McGill
Le Centre Alan-Edwards de recherche sur la DOULEUR

McGill
The Alan Edwards Centre for Research on PAIN

Canada Excellence Research Chairs
Chaire d'excellence en recherche du Canada

Novel Methods to Identify Pain Targets : Genomic/Genetic Approaches

Luda Diatchenko, MD, PhD

Canada Excellence Research Chair in Human Pain Genetics

Alan Edwards Centre for Research on Pain,

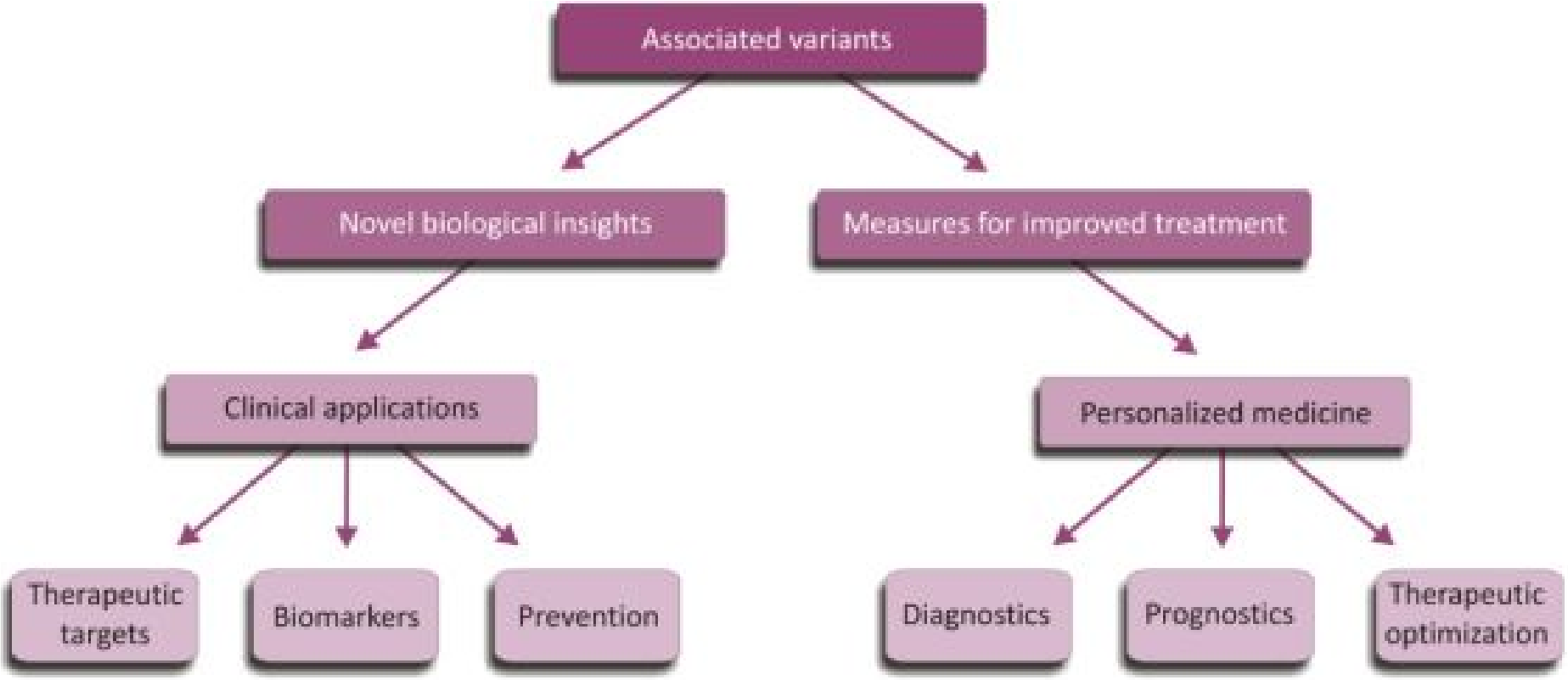
McGill University, Montreal, Canada

The National Academies of SCIENCE ENGINEERING MEDICINE

Advancing Therapeutic Development for Pain and Opioid Use Disorders through Public-Private Partnerships: A Workshop

