Translational pain research
-from molecular biology to the clinic

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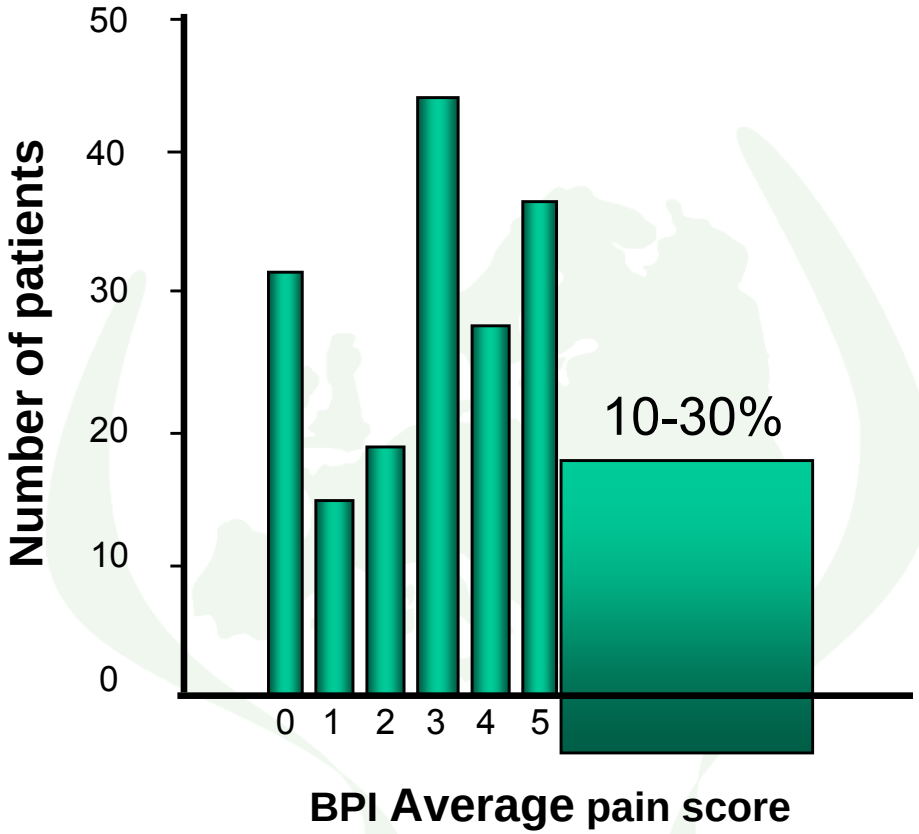
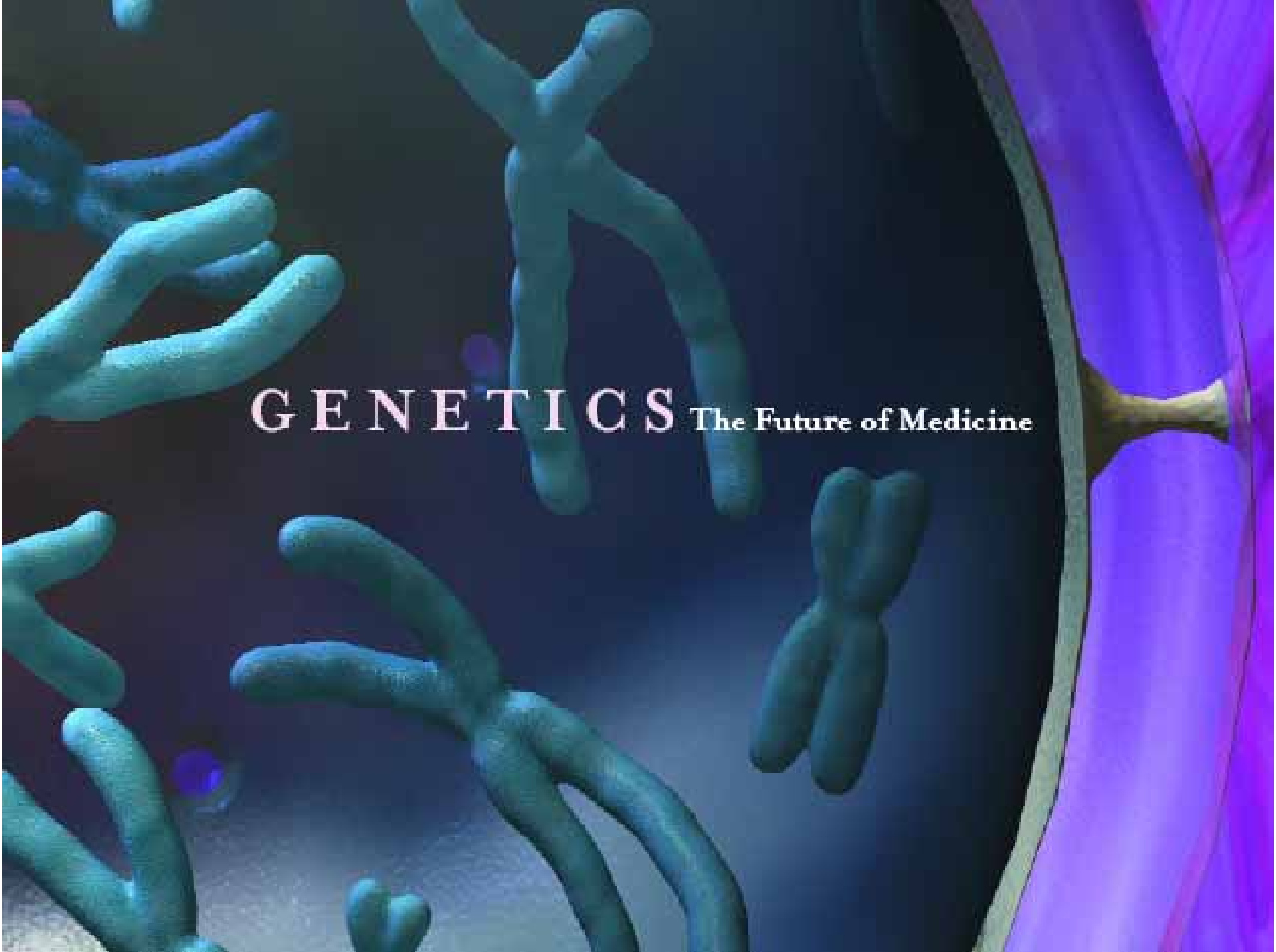
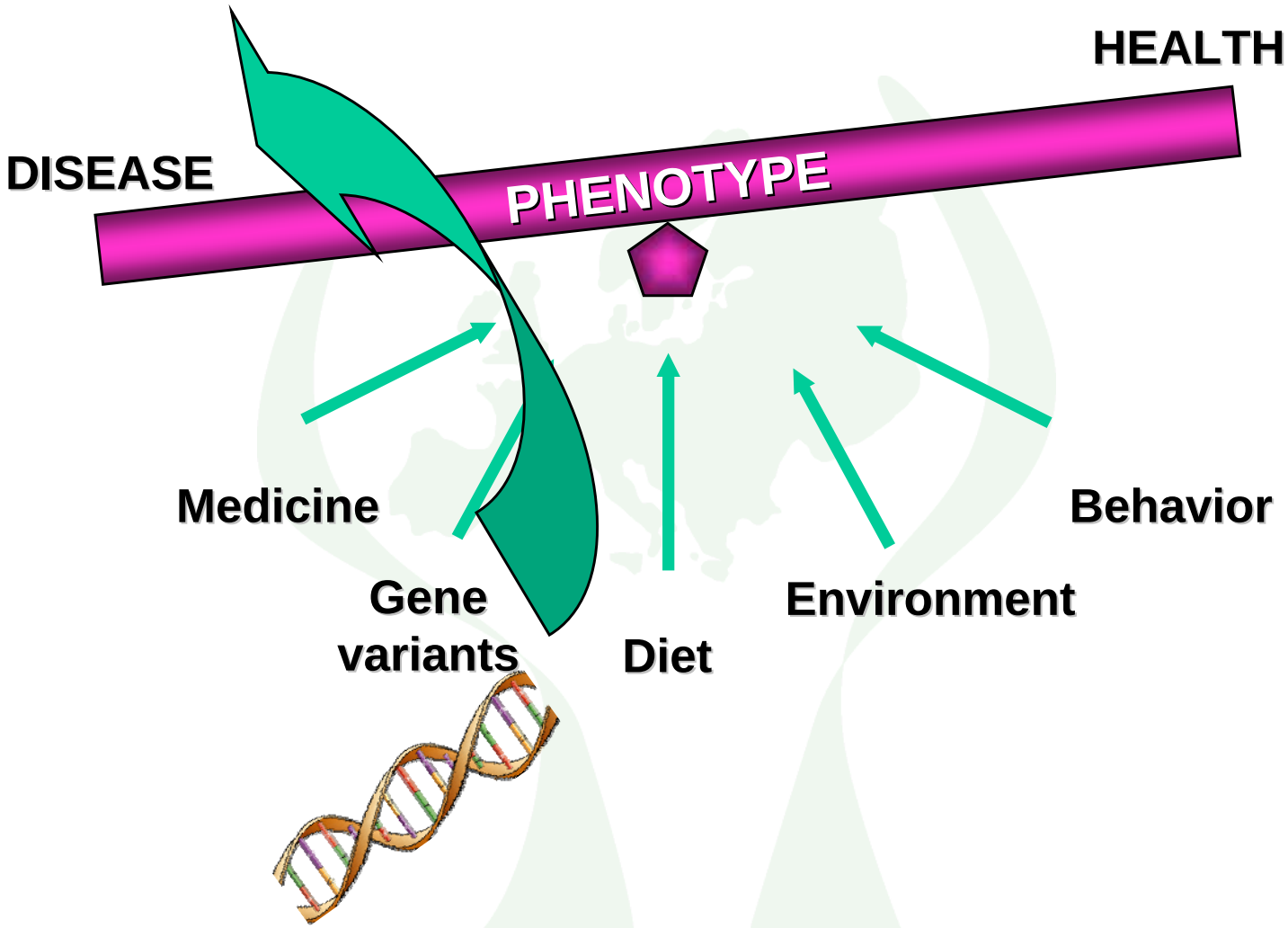


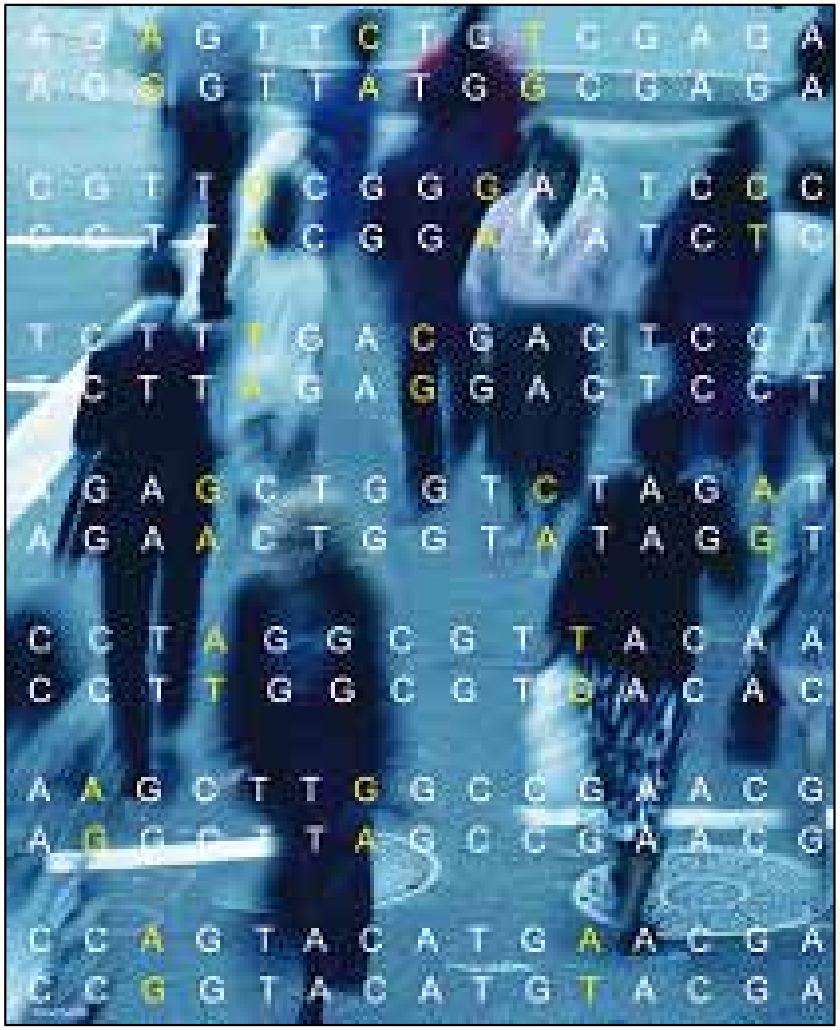
Distribution of BPI pain scores on the item “average pain last 24 hours” among patients admitted to hospital receiving morphine. 0: no pain, 10: pain as bad as you can imagine.

