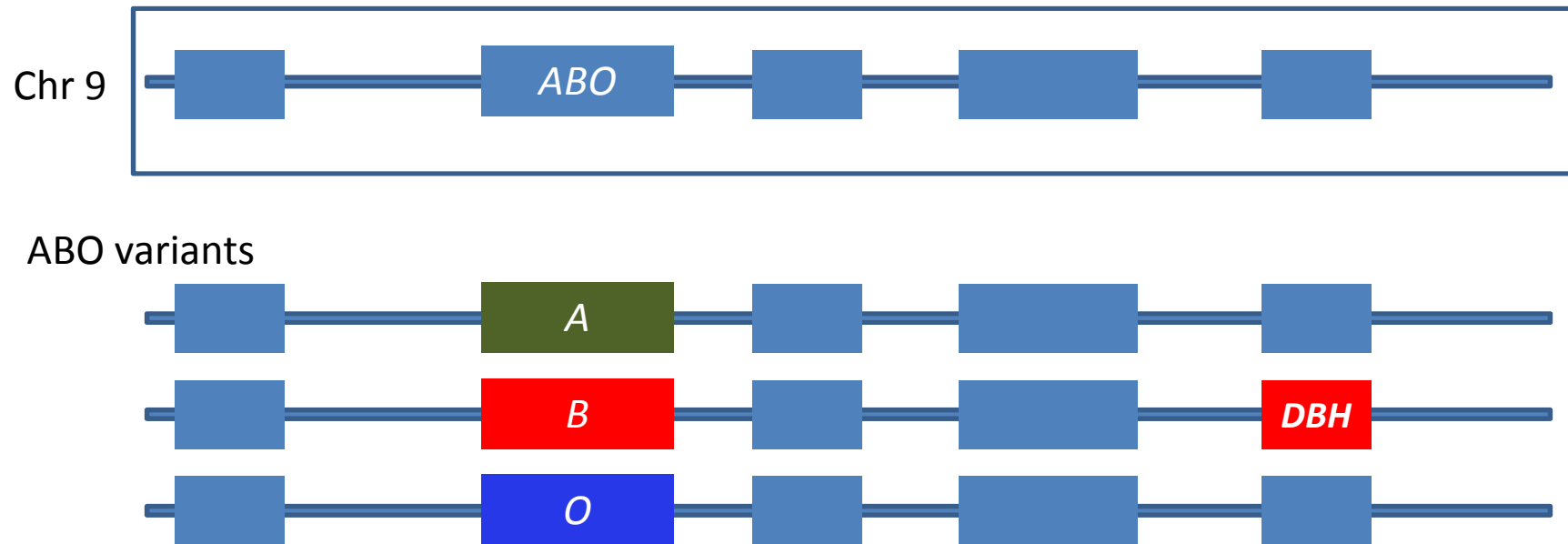
Jan Janský, 1907



Blood group	Psychotics n= N1	Controls n=N2	P value
I (O)	0,35	0,32	n.s
II (A)	0,31	0,36	n.s.
III (B)	0,21	0,18	n.s
IV (AB)	0,13	0,14	n.s

No association of psychosis with blood groups

Janský study from today perspective ?



Hypotheses in the Life Sciences 1 1 pp1-8

ABO group B is associated with personality traits through linkage disequilibrium with low activity dopamine beta hydroxylase

Donna K. Hobgood¹



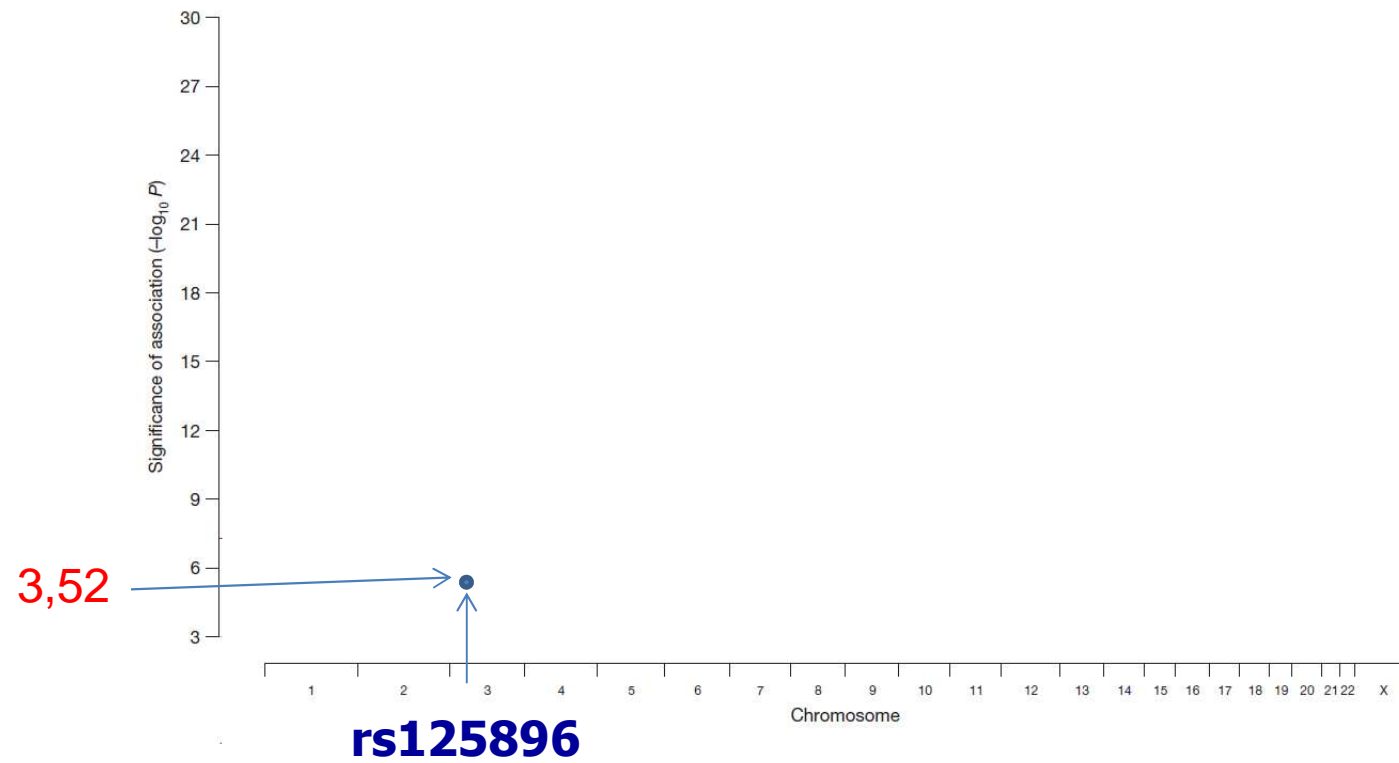
controls

[illegible]