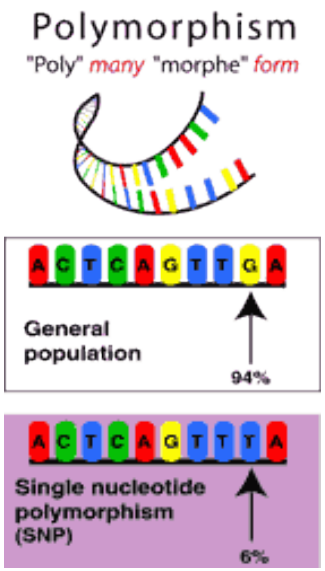
Washington, DC, October 11–12, 2017

Translation of Genetic Information into Clinical Practice

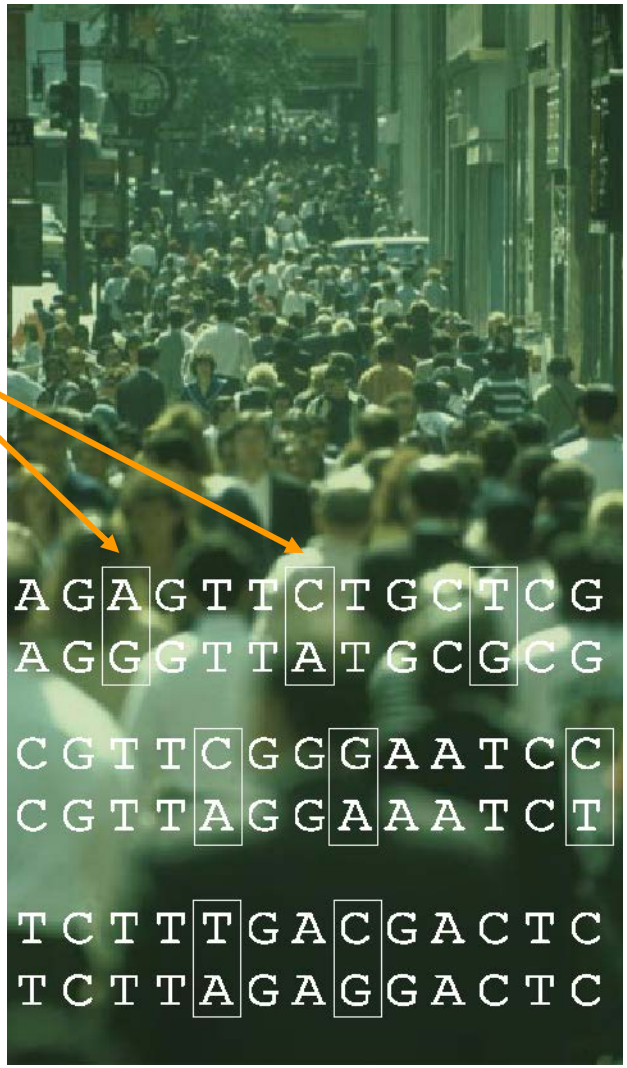


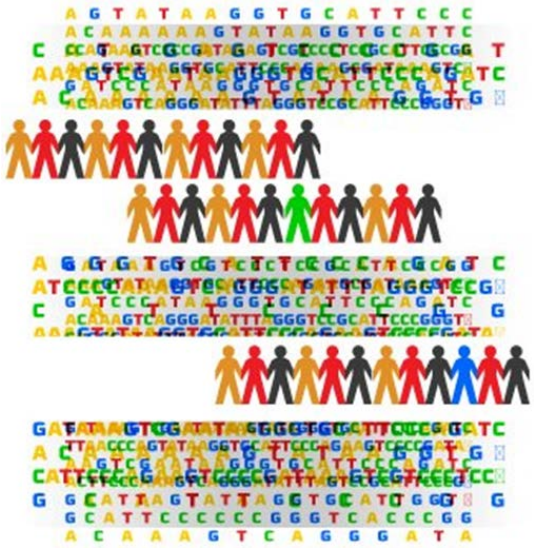
Zemunik and Boraska book edited by David Wagner, ISBN

How are genomes of individuals different?



SNP

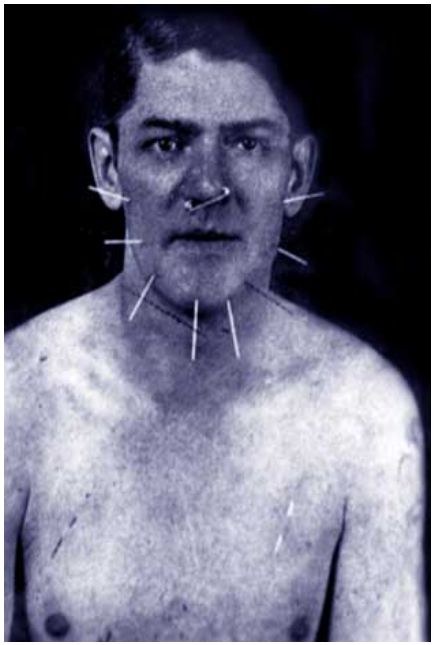




Nature **409**, 822 - 823 (2001)

DNA contains 99.9% of identical sequence in all the individuals with only 0.1% difference. Out of this 0.1% variation, over 80% are single nucleotide polymorphisms (SNPs).

Genes Responsible for Monogenic Pain Disorders



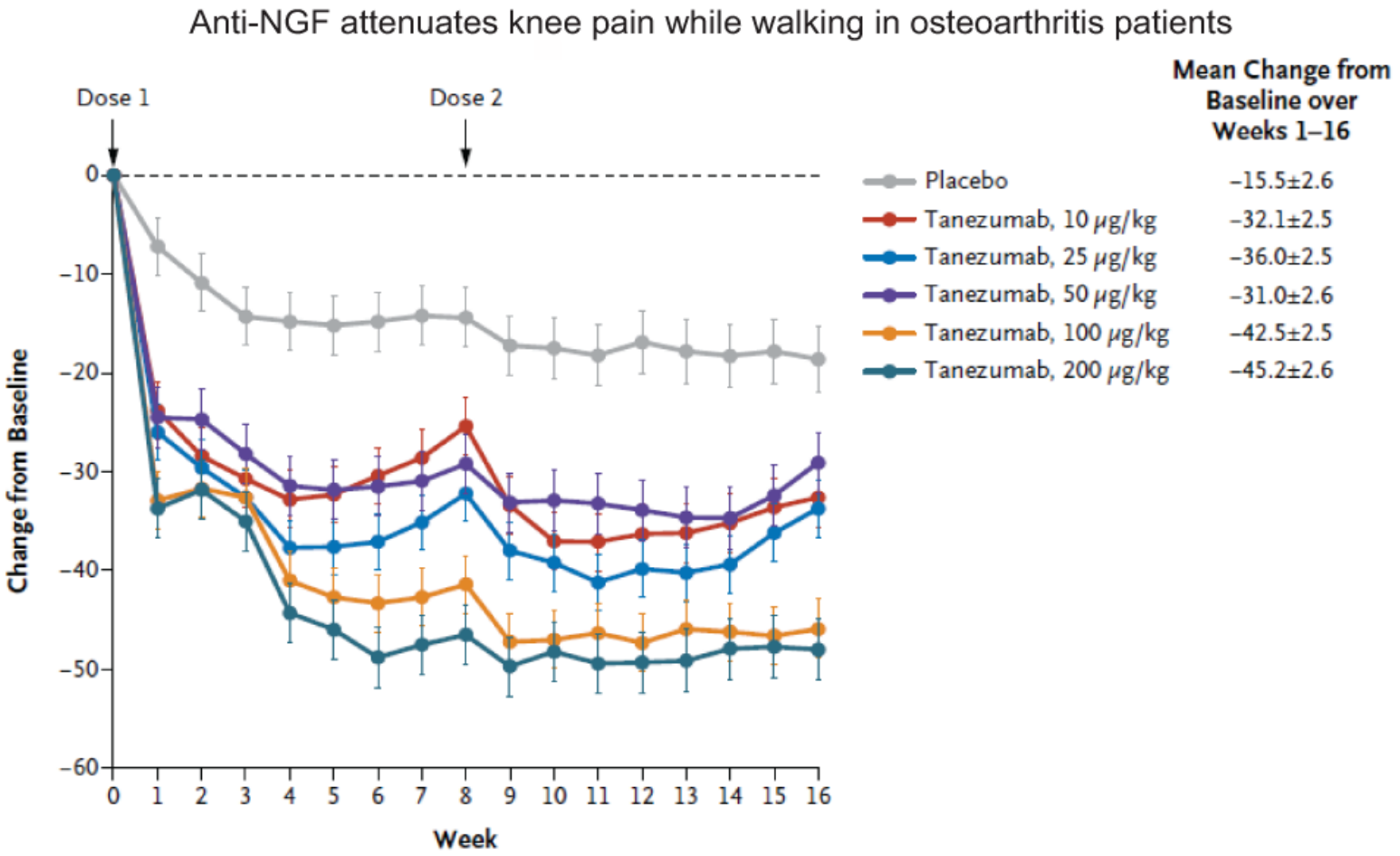
"The Human Pincushion" (congenital insensitivity to pain with anhidrosis; HSN Type IV)

HSN Type I	***SPTLC1***	**sphingolipid synthesis**
HSN Type II	***HSN2***	**(function unknown)**
HSN Type IID	***SCN9A***	**sodium ($Na_v1.7$) channel**
HSN Type III	***IKBKAP***	**transcription factor**
HSN Type IV	***NTRK1***	**neurotrophin receptor**
HSN Type V	***NGFB***	**neurotrophin**
HSN Type ?	***SCN11A***	**sodium (Nav1.9) channel**
FEPS	***TRPA1***	**cation (TRPA1) channel**
PE	***SCN9A***	**sodium ($Na_v1.7$) channel**
PEPD	***SCN9A***	**sodium ($Na_v1.7$) channel**
FHM Type I	***CACNA1A1***	**calcium channel subunit**
FHM Type II	***ATP1A2***	**ion pump subunit**
FHM Type III	***SCN1A***	**sodium ($Na_v1.1$) channel**