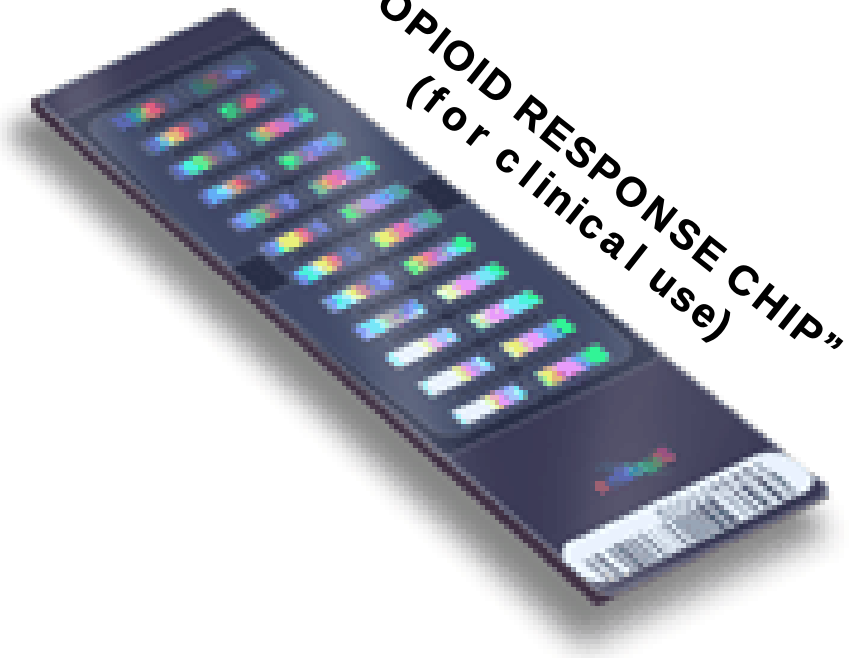
Klepstad P et al., 2003, *Palliat Med* **17**; 679-687.


GENETICS The Future of Medicine


HEALTH
DISEASE
PHENOTYPE
Medicine
Behavior
Gene
variants
Diet
Environment

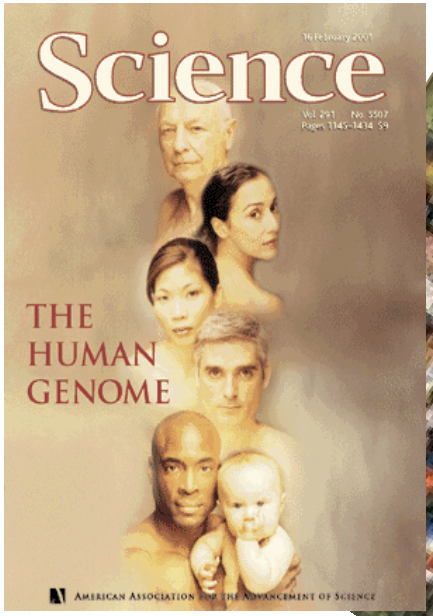
“Identify the profiles of genetic markers able to predict opioid treatment responses”

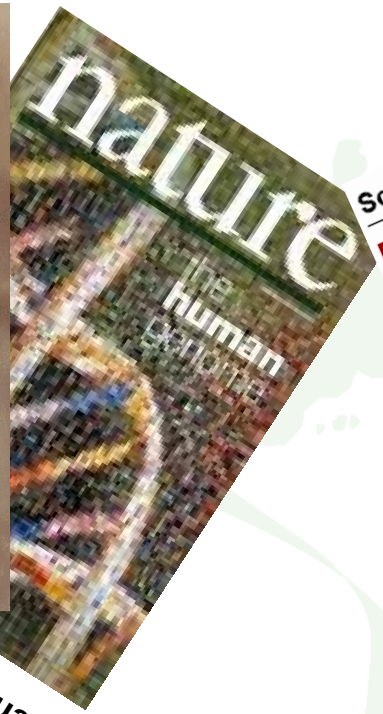




We're more different than we thought!

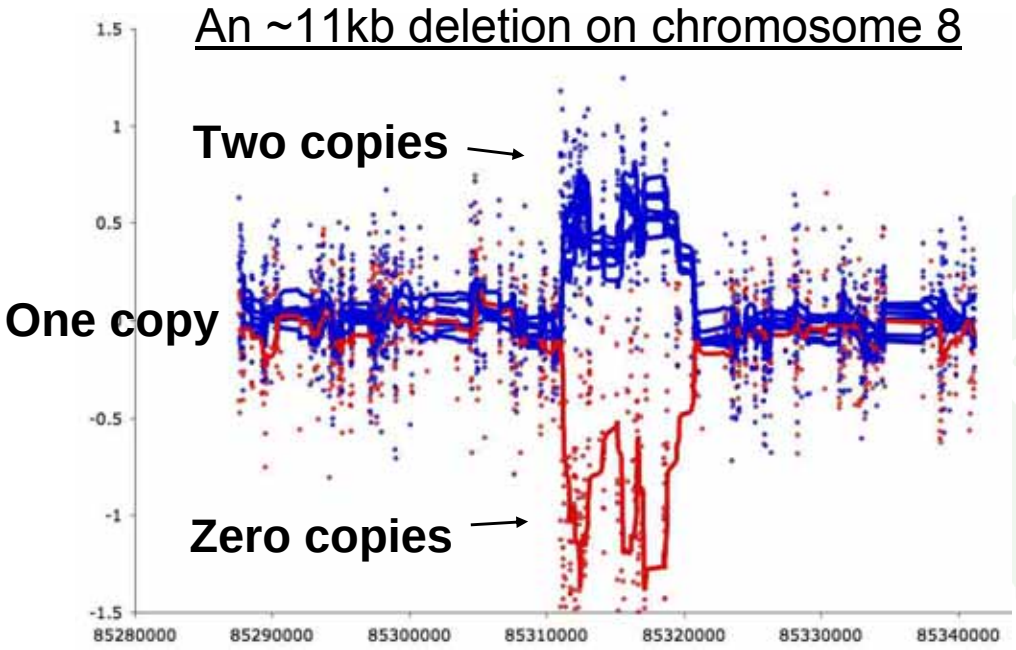
16 February 2001
Vol 291, Issue 5507, Pages 1145-1434



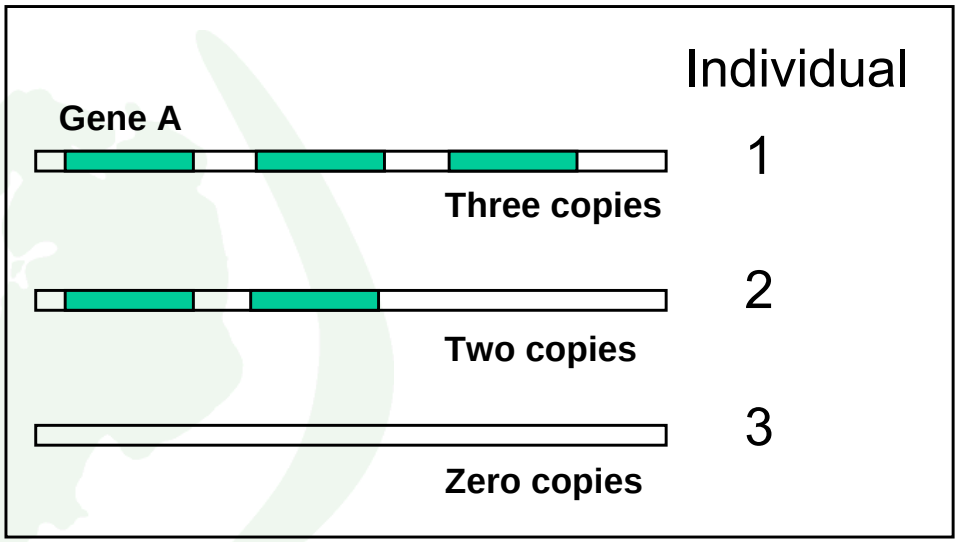


15 February 2001
Vol 409 Number 6822 pp745-964

Copy number variation (CNV)

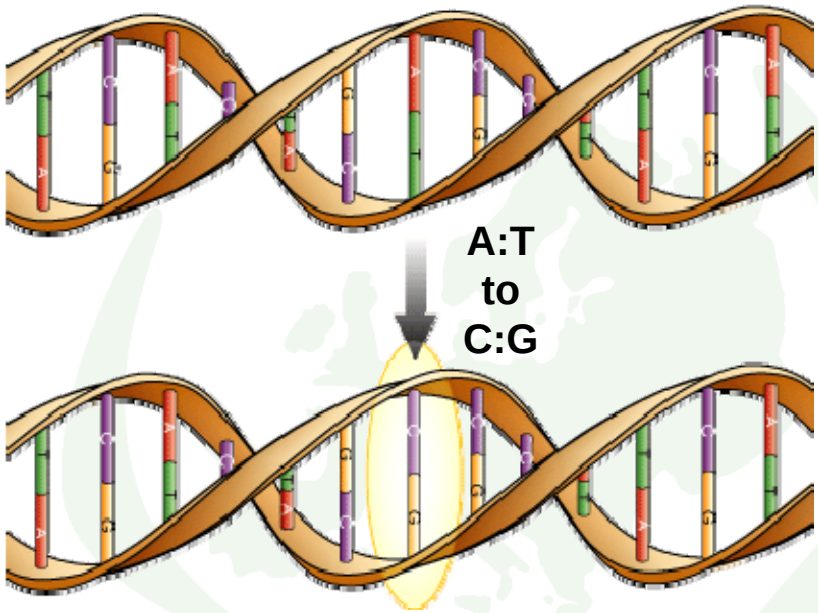


Picture from The Copy Number Variation Project, Wellcome Trust Sanger Institute



- CNV may encompass as much as 10% of our genes
- Impact on human health not known
- Surprise: CNV may even exist among pairs of monozygotic twins!