	C	G	total
A	9	1	10
C	1	9	10
	10	10	20

$X^2 = 12,8$
 $P = 0,0003$
 $-\log_{10} P = 3,52$

plot $-\log_{10}P$ value vs chromosomal position of the SNP



Genome-Wide Human SNP Array 6.0

Pure Power and Performance:

The new Affymetrix® Genome-Wide Human SNP Array 6.0 features 1.8 million genetic markers, including more than 906,600 single nucleotide polymorphisms (SNPs) and more than 946,000 probes for the detection of copy number variation. The SNP Array 6.0 demonstrates industry-leading performance and represents more genetic variation on a single array than any other product, providing maximum panel power and the highest physical coverage of the genome.

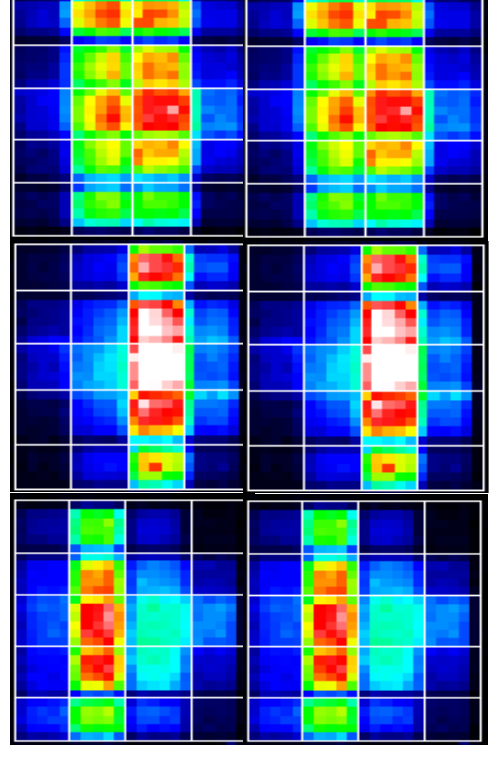
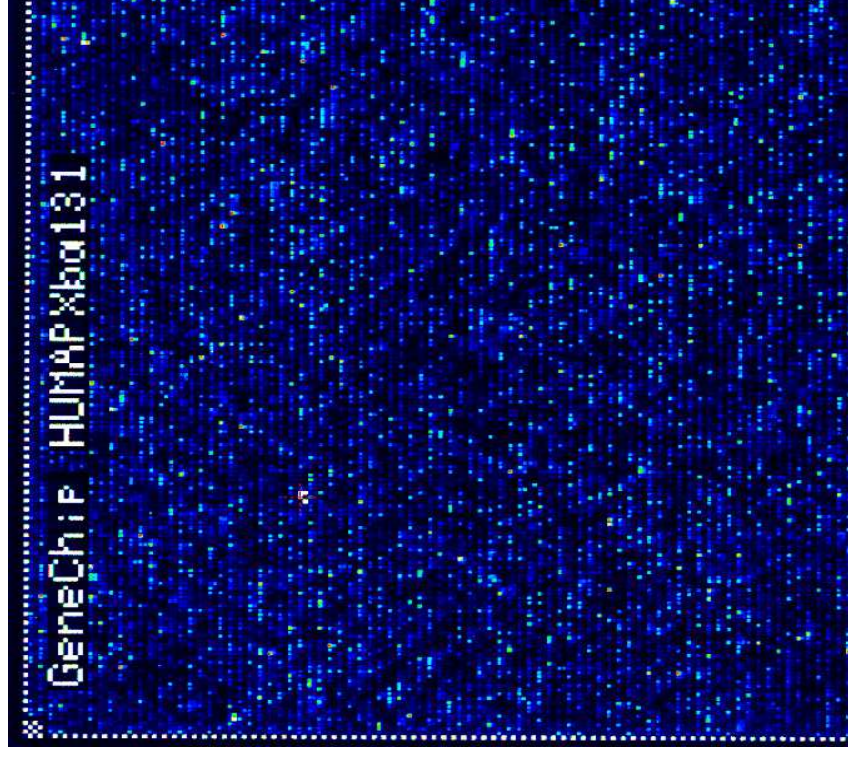
The high price-performance value of the SNP Array 6.0 enables researchers to design association studies with larger sample sizes in the initial scan and replication phases, thereby significantly increasing the overall genetic power of their studies.

More than 906,600 SNPs:

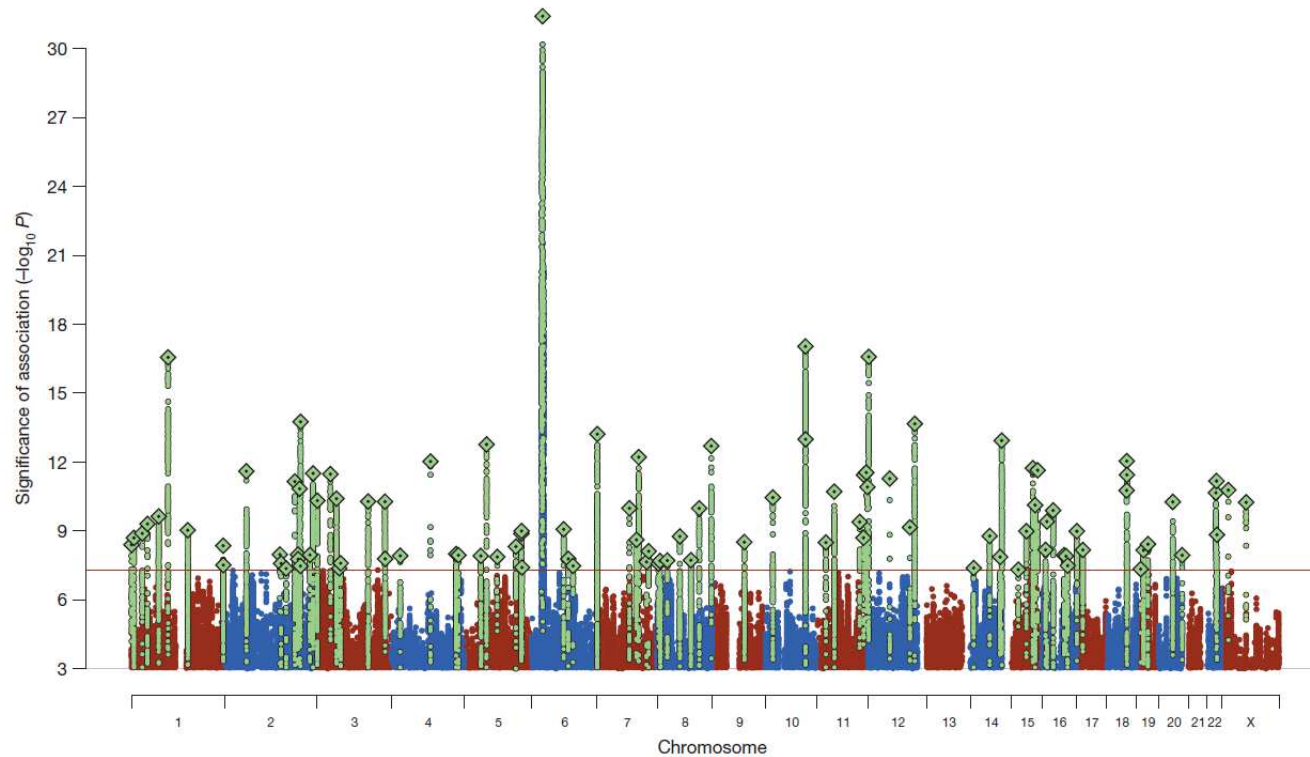
- Unbiased selection of 482,000 SNPs; historical SNPs from the SNP Array 5.0
- Selection of additional 424,000 SNPs
 - Tag SNPs
 - SNPs from chromosomes X and Y
 - Mitochondrial SNPs
- New SNPs added to the dbSNP database
- SNPs in recombination hotspots

More than 946,000 copy number probes:

- 202,000 probes targeting 5,677 CNV regions from the Toronto Database of Genomic Variants
- Regions resolve into 3,182 distinct, non-overlapping segments; on average 61 probe sets per region
- 744,000 probes, evenly spaced along the genome