FEPS: familial episodic pain syndrome; HSN: hereditary sensory neuropathy;
PE: primary erythromelalgia; PEPD: paroxysmal extreme pain disorder; FHM: familial hereditary migraine

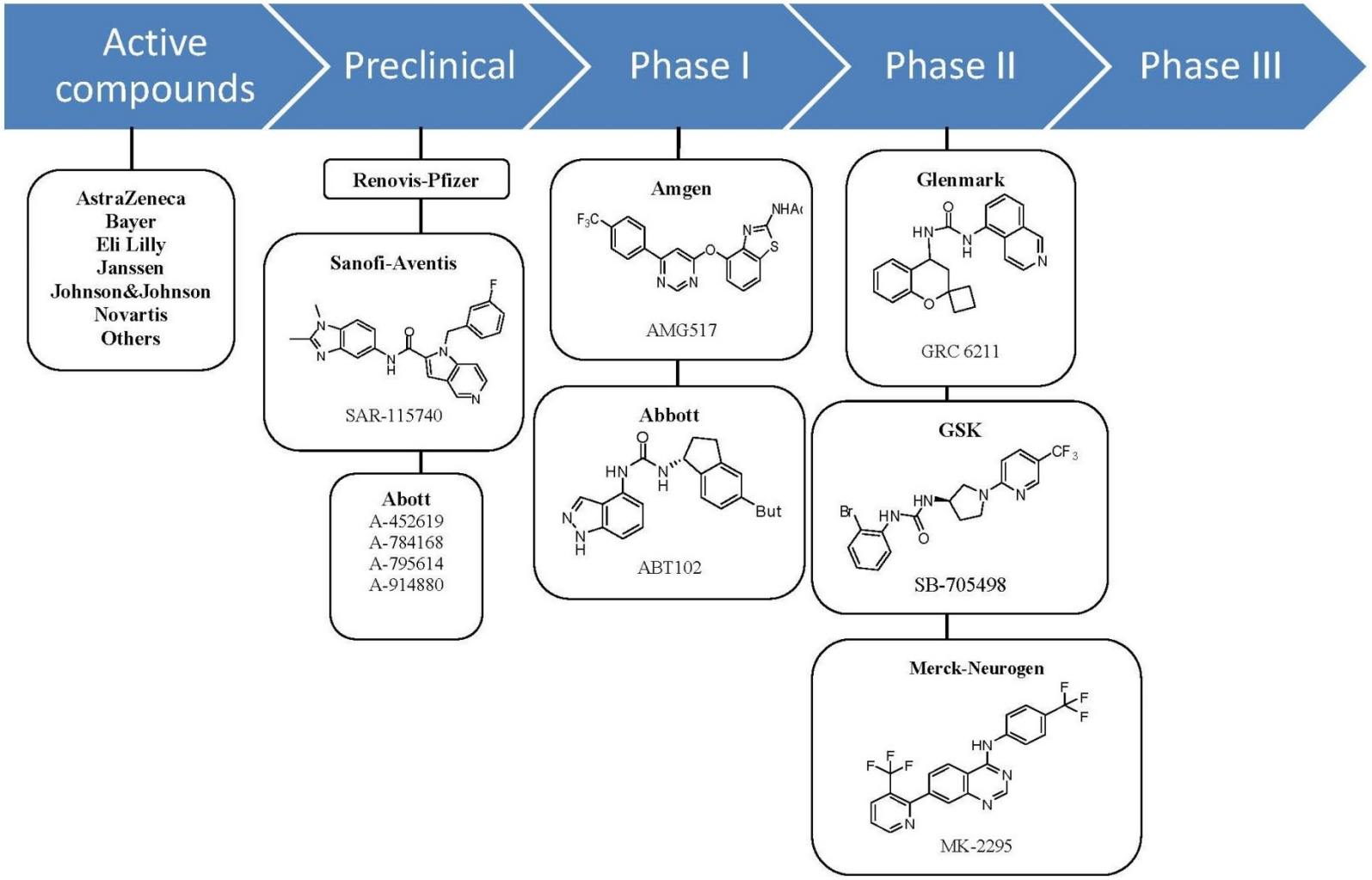
Courtesy from Dr. Mogil

Drug Development Based on Monogenic Pan Disorders -



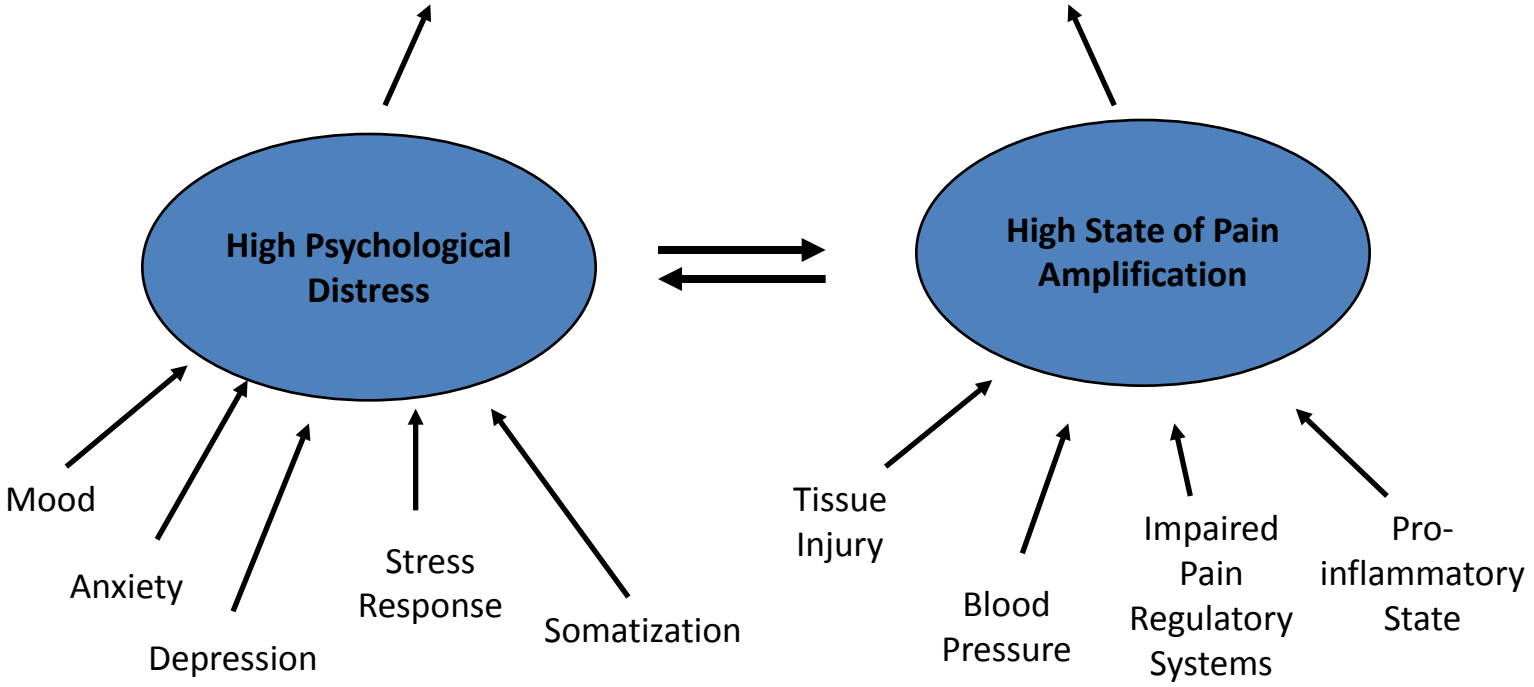
Mantyh et al , Anesthesiology, 2011

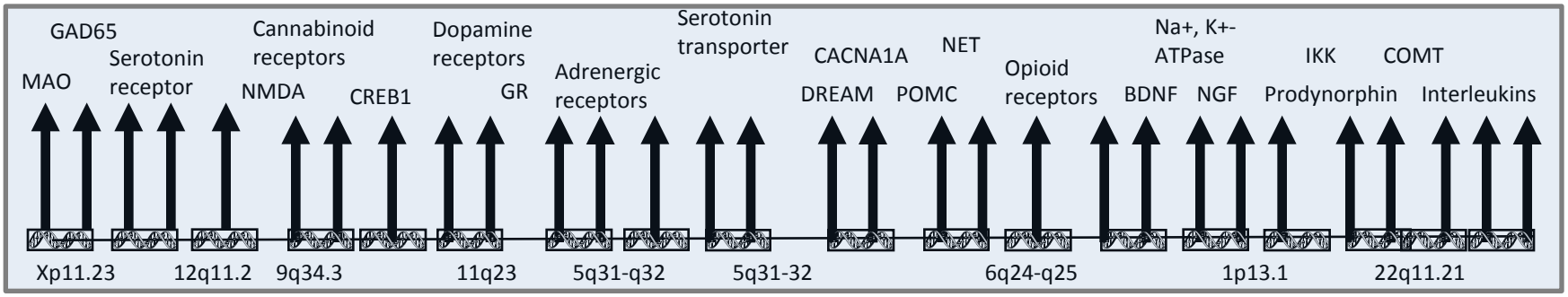
Drug Development Based on Monogenic Pan Disorders – Sodium Channel blockers



Common Persistent Pain Conditions

ENVIRONMENTAL CONTRIBUTION

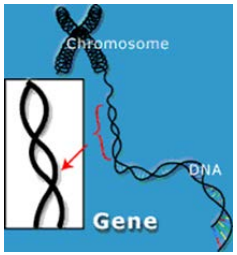




Diatchenko et al, Pain 123: 226-30, 2006

Development of Pain Genetics Field

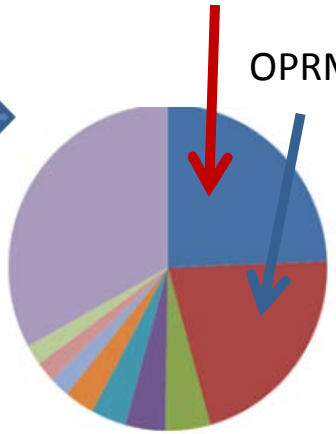
Questioning genetic component of human pain

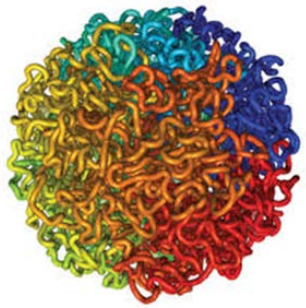


Single gene association studies

COMT

OPRM1





Genome-wide analysis

? ? ? ? ? ? ? ? ? ?

Needs for integration of multiple genome-wide datasets