A SNP occurs when a basepair in the DNA sequence is replaced by a different basepair

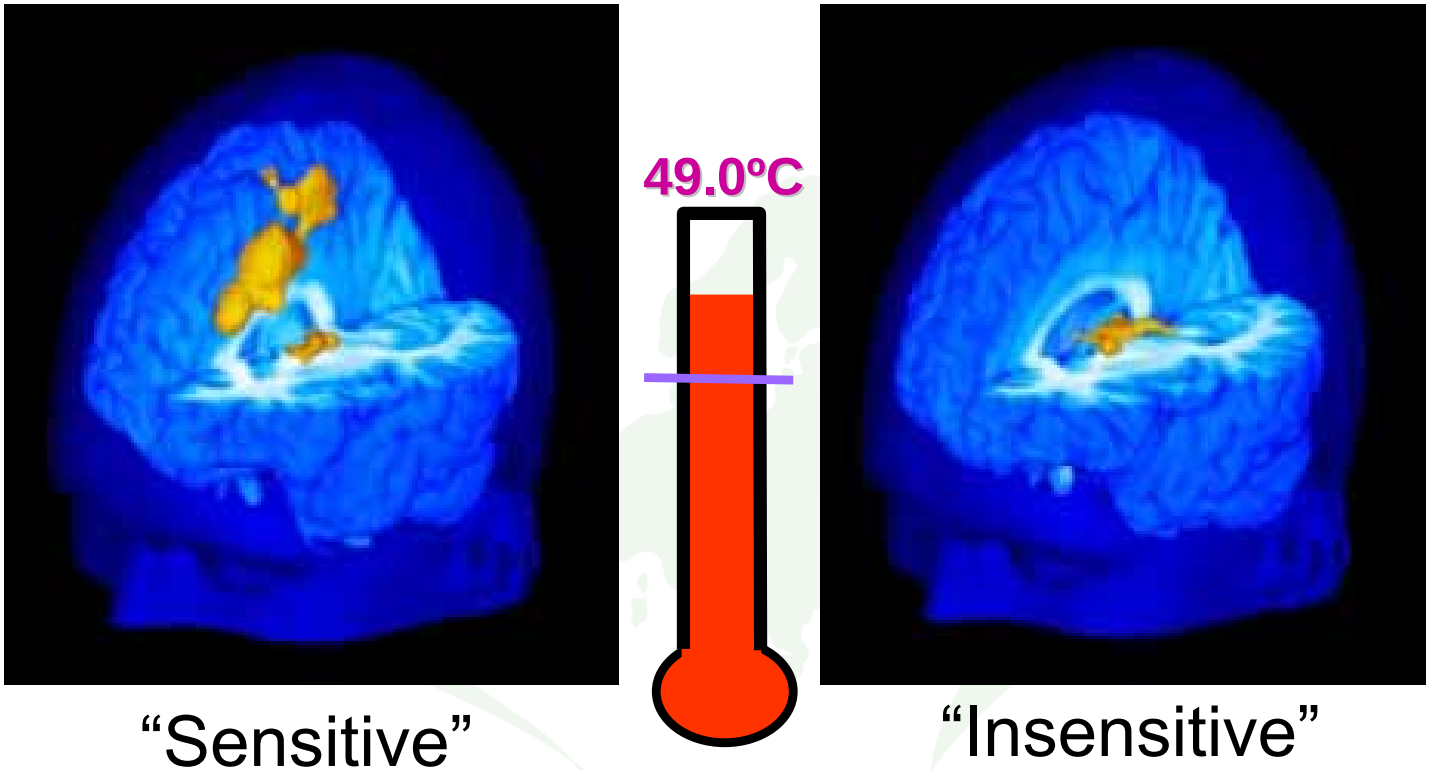


Allele 1

Allele 2

- The genomes of two unrelated individuals may differ by as many as ~3 mill nucleotides.
- A SNP may change the protein produced by the genetic code.
- These differences contribute to different physical appearance, different susceptibility to disease, or different response to drugs or other exposures.

Pain thresholds vary greatly among individuals

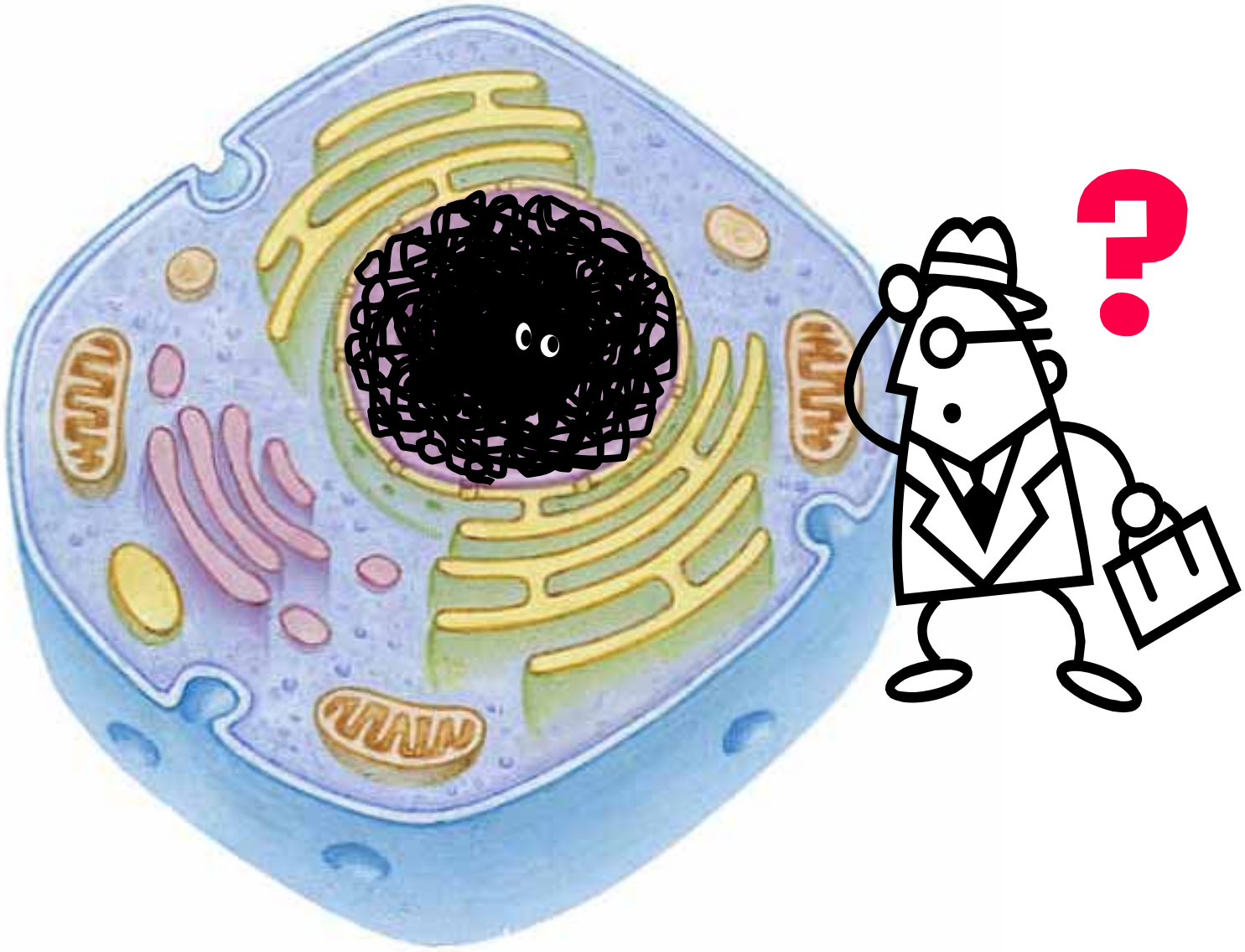


Multiple variables account for variability in pain response, including genetic- and environmental factors as well as measurement errors

The human genome contains approximately 25000 genes

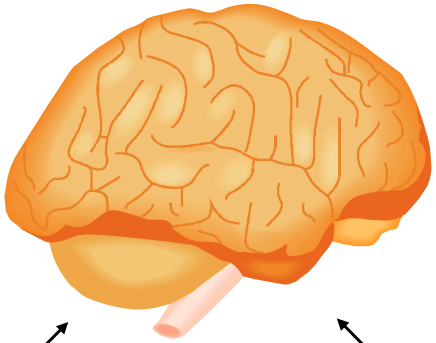
Picture from National Human Genome Research Institute.

How do we look up the relevant genes?