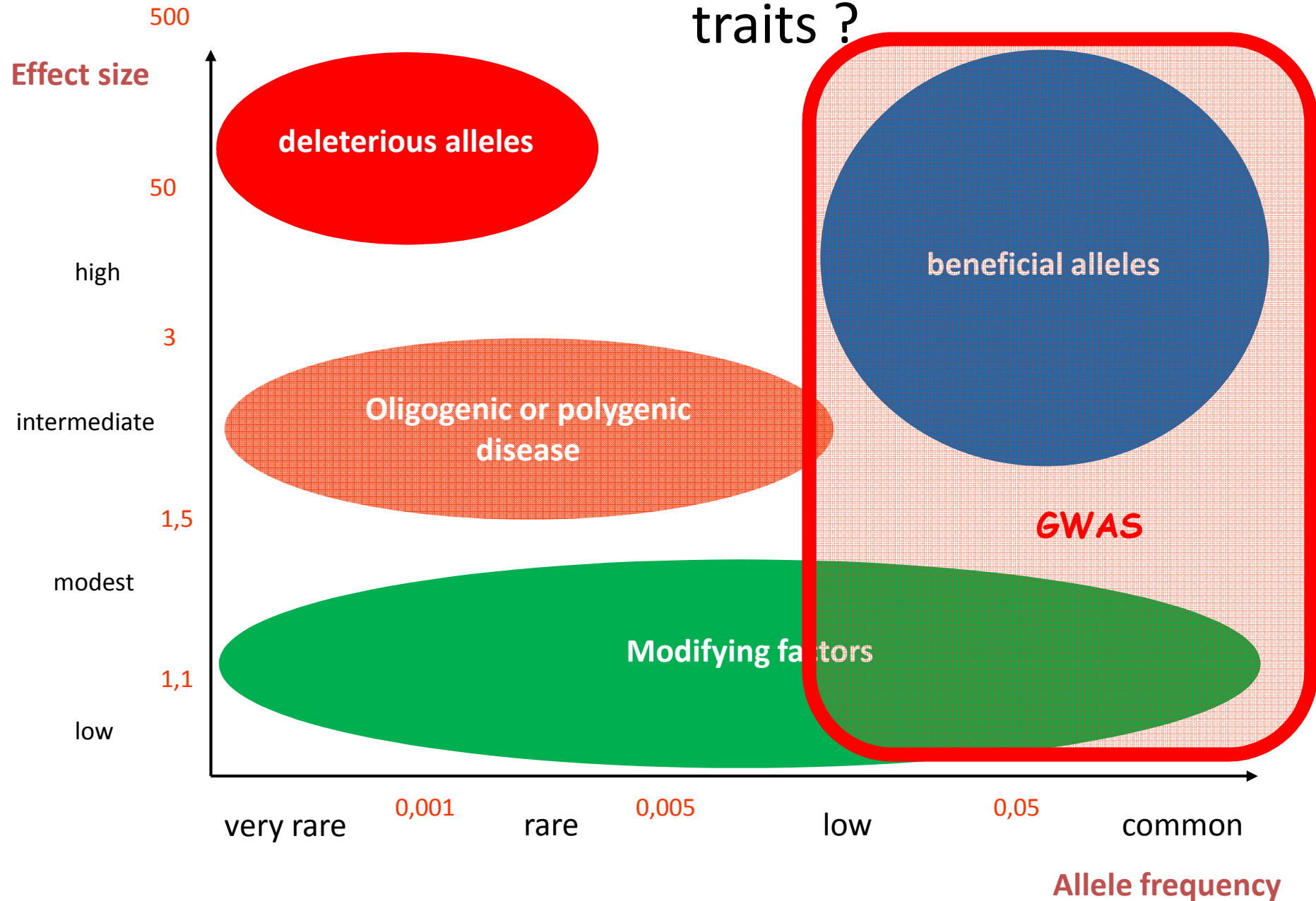


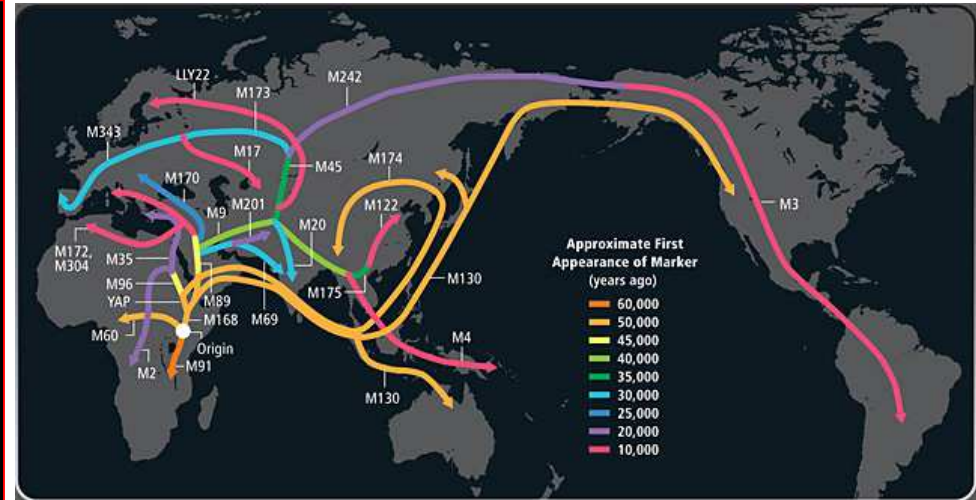
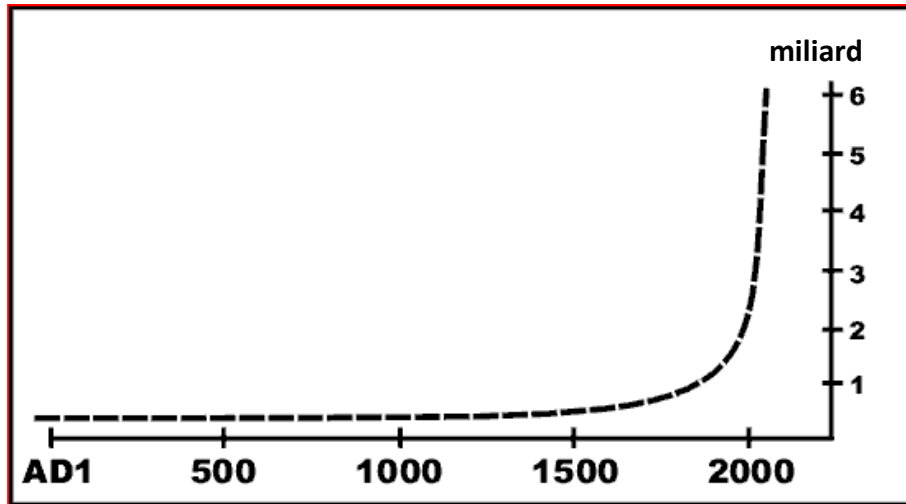
plot $-\log_{10}P$ values vs chromosomal positions of many SNPs



Manhattan plot

Neuropsychiatric and behavioral traits ?





genome mutability (de novo)