2000 **2017** years

We are here

HPGdb: DEVELOPMENT OF A COMPREHENSIVE REPOSITORY FOR HUMAN PAIN GENETICS

To create a database that aggregates relevant and up-to-date human pain genetics data and complementary resources in one centralized location to be used as a resource for clinicians and pain researchers

Human Pain Genetics Lab

Human Pain Genes Database

Home | Charts | Downloads | Contact Us | About the HPGDB

Search:

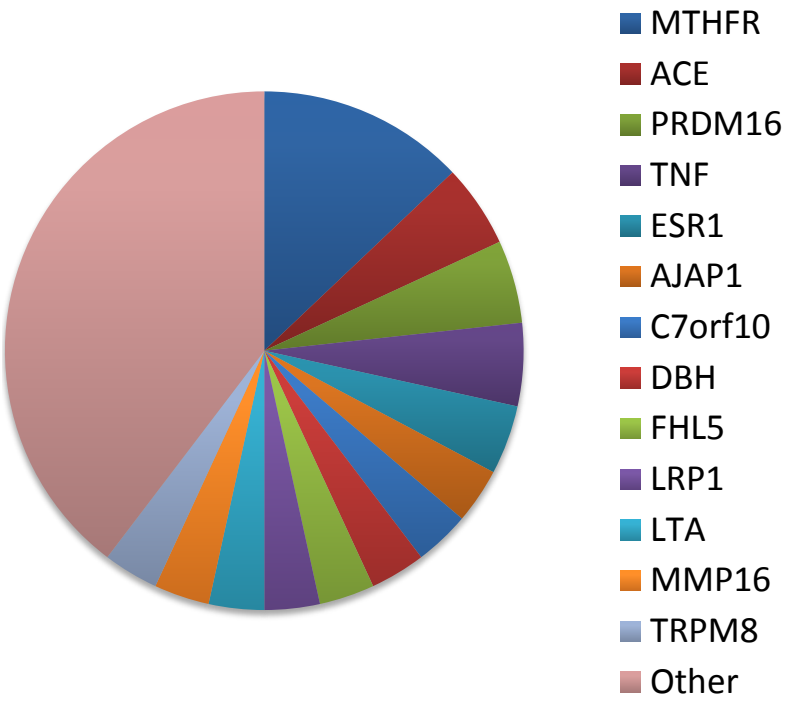
Loci	Variants	Alleles	Direction	Phenotype	Publication
ABCB1	rs1045642	C	↓	Analgesia	Campa, 2008
ABCB1	rs1045642	T/T	↓	Analgesia	Candiotti, 2013
ABCB1	rs1045642	T	↓	Analgesia	Zwisler, 2010
ABCB1	rs1045642	T/T	↑	Post-operative Pain	Sia, 2010
ABCB1	rs1045642	T/T	↑	Analgesia	Rhodin, 2013
ABCB1	rs1045642	C/C	↑	Post-operative Pain	Mamie, 2013
ABCB1	rs1045642	C	↑	Post-operative Pain	Mamie, 2013
ABCB1	rs1045642	C	↓	Analgesia	Hajj, 2015
ABCB1	rs1045642	C/C	↑	Cancer Pain	Wang, 2015