Pharmacodynamics

Pharmacokinetics



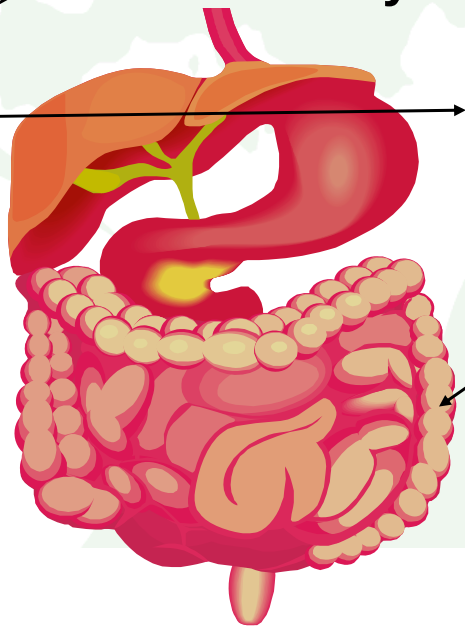
Receptor interactions

CNS distribution

Opioid administration

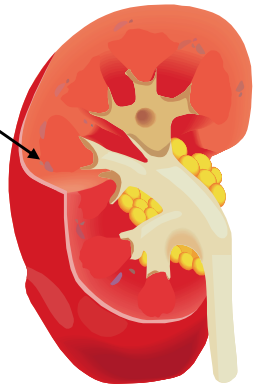
Bioavailability

Opioid compound

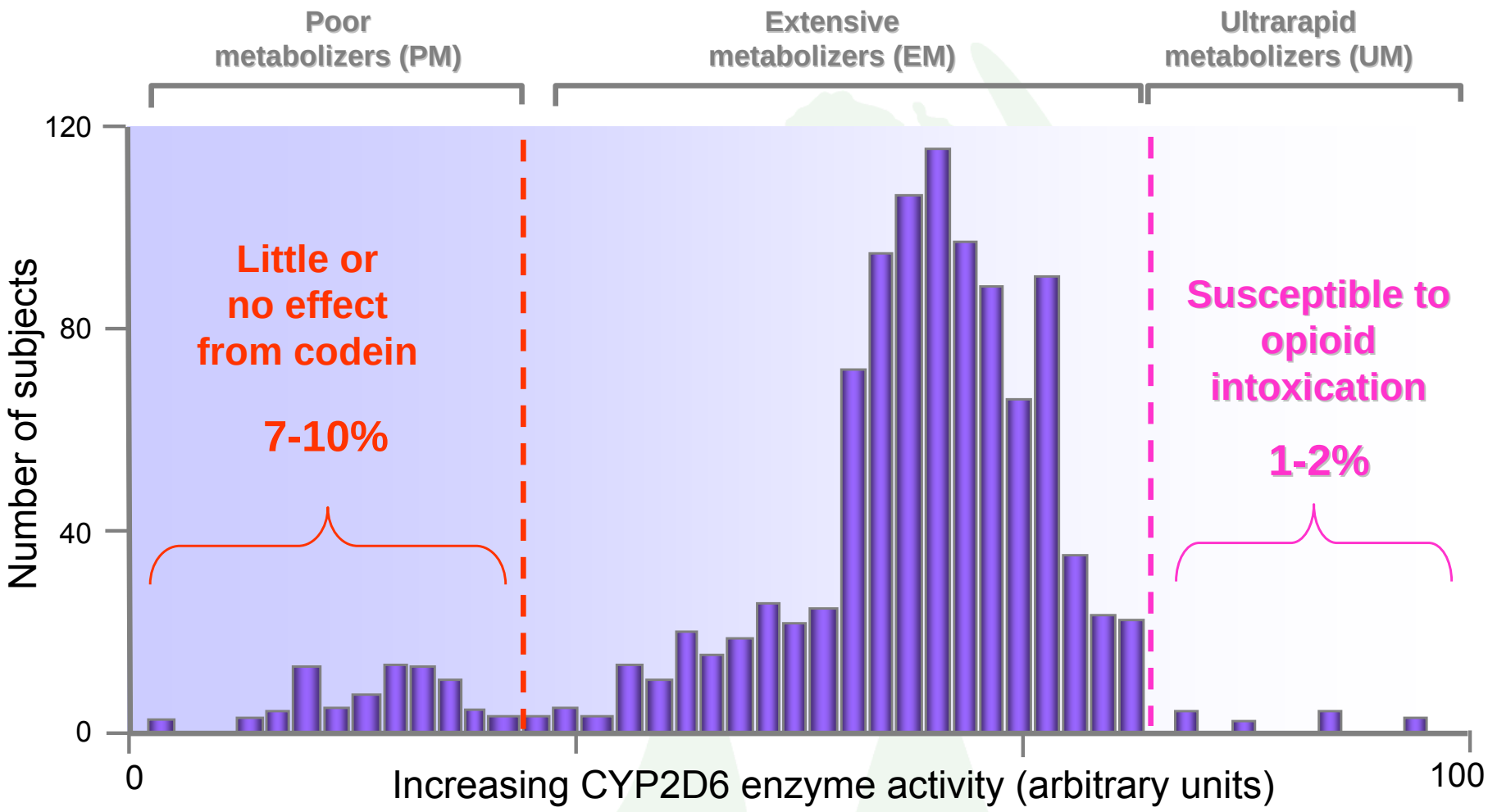


Metabolites

Elimination



CYP2D6 polymorphism and the use of codeine as an analgesic

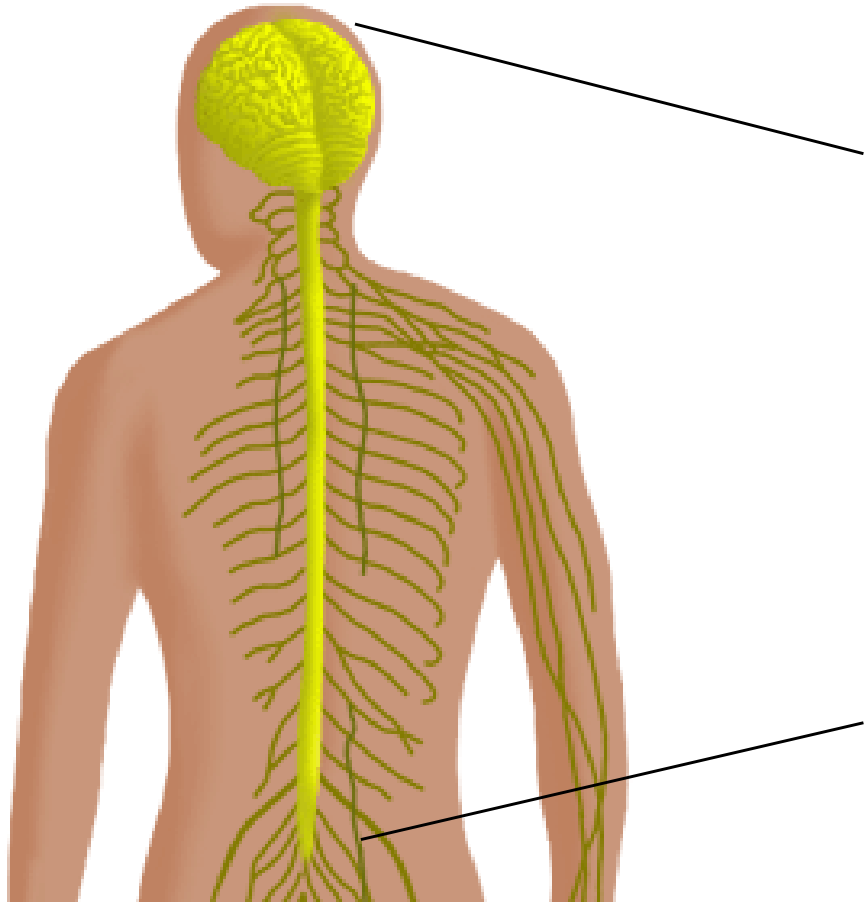


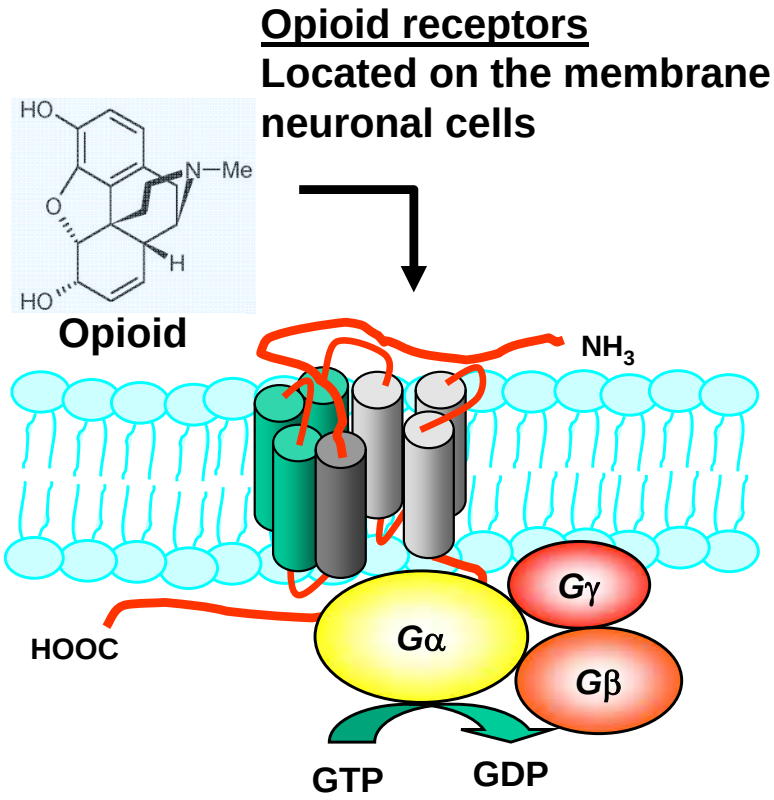
Example illustrates distribution in European Caucasians

- **Examples of polymorphisms in genes that have emerged as promising candidates for influencing opioid response.**

- **What are the major challenges for genetic research in palliative care?**

Opioids work through opioid receptors



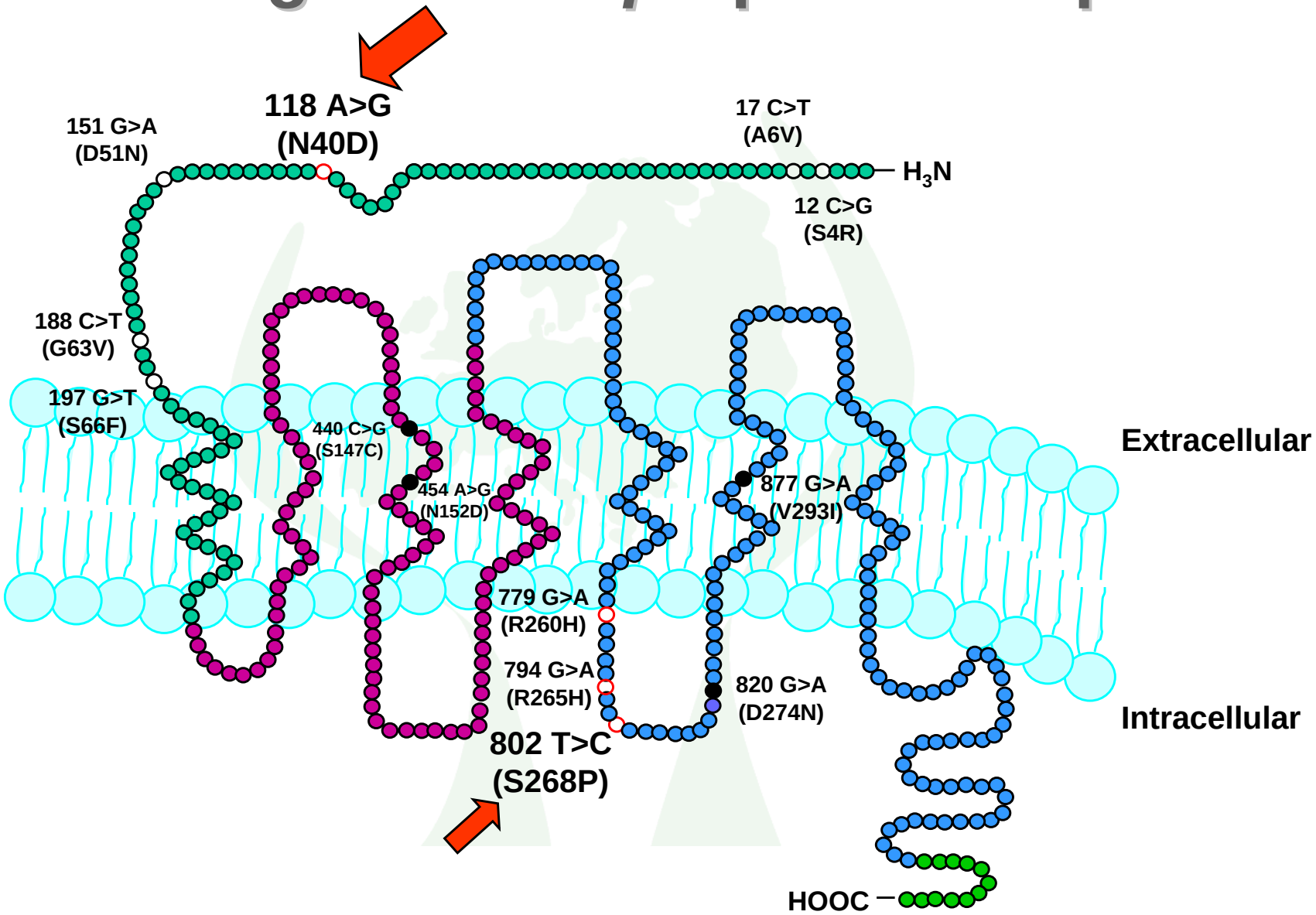


- Classified into three types: μ, δ and κ
- G-protein coupled receptors (GPCRs), with seven membrane-spanning domains

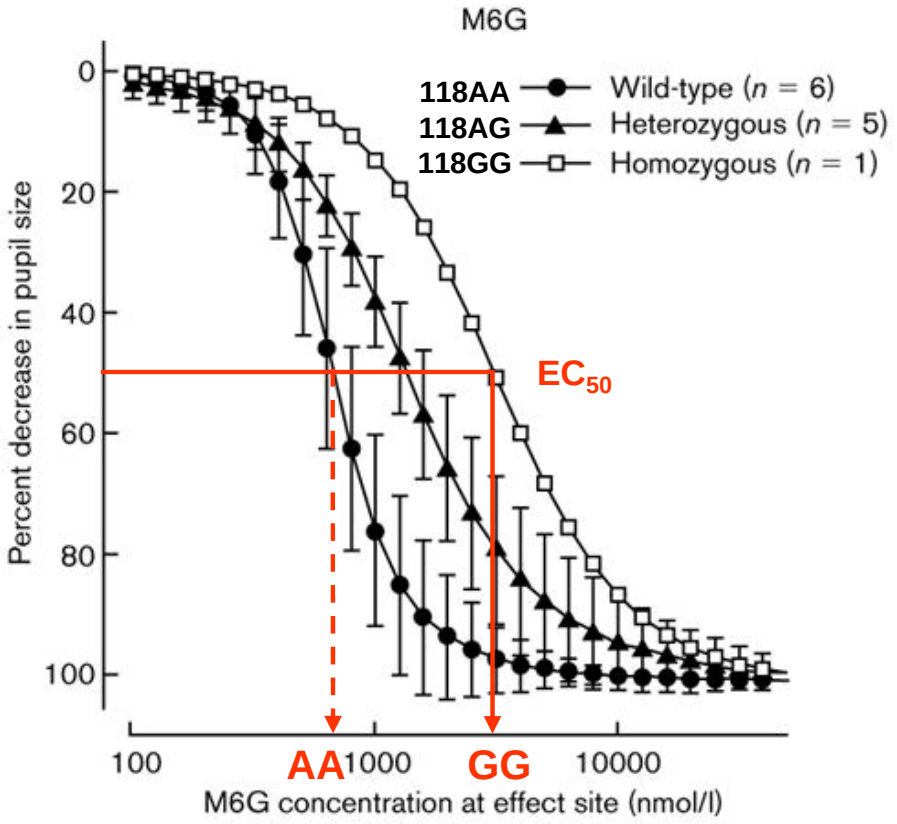
Some receptor-mediated effects of opioids

Effect	*Mu*	*Delta*	*Kappa*
Analgesia			
• Supraspinal	+++	-	-
• Spinal	++	++	+
• Peripheral	++	-	++
Respiratory depression	+++	++	+
Pupil constriction	++	-	-
Obstipation	++	++	+
Sedation	++	-	++
Euphoria	++	-	-
Dysphoria	-	-	+++
Dependence	+++	-	+/-?