+

explosive population growth

+

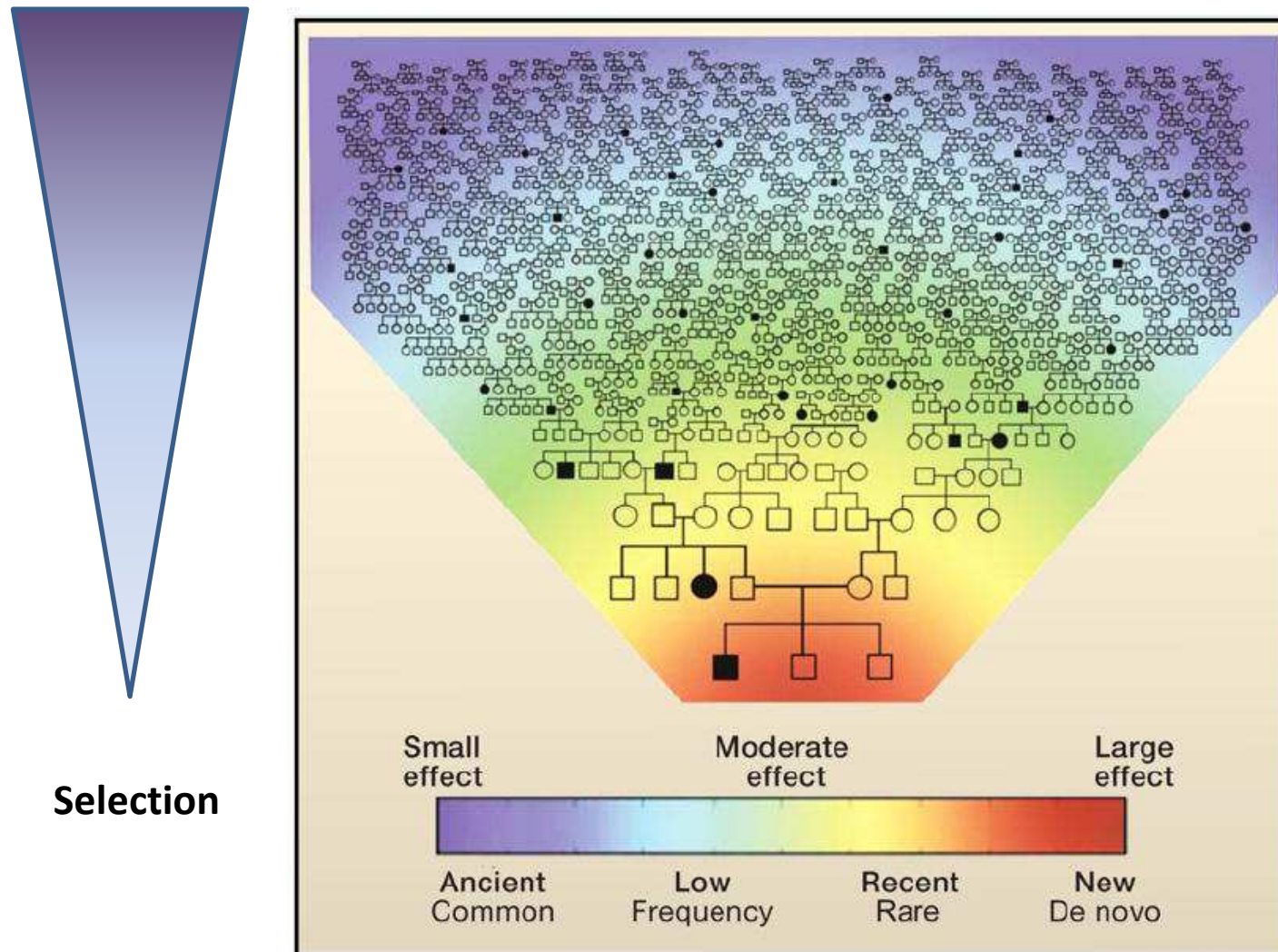
migration

=

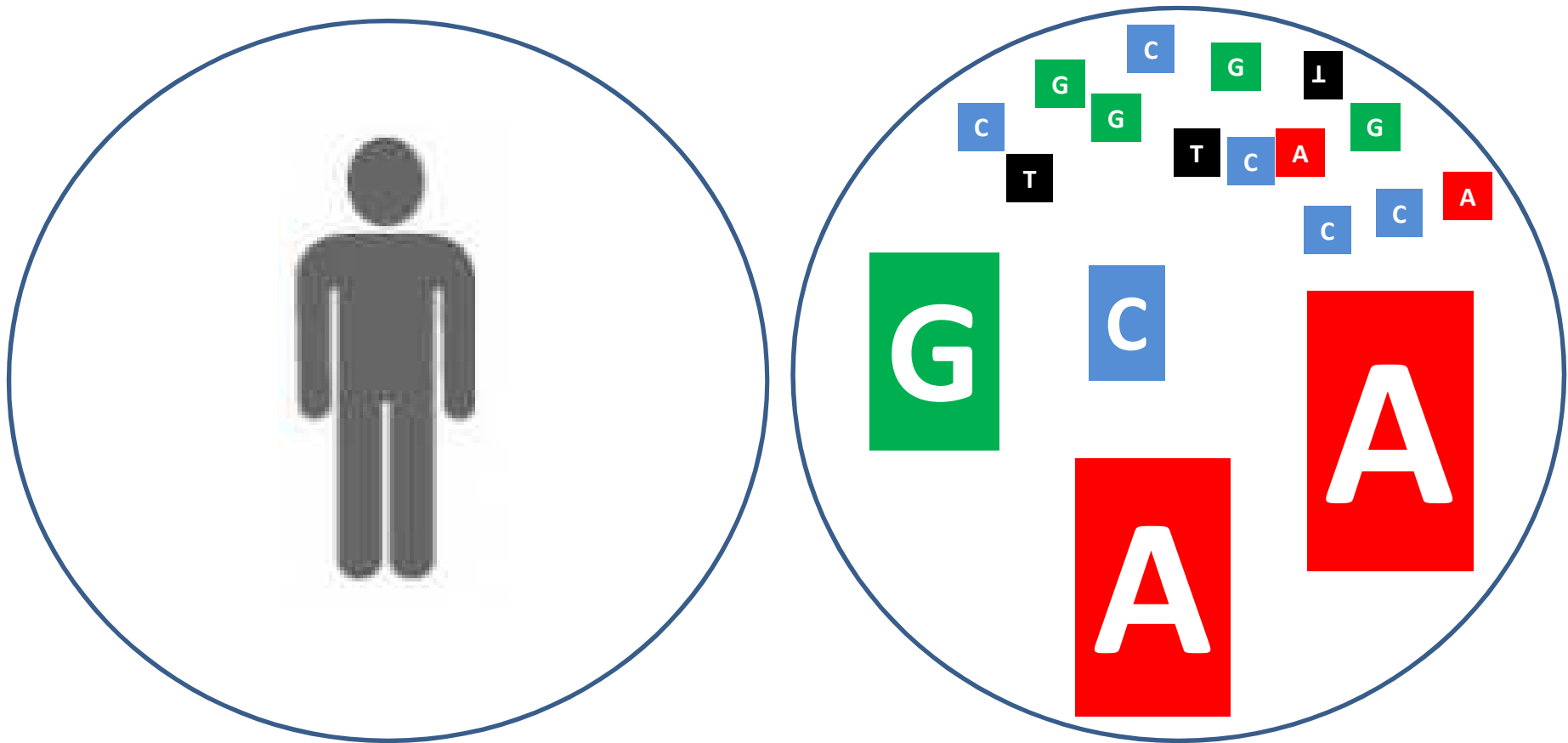
Increase load of rare variants

which is likely to play a role in the individual or familial genetic burden of complex disease risk

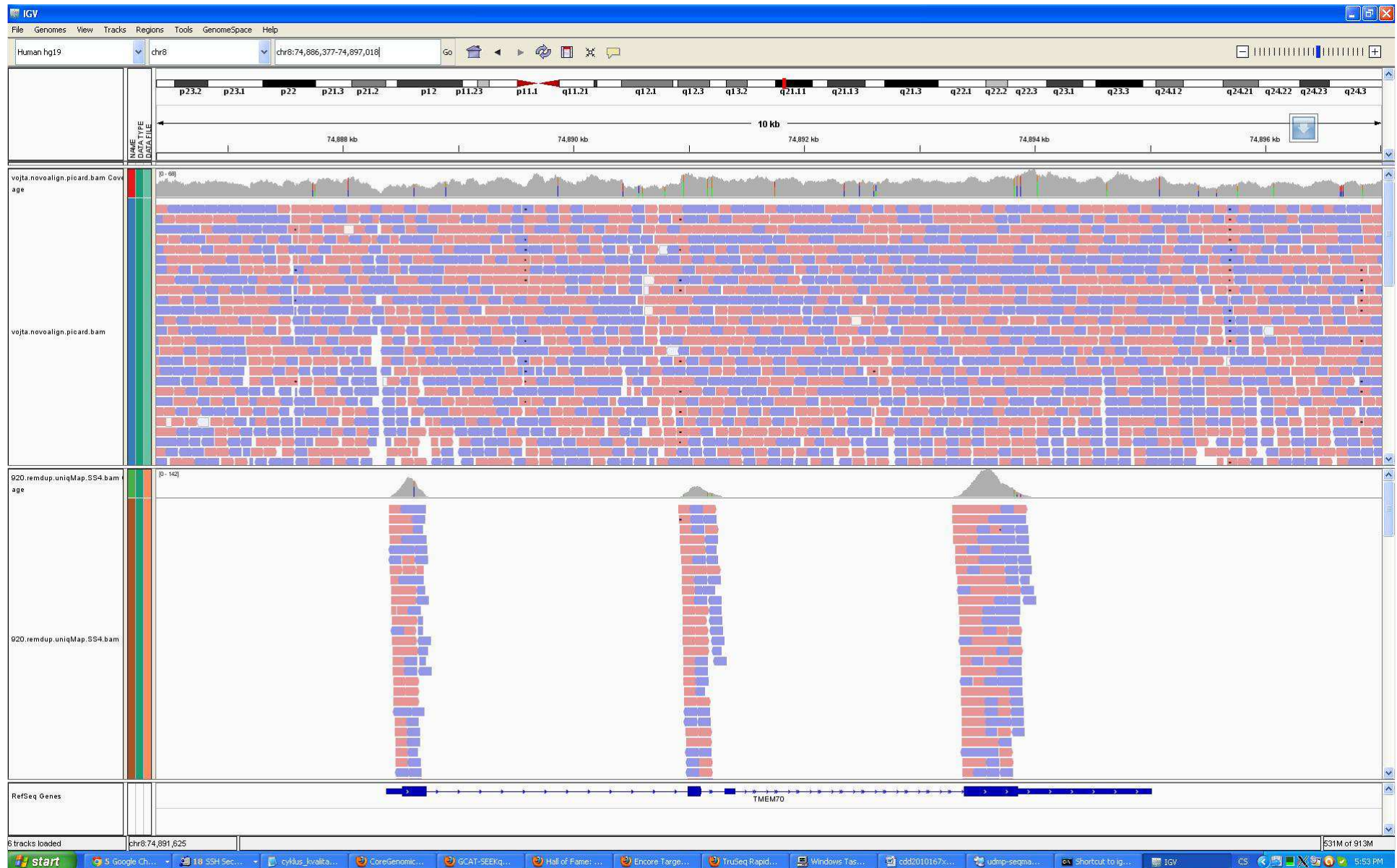
From rare Mendelian traits to the general population *focus on diseases in families and 'clans'*