Meloto et in revvision

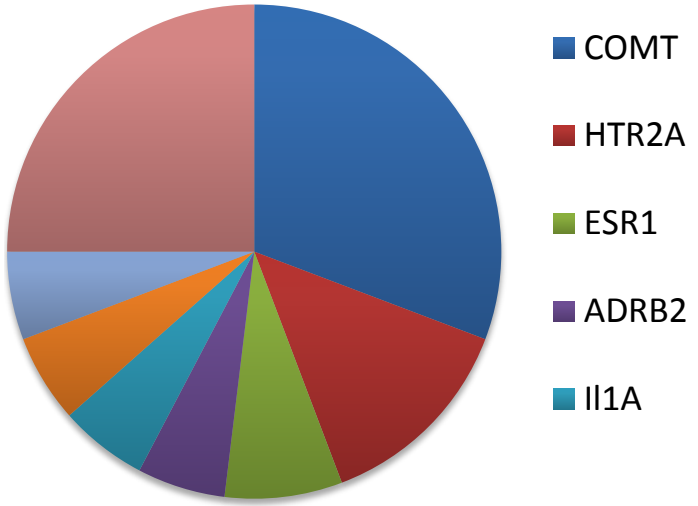
Genetic Loci Associated With

Quantified By The Number Of Genetic Association Studies

Migraine

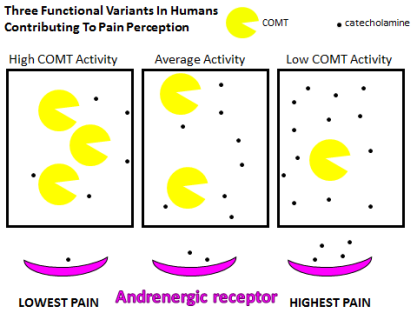


Musculoskeletal Pain Disorders



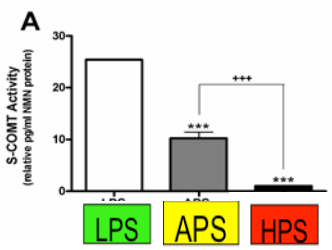
Zorina-Lichtenwalter et al, *Neuroscience*, 2016

The Translational Research Clock – closing the circle

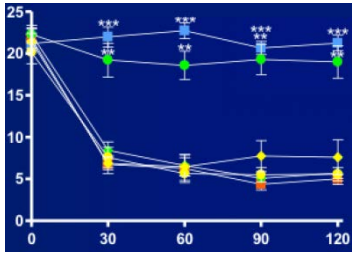


Association study results, *HMG*, 2005
(942 citations)

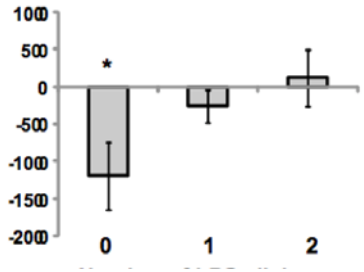
Molecular genetics of functional variants, *Science,* 2006
(607 citations)

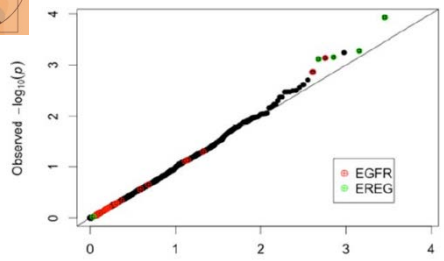


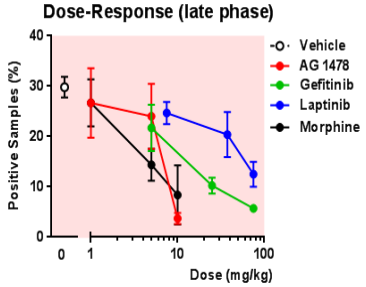
The animal behavior study – target identification, *Pain* 2007
(198 citations)

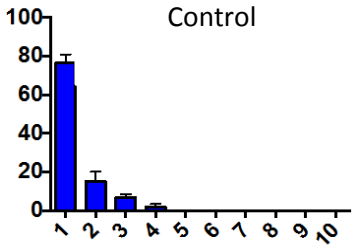


Clinical trial – *Pharmacogenet Genomics*, 2010
(83 citations)