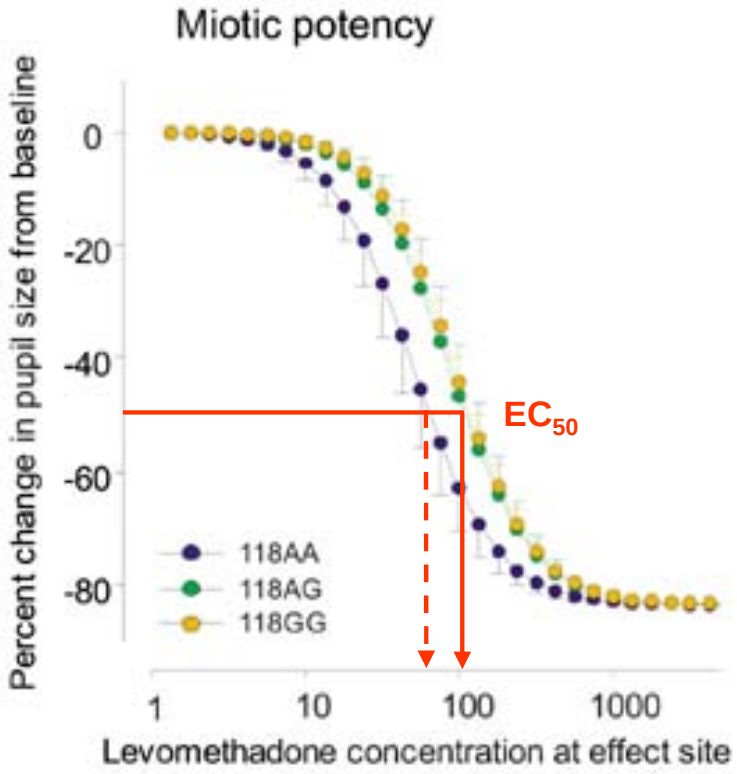
Polymorphisms associated with amino acid changes in the *μ* opioid receptor



The N40D (118A>G) polymorphism modulates central nervous effects of M6G, morphine and levomethadone in healthy volunteers

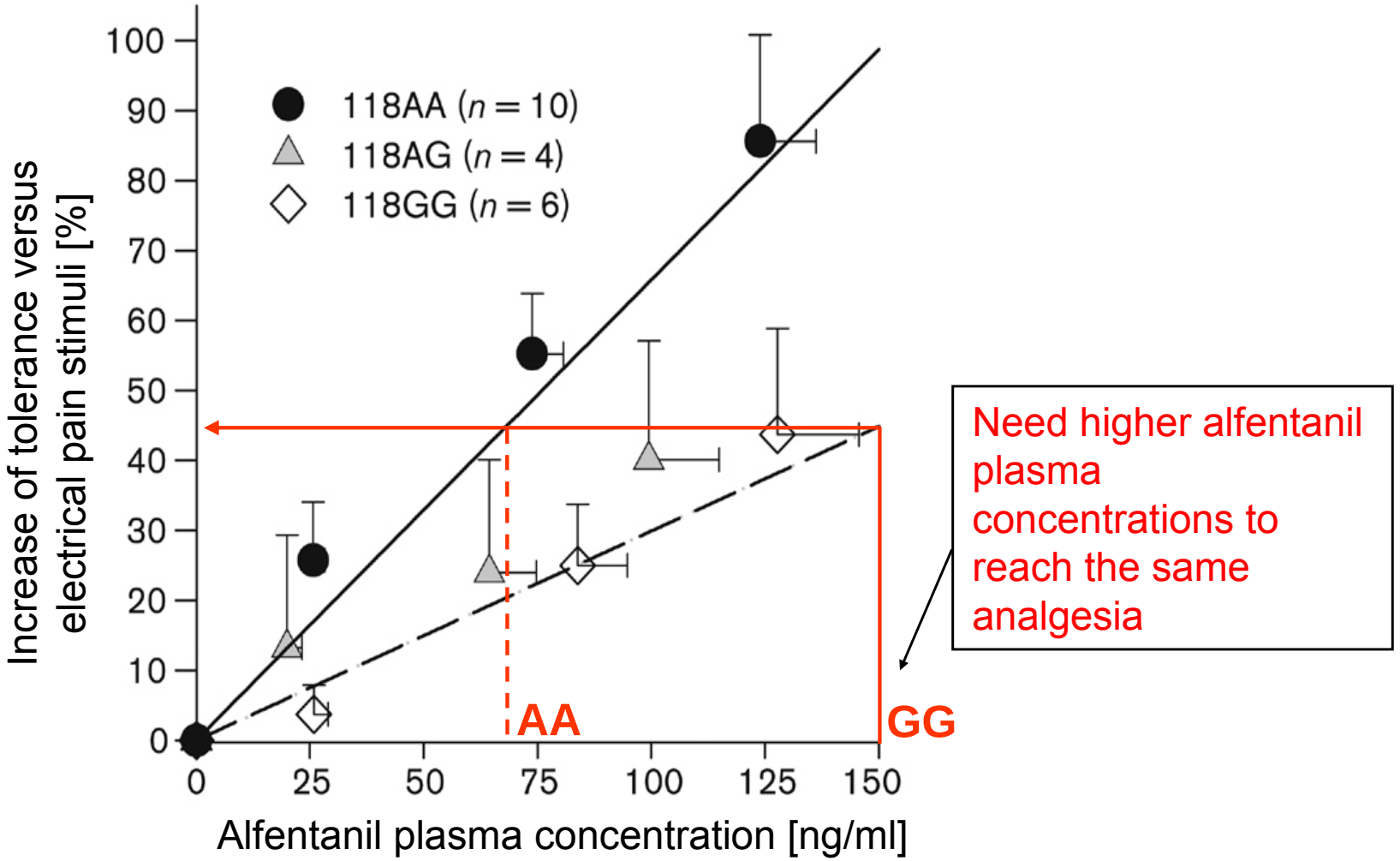


Lötsch et al., *Pharmacogenetics* 2002; **12**: 3-9



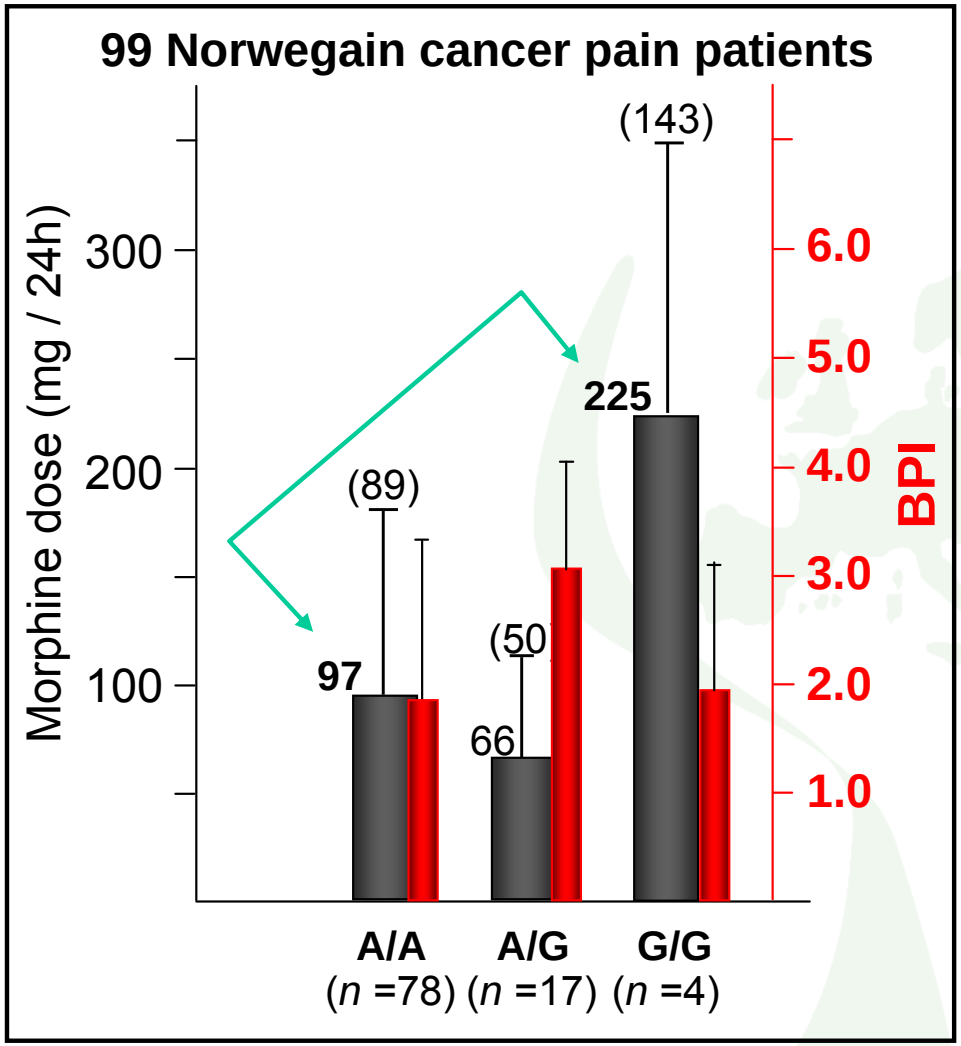
Lötsch et al., *Clin Pharmacol Ther* 2006; **79**: 72-98.