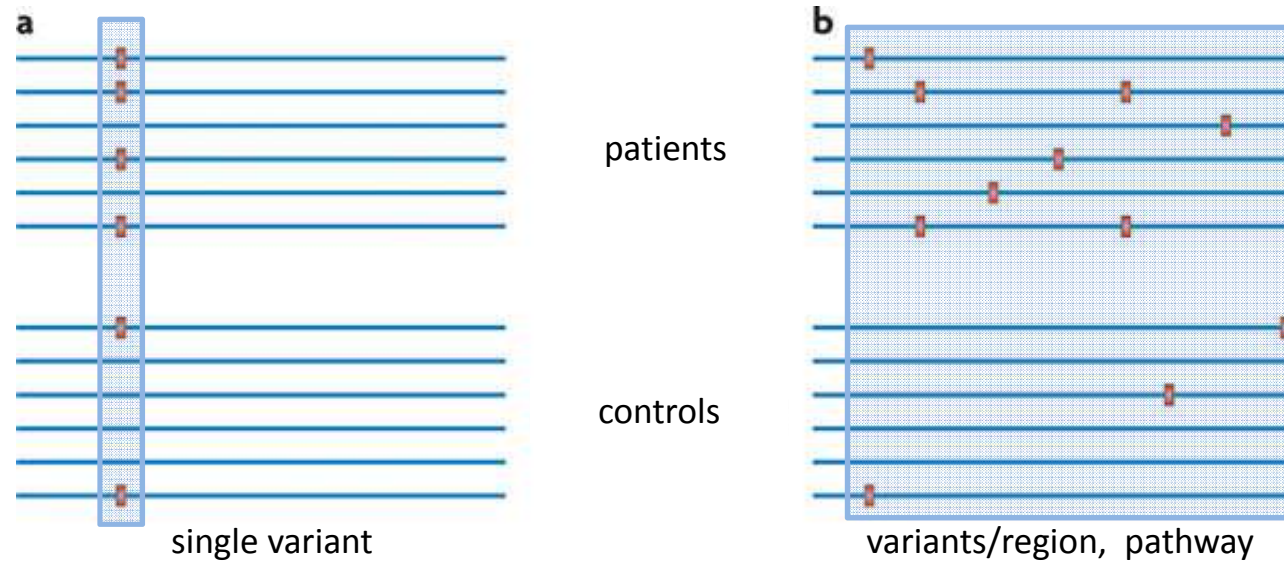
Focus on individual genetic variance of the trait



NGS sequencing; genome vs exome



Single variant association vs aggregative testing



Violent behavior

- **Typical complex trait** that results from interactions between multiple genetic, biological, environmental, and sociological factors
- Violent crime **runs in families** (OR for sibs 4, for arson 22)
- Twin and family studies have suggested that violence, has substantial **heritability, ranging from 44%–72%**
- High heritability implies **genetic determination**
- Genetic studies (SVAS, GWAS) revealed **only small fraction of the genetic variation** (eg. *MAOA*, *HTR2B*, *CDH13*)