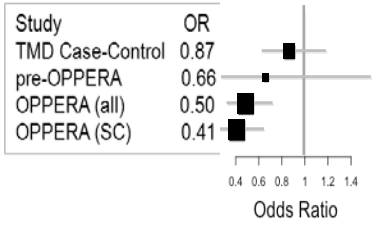


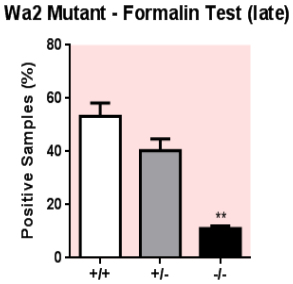


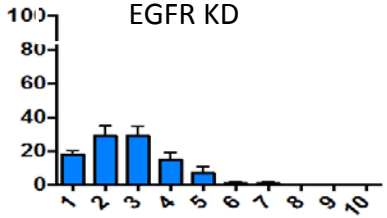




Chronic Pain Risk







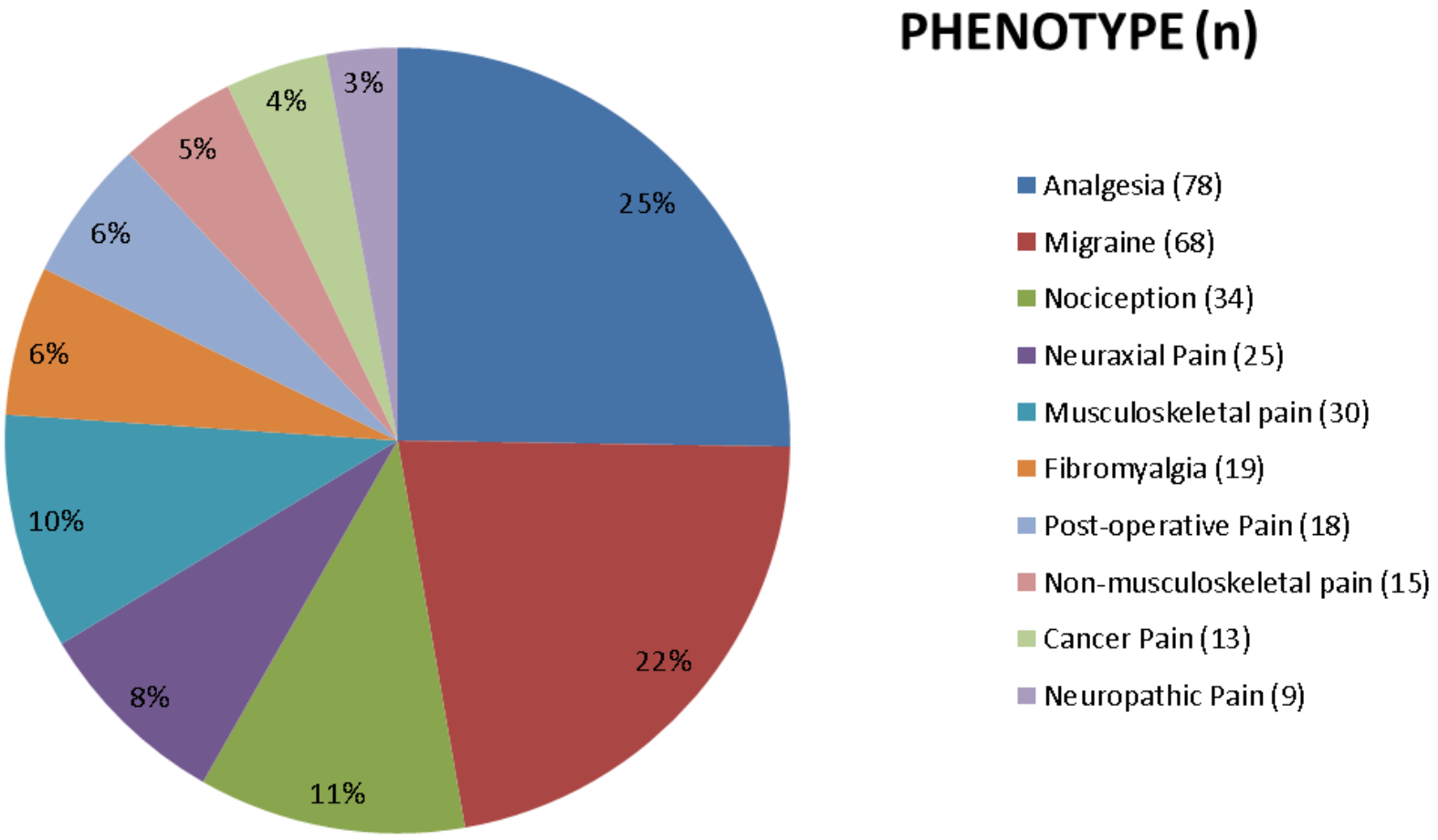
The Journal of Clinical Investigation

RESEARCH ARTICLE

Epiregulin and EGFR interactions are involved in pain processing

Loren J. Martin,[1,2] Shad B. Smith,[3] Arkady Khoutorsky,[4] Claire A. Magnussen,[5] Alexander Samoshkin,[6] Robert E. Sorge,[1] Chulmin Cho,[2] Noosha Yosefpour,[5] Sivaani Sivaselvachandran,[2] Sarasa Tohyama,[2] Tiffany Cole,[7] Thang M. Khuong,[7] Ellen Mir,[3] Dustin G. Gibson,[3] Jeffrey S. Wieskopf,[1] Susana G. Sotocinal,[1] Jean Sebastien Austin,[1] Carolina B. Meloto,[6] Joseph H. Gitt,[3] Christos Gkogkas,[4] Nahum Sonenberg,[4] Joel D. Greenspan,[8] Roger B. Fillingim,[9] Richard Ohrbach,[10] Gary D. Slade,[11] Charles Knott,[12] Ronald Dubner,[8] Andrea G. Nackley,[3] Alfredo Ribeiro-da-Silva,[5] G. Gregory Neely,[7] William Maixner,[3] Dmitri V. Zaykin,[13] Jeffrey S. Mogil,[1] and Luda Diatchenko[6]