The N40D (118A>G) polymorphism and alfentanil analgesia in experimental pain

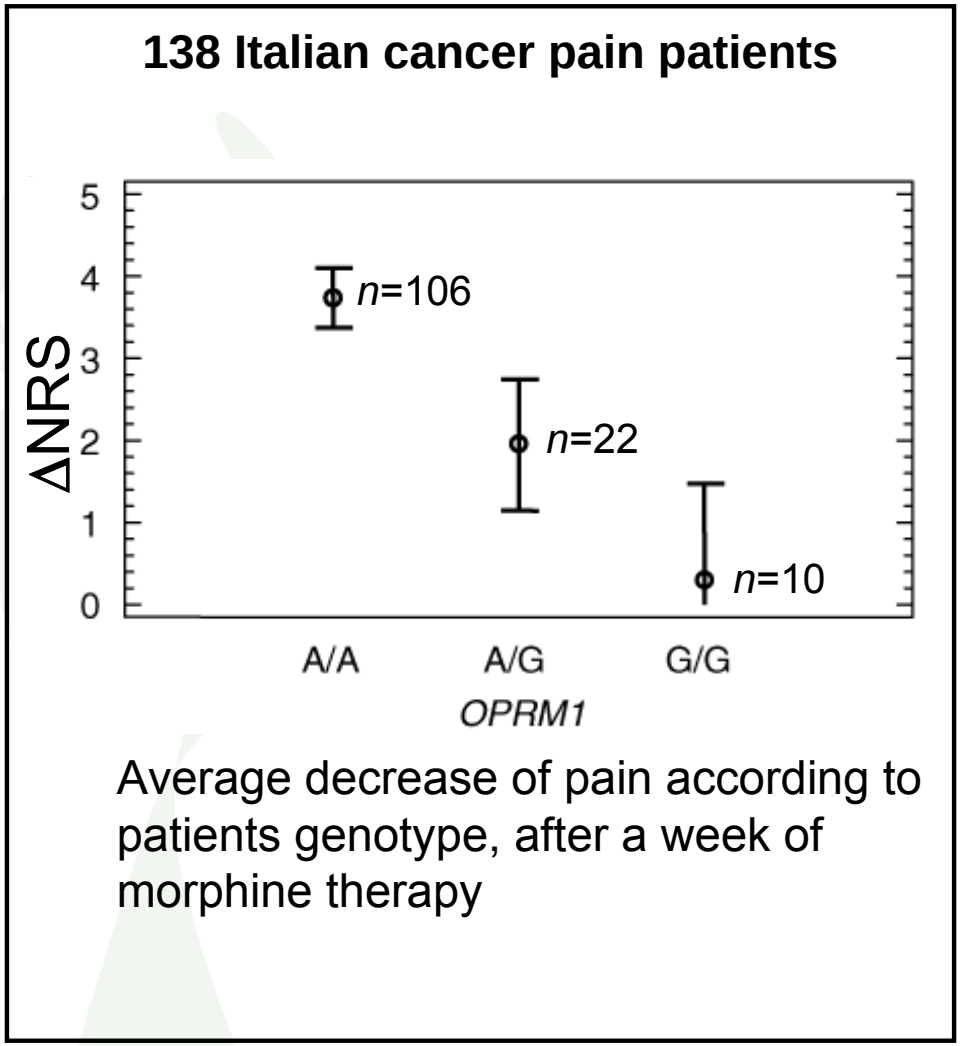


From: Oertel et al. *Pharmacogenet Genomics* 2006; **16**: 625-636

The N40D (118A>G) polymorphism and morphine consumption in cancer pain



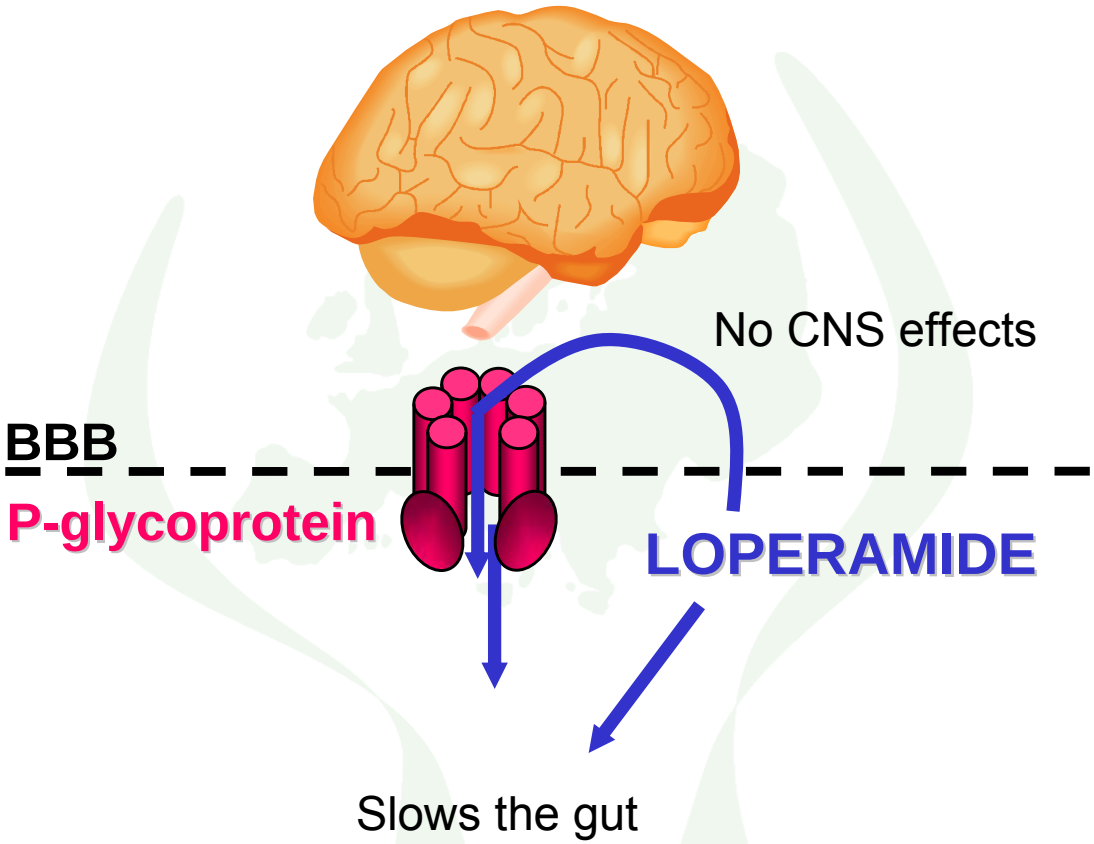
Klepstad P *et al.*, *Acta Anaesthesiol Scand* 2004; **48**: 1232-1239



Average decrease of pain according to patients genotype, after a week of morphine therapy

Campa D et al., 2007, *Clin Pharmacol Ther,* [Epub]

Efflux transporters at the Blood-Brain-Barrier (BBB)



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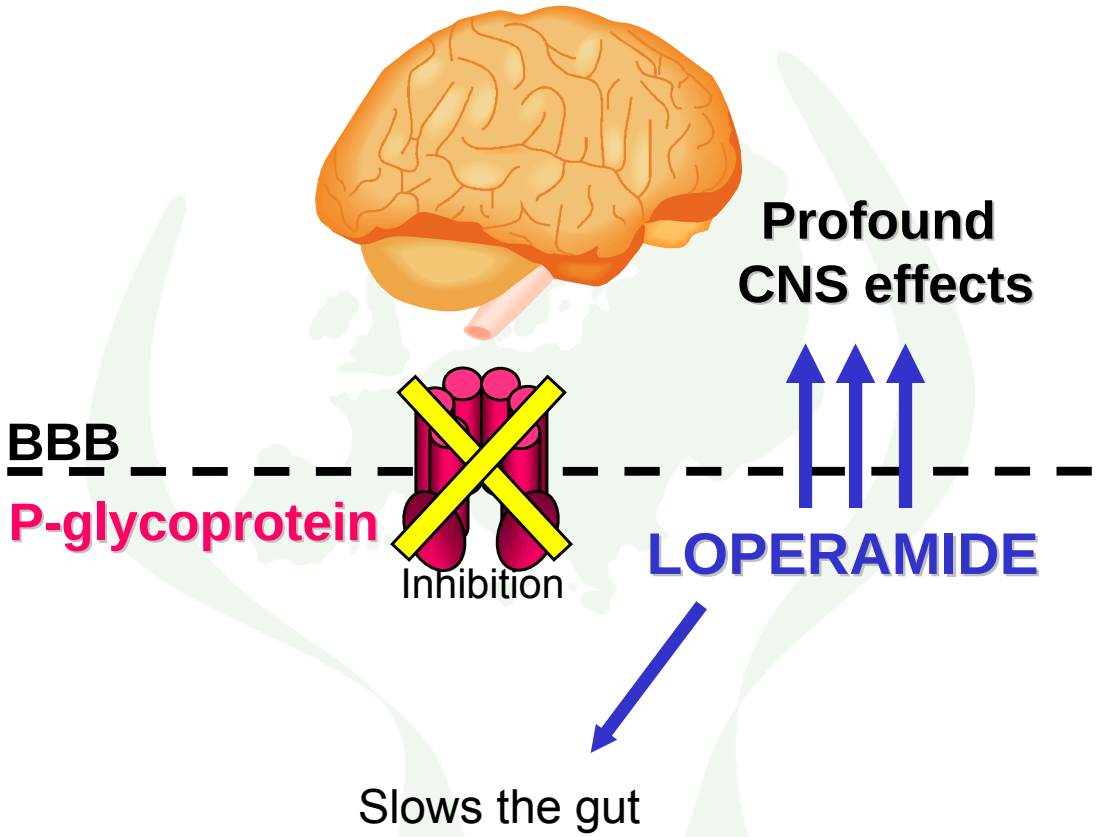
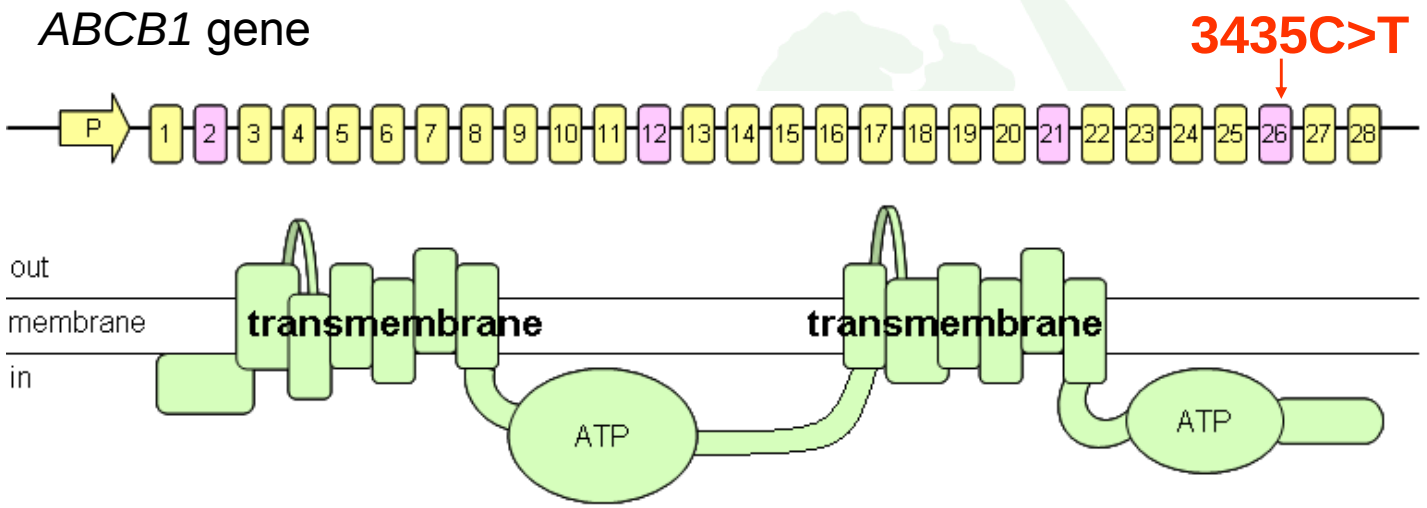