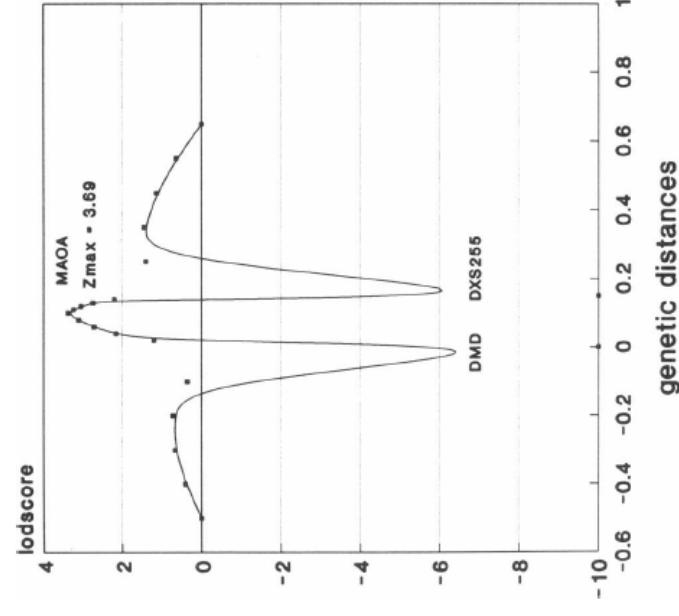
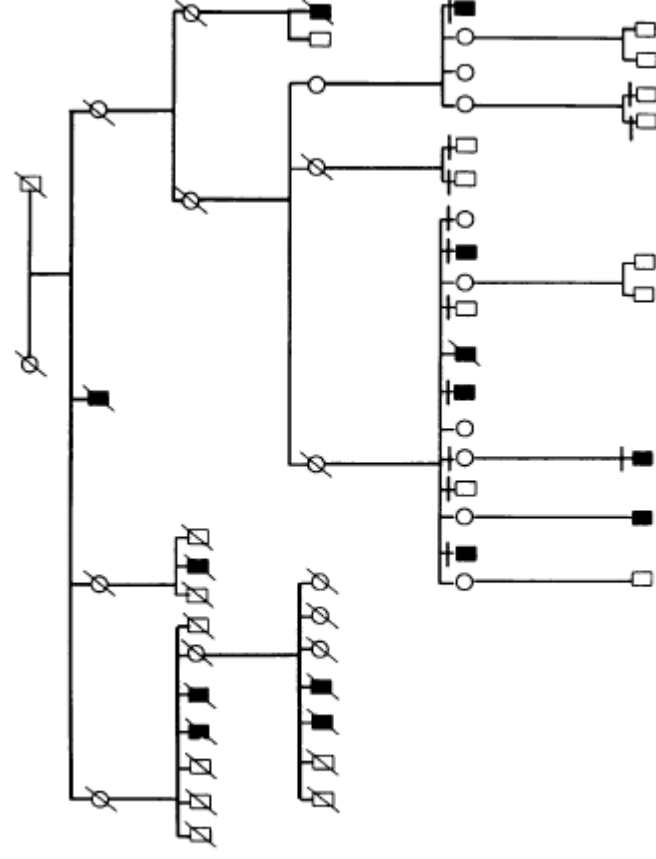
Candidate genetic factors

- Y chromosome
- Testosterone production
- Androgen synthesis
- Male determining factors (*SRY*)
- Stress response components (GR, DBH, COMT, ADRB's, NET1)
- Serotonine pathway (MAOA, MAOB, SLC6A4, TPH1 and 2
- Blood sugar levels
- Brain glucose uptake
- Nitric oxide synthase
- Arginine vasopressin receptor
-

X-Linked Borderline Mental Retardation with Prominent Behavioral Disturbance: Phenotype, Genetic Localization, and Evidence for Disturbed Monoamine Metabolism

H. G. Brunner,* M. R. Nelen,* P. van Zandvoort,* N. G. G. M. Abeling,† A. H. van Gennip,†
E. C. Wolters,‡ M. A. Kuiper,‡ H. H. Ropers,* and B. A. van Oost*

*Department of Human Genetics, Nijmegen; †Departments of Pediatrics and Clinical Chemistry, Academic Medical Center, University of Amsterdam; and ‡Department of Neurology, Free University, Amsterdam



Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A

H. G. Brunner,* M. Nelen, X. O. Breakefield, H. H. Ropers,
B. A. van Oost

Genetic and metabolic studies have been done on a large kindred in which several males are affected by a syndrome of borderline mental retardation and abnormal behavior. The types of behavior that occurred include impulsive aggression, arson, attempted rape, and exhibitionism. Analysis of 24-hour urine samples indicated markedly disturbed monoamine metabolism. This syndrome was associated with a complete and selective deficiency of enzymatic activity of monoamine oxidase A (MAOA). In each of five affected males, a point mutation was identified in the eighth exon of the MAOA structural gene, which changes a glutamine to a termination codon. Thus, isolated complete MAOA deficiency in this family is associated with a recognizable behavioral phenotype that includes disturbed regulation of impulsive aggression.

ARTICLE

20 ans après: a second mutation in MAOA identified by targeted high-throughput sequencing in a family with altered behavior and cognition

Amélie Piton^{*,1,2,10}, Hélène Poquet^{3,4,10}, Claire Redin^{1,2}, Alice Masurel³, Julia Lauer⁵, Jean Muller^{1,5}, Julien Thevenon^{3,6}, Yvan Herenger⁵, Sophie Chancenotte^{3,7}, Marlène Bonnet⁷, Jean-Michel Pinoit⁴, Frédéric Huet³, Christel Thauvin-Robinet^{3,6}, Anne-Sophie Jaeger⁵, Stéphanie Le Gras⁸, Bernard Jost⁸, Bénédicte Gérard⁵, Katell Peoc'h⁹, Jean-Marie Launay⁹, Laurence Faivre^{3,6,10} and Jean-Louis Mandel^{*,1,2,5,10}

CNVs

RESEARCH ARTICLE

AMERICAN JOURNAL OF
medical genetics
Neuropsychiatric Genetics

Genomic Architecture of Aggression: Rare Copy Number Variants in Intermittent Explosive Disorder

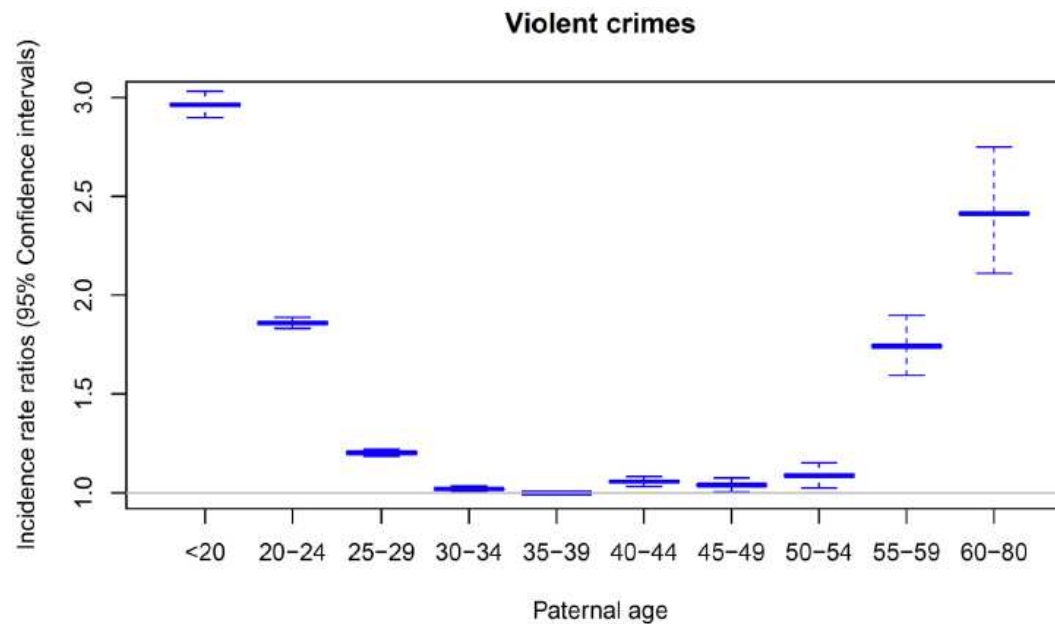
Tiffany H. Vu,¹ Emil F. Coccaro,² Evan E. Eichler,^{1,3} and Santhosh Girirajan^{1*}

De novo variants ?