Phenotypes categories included in the HPGdb

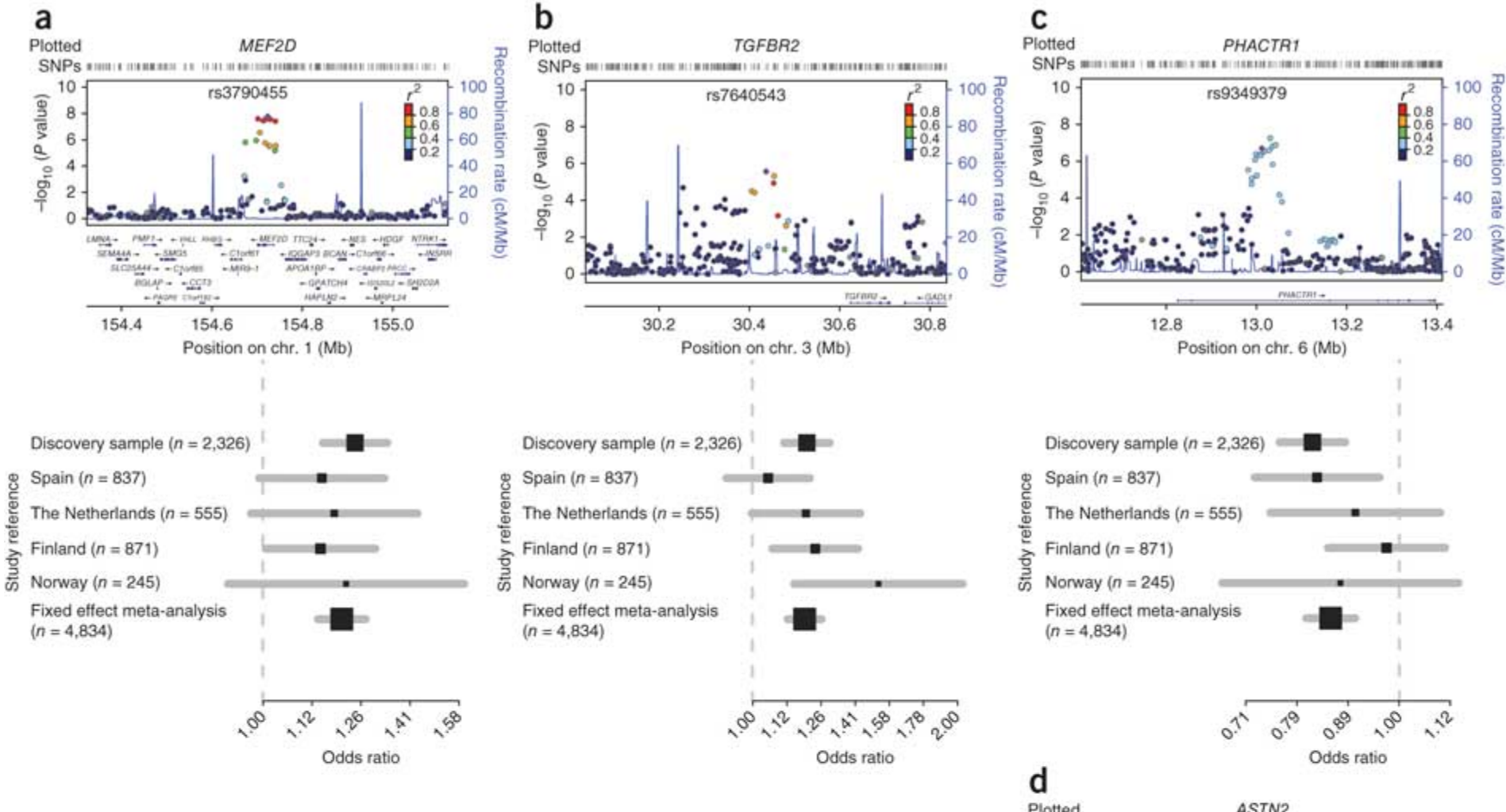


Human Pain Genetics Lab

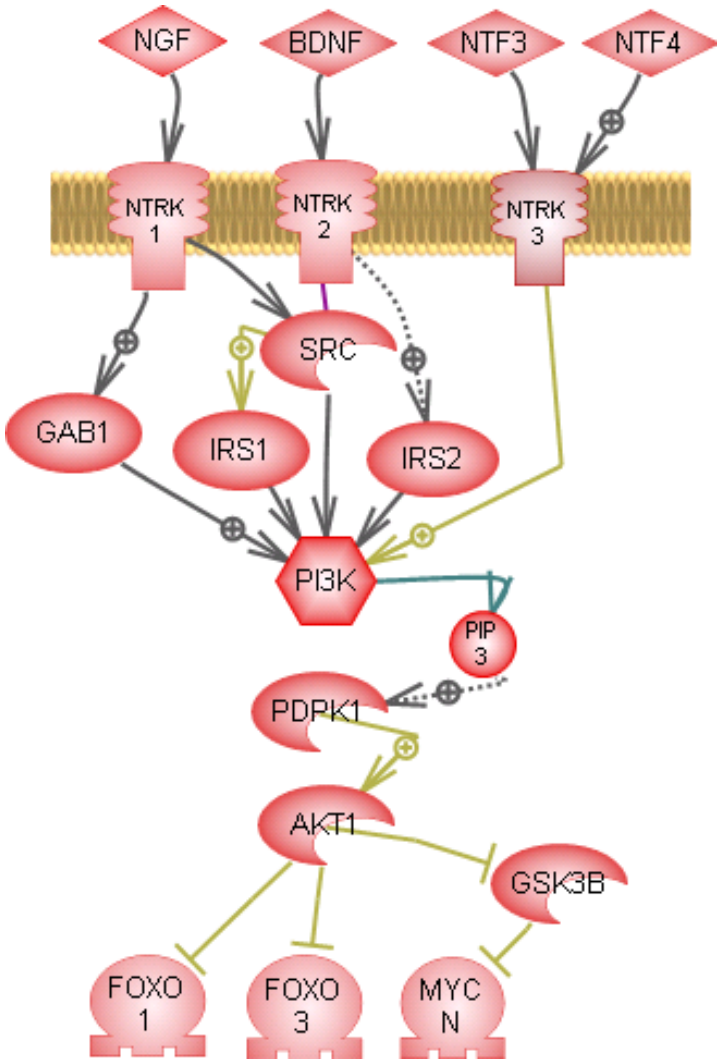
Meloto et al, Pain, Submitted

Multiple Roads to Migraine

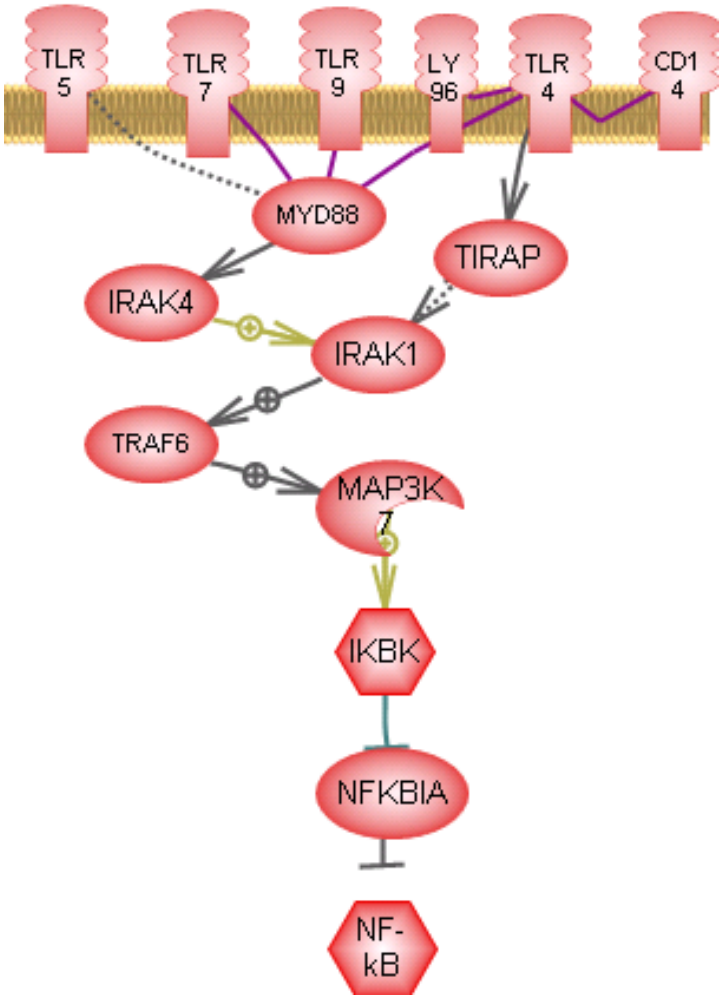
Freilinger et al *Nature Genetics* 2012



Heterogeneity of patient population

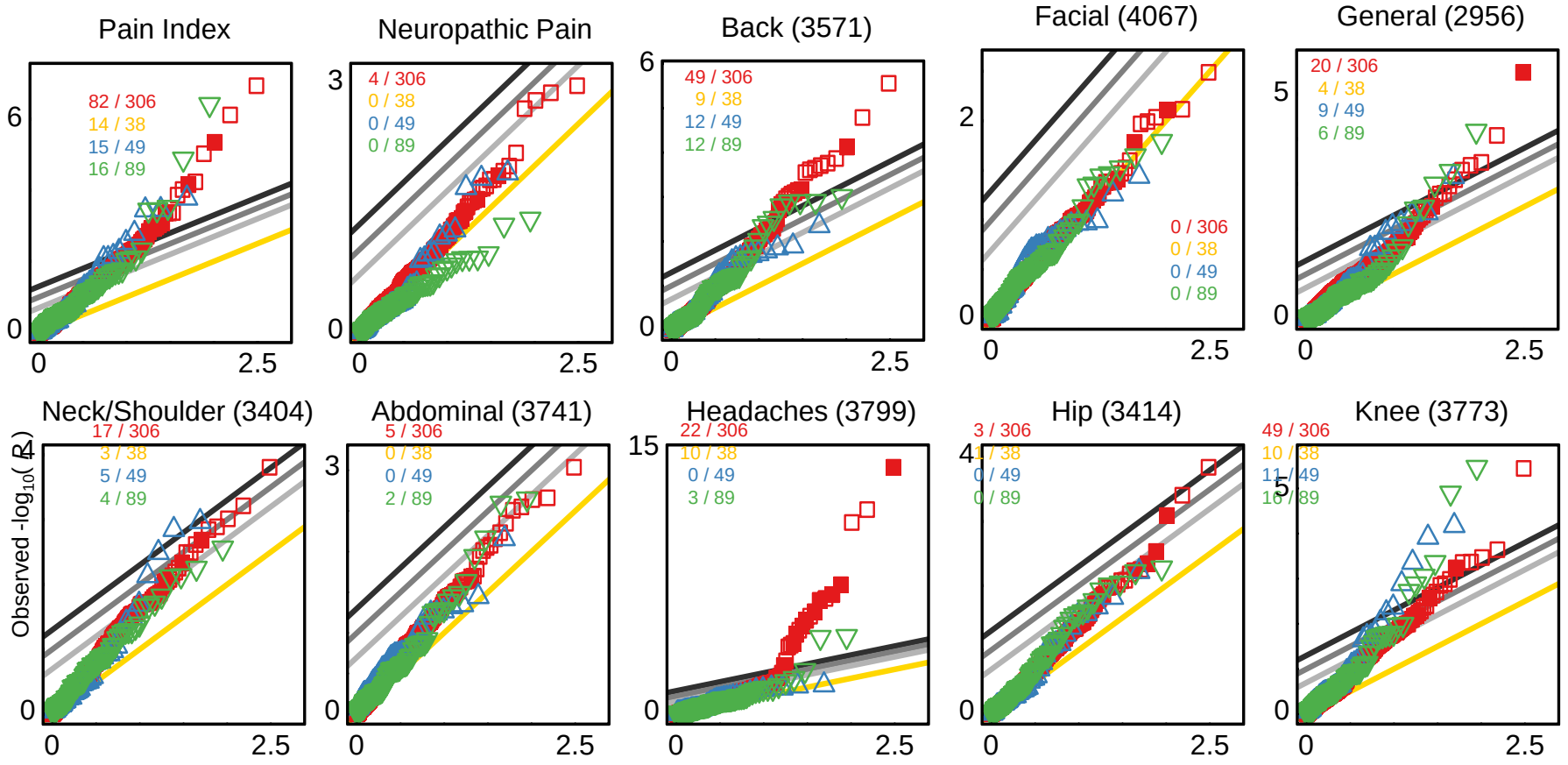