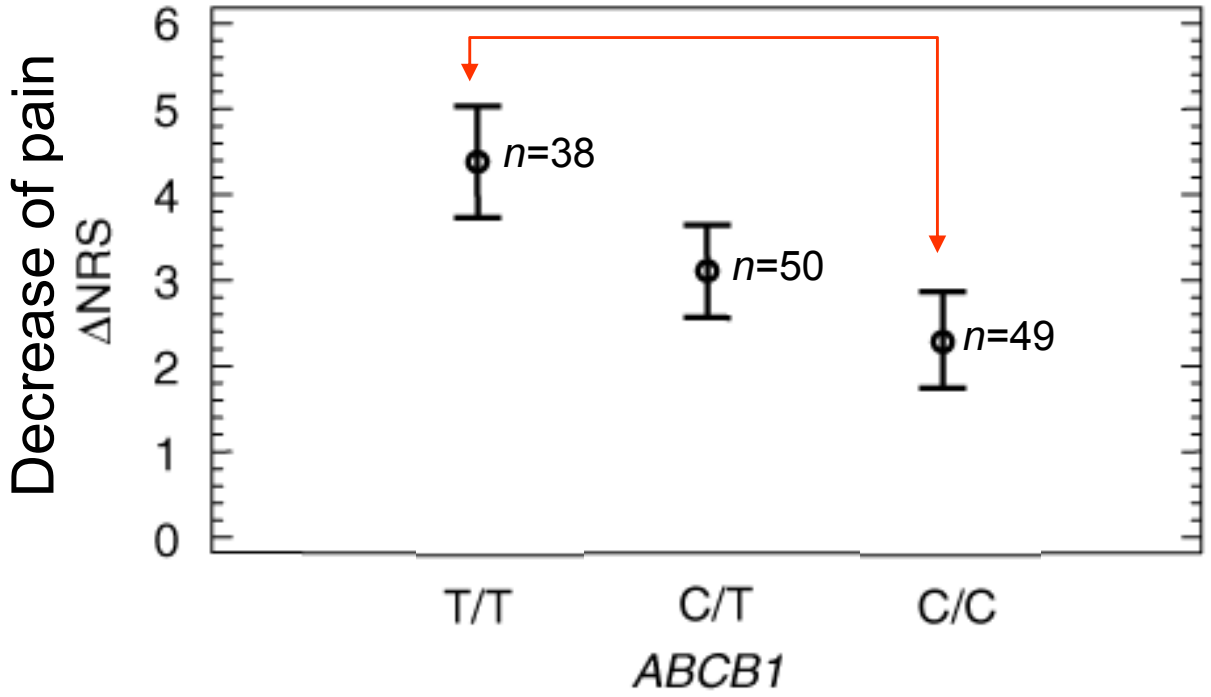
- Morphine, M6G, methadone, fentanyl, sufentanil and alfentanil are potential substrates for P-glycoprotein

Schematic structure of the *ABCB1* (*MDR1*) gene



- T-allele associated with reduced P-glycoprotein expression
- 25% of European Caucasians homozygous for the T-allele

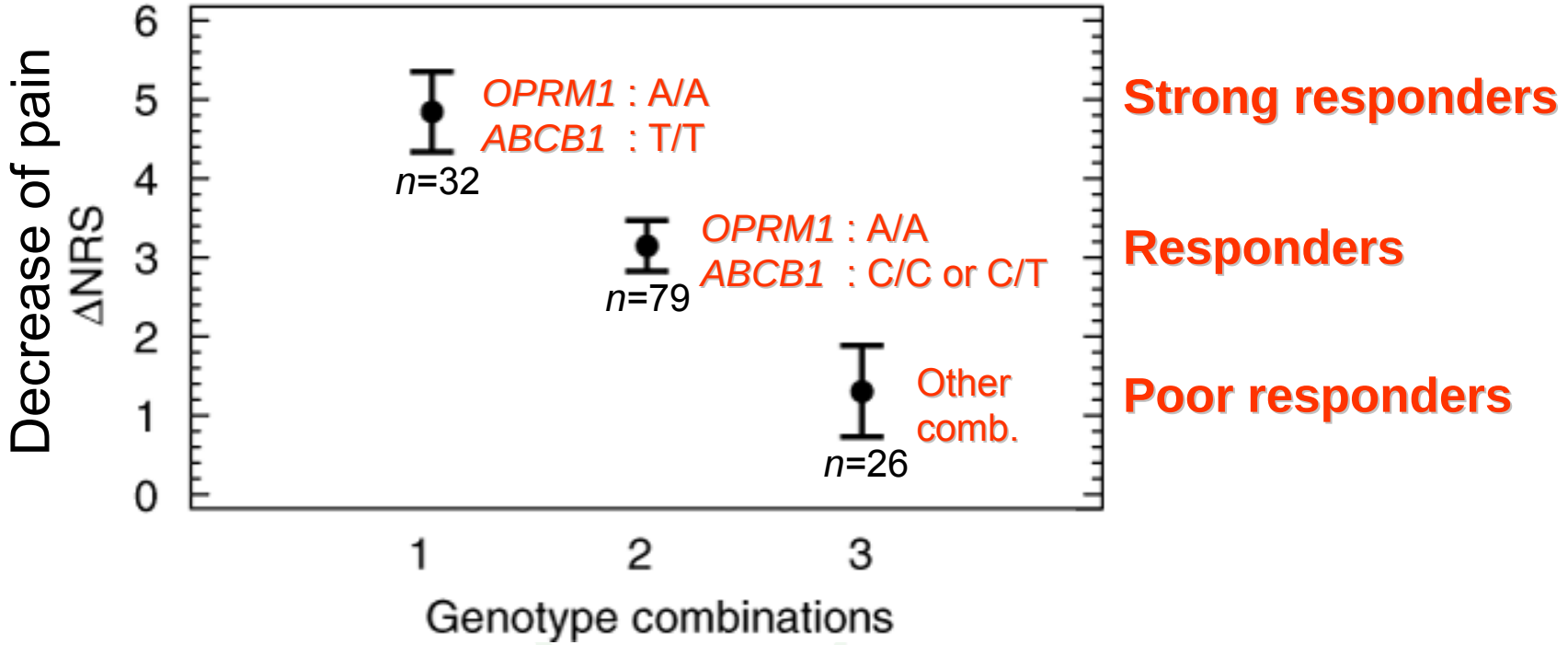
Effect of *ABCB1* 3435C>T polymorphism in 137 Italian cancer pain patients



Average decrease of pain according to patients genotype, after a week of morphine therapy

Fig. from Campa D et al., 2007, *Clin Pharmacol Ther* [Epub]

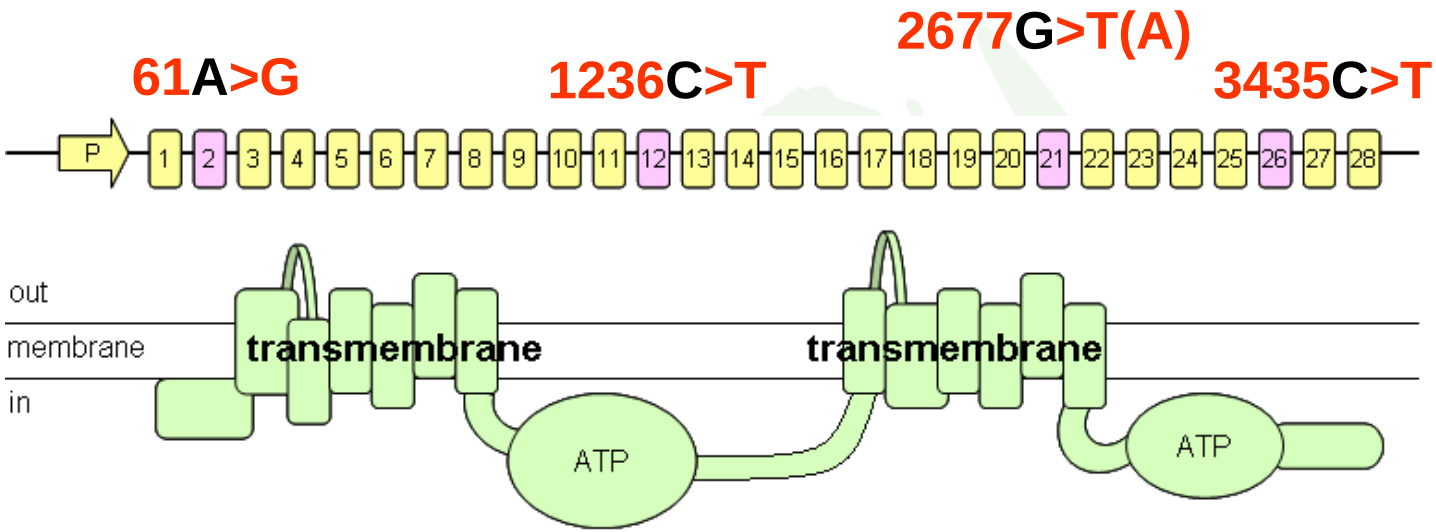
Joint effects of *ABCB1* 3435C>T and *OPRM1* 118A>G polymorphism



Pain intensity decrease experienced by patients according to their genotypes of *ABCB1* 3435C>T and *OPRM1* 118A>G

Fig. from Campa D et al., 2007, *Clin Pharmacol Ther* [Epub]

Other common *ABCB1* polymorphisms and resulting haplotypes

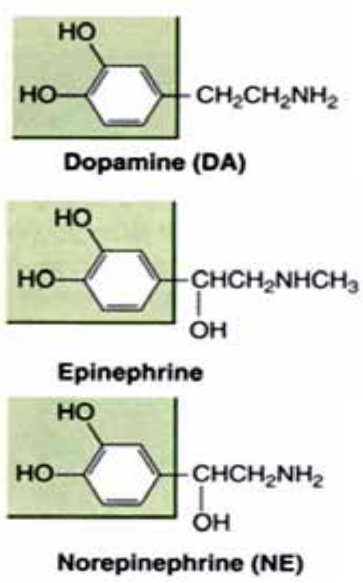


Haplotype 1	A	C	G	C
Haplotype 2	A	T	T	T
Haplotype 3	A	C	G	T
Haplotype n	X	X	X	X

Ross J R et al., *Cancer 2008;* **112**: 1390-1403

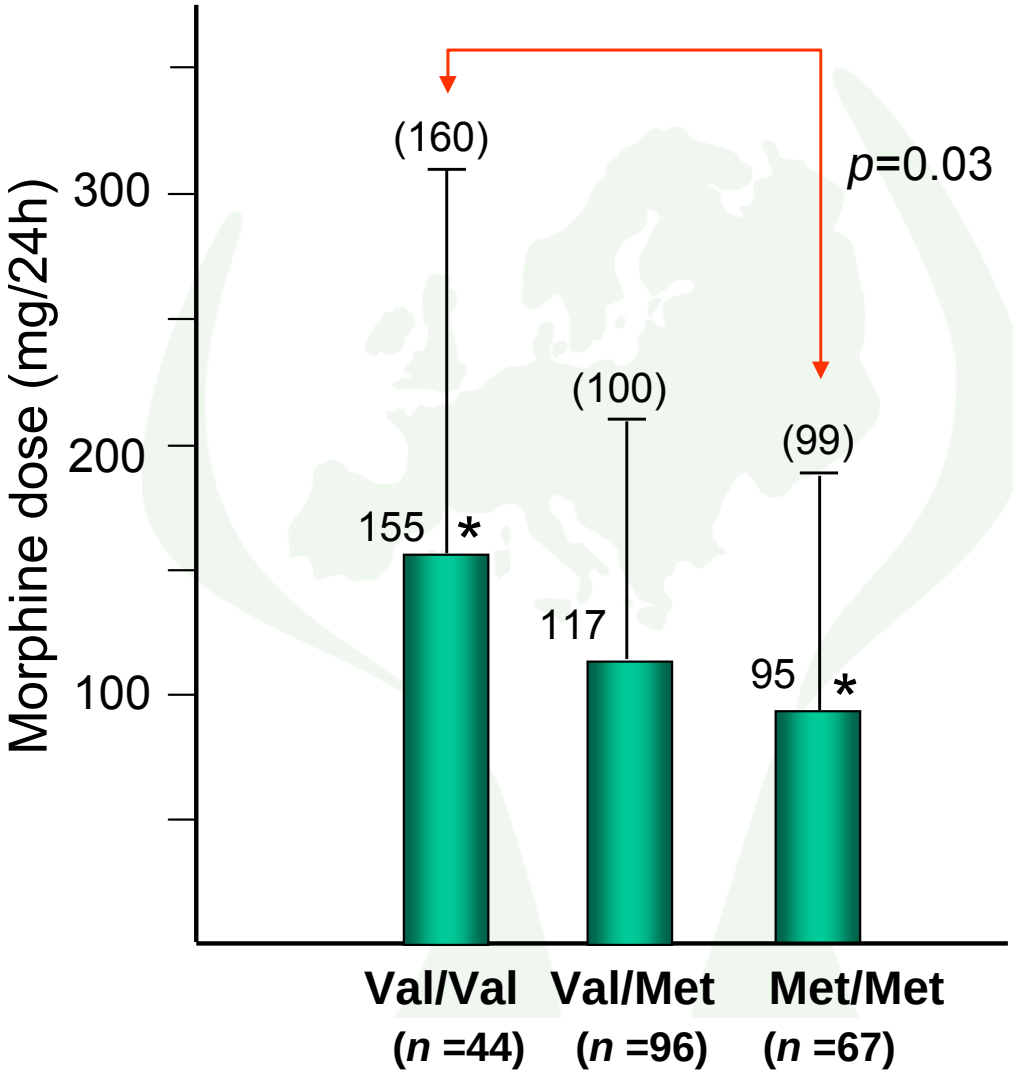
Catechol-*O*-methyltransferase (COMT)