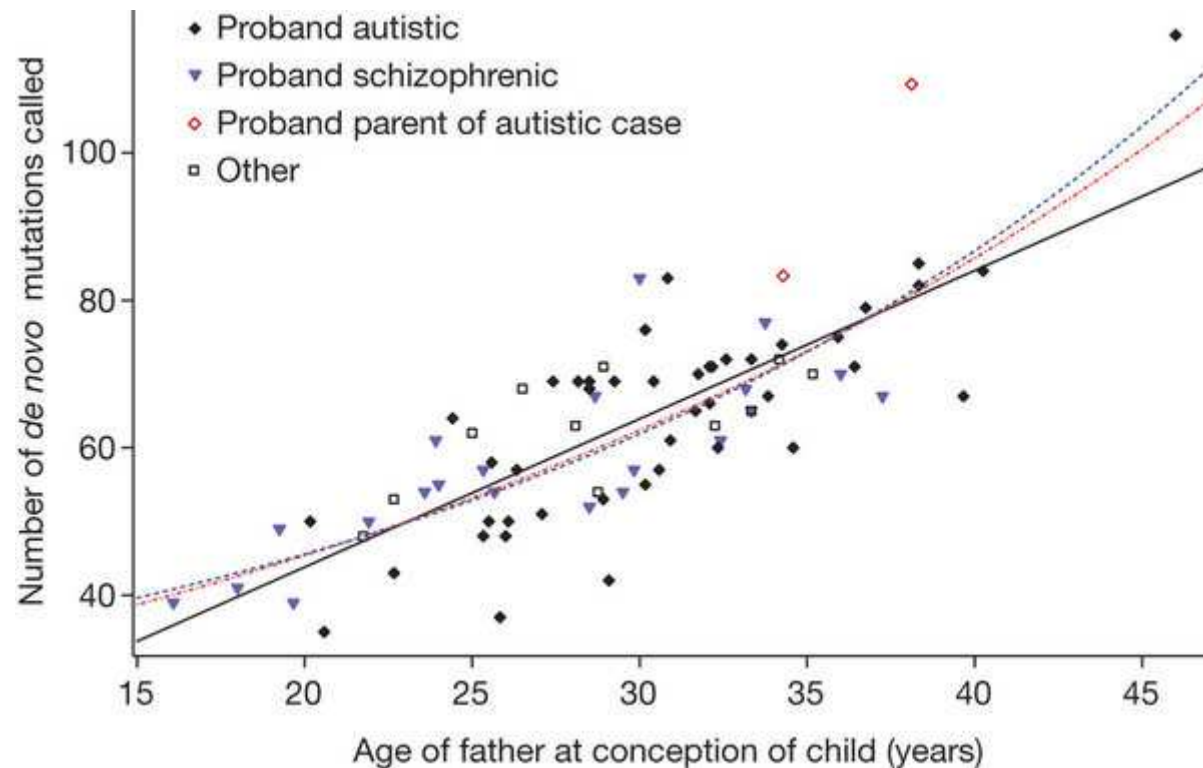
Dev Psychopathol. 2012 August ; 24(3): 739–753. doi:10.1017/S095457941200034X.

Advancing paternal age and offspring violent offending: A sibling-comparison study

Ralf Kuja-Halkola^{1,2,3}, Yudi Pawitan¹, Brian M D'Onofrio⁴, Niklas Långström^{1,2,3}, and Paul Lichtenstein¹



Load of de novo variants increases with paternal age !



ORIGINAL ARTICLE

Genetic background of extreme violent behavior

J Tiihonen^{1,2,3,19}, M-R Rautiainen^{3,19}, HM Ollila^{3,4}, E Repo-Tiihonen², M Virkkunen^{5,6}, A Palotie^{7,8,9,10,11}, O Pietiläinen³, K Kristiansson³, M Joukamaa¹², H Lauerma^{3,13,14}, J Saarela¹⁵, S Tyni¹⁶, H Vartiainen¹⁶, J Paananen¹⁷, D Goldman¹⁸ and T Paunio^{3,5,6}

In developed countries, the majority of all violent crime is committed by a small group of antisocial recidivistic offenders, but no genes have been shown to contribute to recidivistic violent offending or severe violent behavior, such as homicide. Our results, from two independent cohorts of Finnish prisoners, revealed that a monoamine oxidase A (MAOA) low-activity genotype (contributing to low dopamine turnover rate) as well as the CDH13 gene (coding for neuronal membrane adhesion protein) are associated with extreme signal was observed for **MAOA, CDH13** homicides, attempted homicides or batteries). No substantial t offenders, indicating that findings were specific for violent ocial personality disorder. These results indicate both low monoamine metabolism and neuronal membrane dysfunction as plausible factors in the etiology of extreme criminal violent behavior, and imply that at least about 5–10% of all severe violent crime in Finland is attributable to the aforementioned MAOA and CDH13 genotypes.

Nature. 2010 December 23; 468(7327): 1061–1066. doi:10.1038/nature09629.

A POPULATION-SPECIFIC *HTR2B* STOP CODON PREDISPOSES TO SEVERE IMPULSIVITY

Laura Bevilacqua¹, Stéphane Doly², Jaakko Kaprio^{3,4,5}, Qiaoping Yuan¹, Roope Tikkanen⁶, Tiina Paunio⁷, Zhifeng Zhou¹, Juho Wedenoja^{8,9}, Luc Maroteaux², Silvina Diaz², Arnaud Belmer², Colin A. Hodgkinson¹, Liliana Dell’Osso¹⁰, Jaana Suvisaari⁷, Emil Coccaro¹¹, Richard J Rose¹², Leena Peltonen^{*,8,9}, Matti Virkkunen^{6,13}, and David Goldman¹