- COMT metabolizes catecholamines such as dopamine, adrenaline and noradrenaline.
- Val158Met polymorphism.
  Met-allele associated with threefold decrease in enzyme activity.
- Met/Met homozygous individuals have:
  - Higher sensory and affective pain ratings
  - Lower levels of endogenous opioids,
  - and a compensatory increased μ-opioid receptor concentration in various brain regions



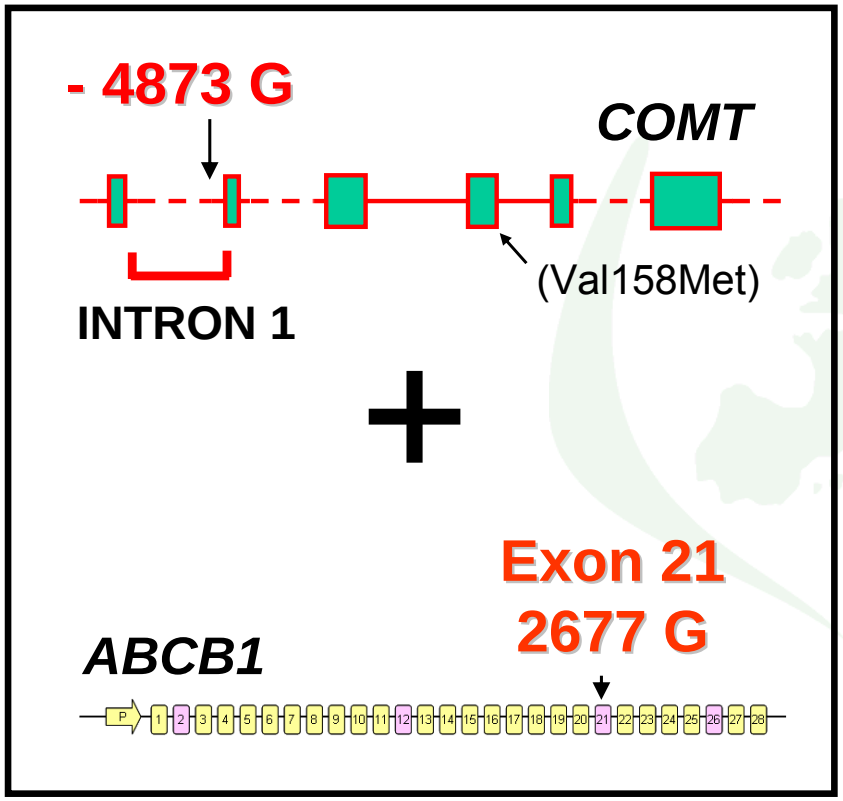
Zubieta J-K et al., *Science* 2003; **299**: 1240-1243

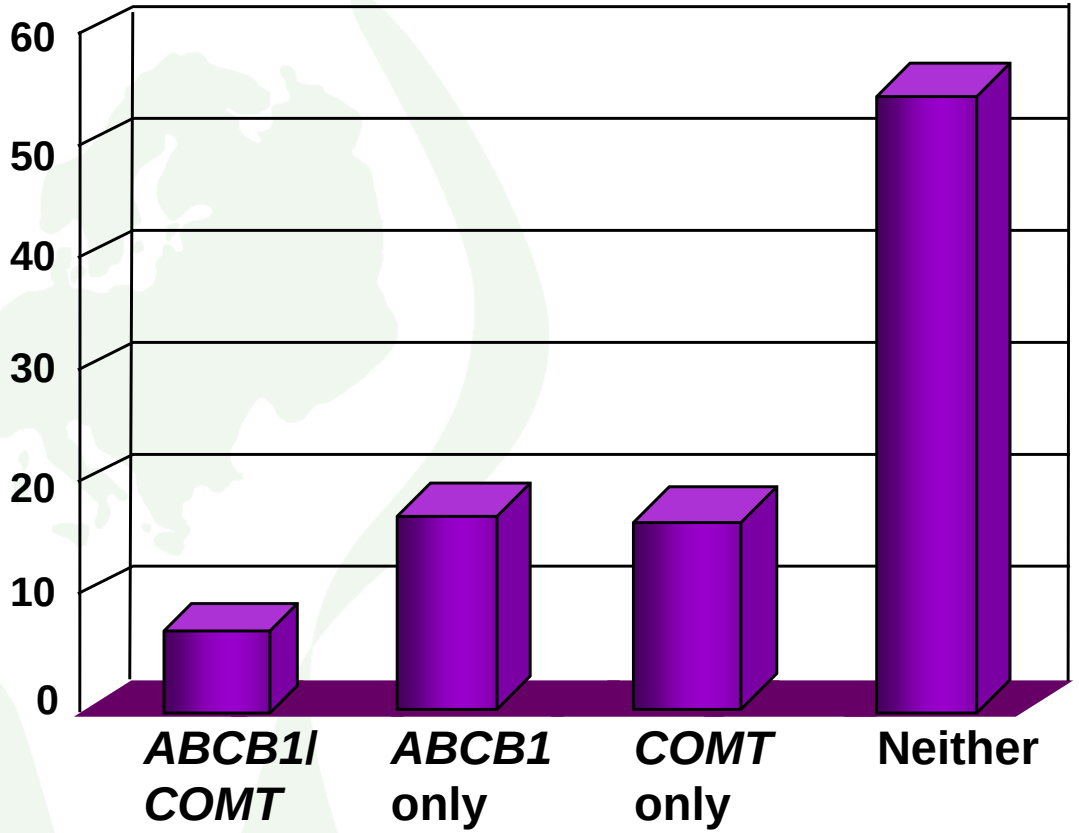
The COMT Val158Met polymorphism may influence morphine requirements in cancer pain patients



Rakvåg TT et al., *Pain* 2005; **116**: 73-78.

Cancer patients with certain combinations of *COMT*- and *ABCB1* alleles are less likely to experience opioid-induced central side effects





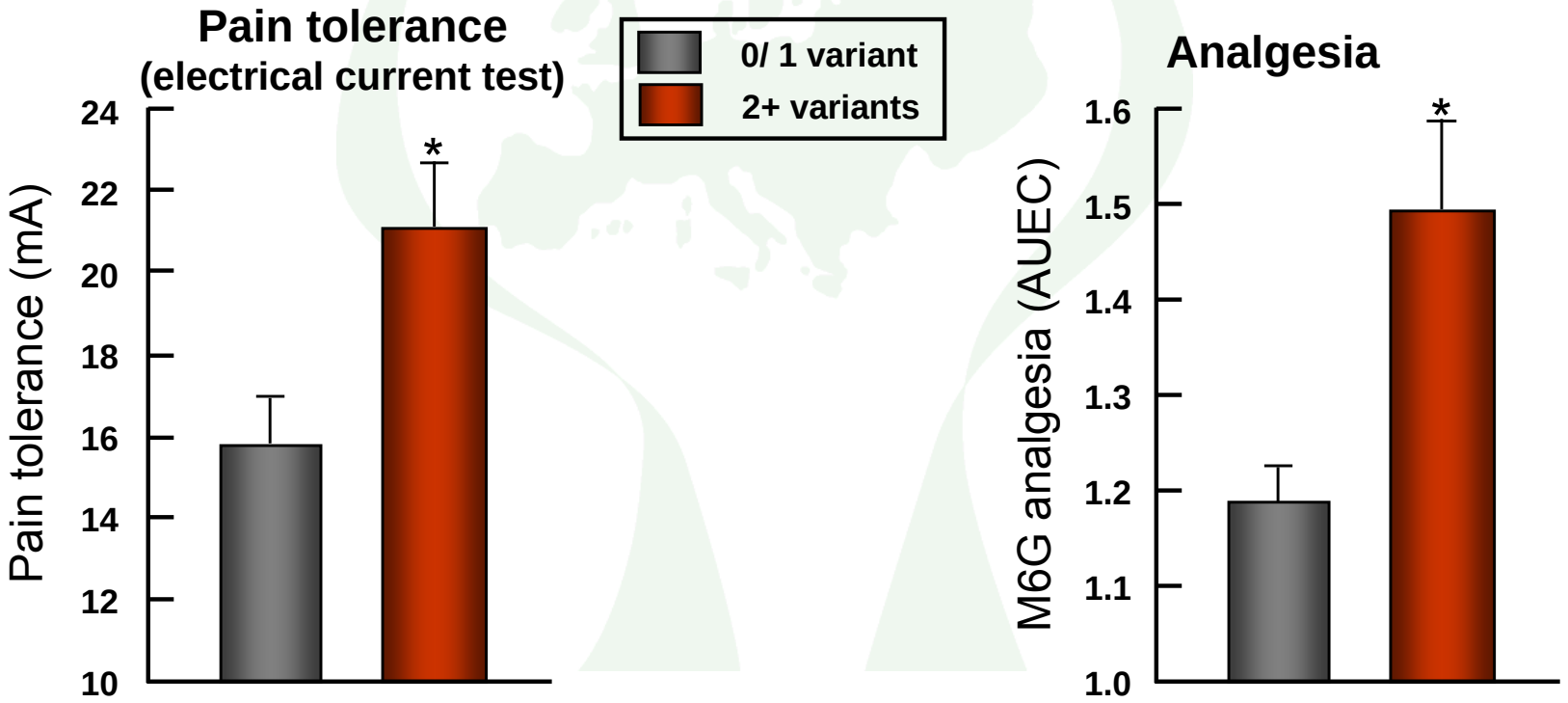
The percentage of patients with moderate or severe central side effects according to combinations of protective alleles

Ross J R et al., *Cancer 2008;* **112**: 1390-1403

The red hair and fair skin phenotype: melanocortin-1 receptor (MC1R)

- **Women only**
- **More sensitive to pain?**
- **Need more anesthetics?**

Women and men with non-functional melanocortin-1 receptors display reduced pain sensitivity and increased analgesic response to the *μ* opioid M6G



Figures modified from Mogil et al. *J Med Genet* 2005; **42**:583-587

Summary and future perspectives

Studies carried out in the last few years have uncovered several genetic variants that may influence opioid response

but

Single gene effects on opioid responses are small,

and do not account for enough variation in response to be clinically useful

Most studies performed so far have

- looked at the isolated effects of one or a few polymorphisms in the clear candidate genes
- addressed only a few opioids (mainly morphine)
- been carried out with small cohorts
- mainly been carried out in healthy volunteers or post-operative patients

- Healthy volunteers
- Experimental pain
- Opioid naïve
- No/little co-medication

≠

- Cancer disease
- Co-morbidity
- Long-term opioid treatment
- Extensive co-medication

To move forward

- Perform studies in the relevant group of patients: i.e. cancer pain patients in palliative care
- Scale the studies to sufficient statistical power. Increase the sample size through international cooperation
- Explore the joint effects of multiple genes and genetic variants
- Study different opioids
- Develop and implement (and use) **international standards** for the assessment of subjective symptoms

European Pharmacogenetic Opioid Study (EPOS)

European Palliative Care Research Collaborative (EPCRC)

"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind"

Lord Kelvin (1824-1907; William Thomson)
From *Lecture to the Institution of Civil Engineers, 3 May 1883*