patients subgroup 1



patients subgroup 2

HPGdb: DEVELOPMENT OF A COMPREHENSIVE REPOSITORY FOR HUMAN PAIN GENETICS

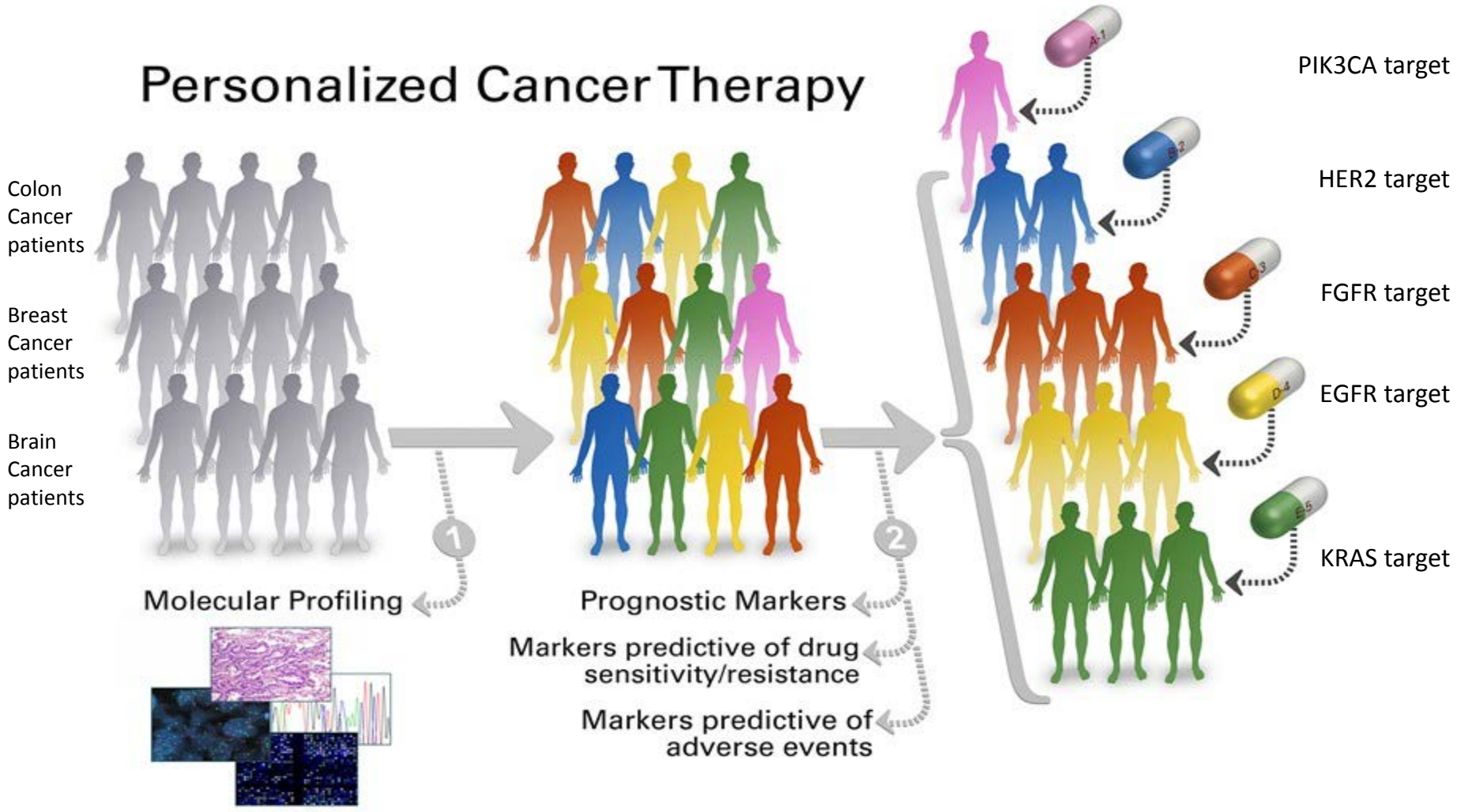


QQ plots for SNPs replication in the UK BioBank. Ratios are number of SNPs better than 20% FDR to the total number of SNPs in respective SNP groups (SNPs from GWAS in orange).

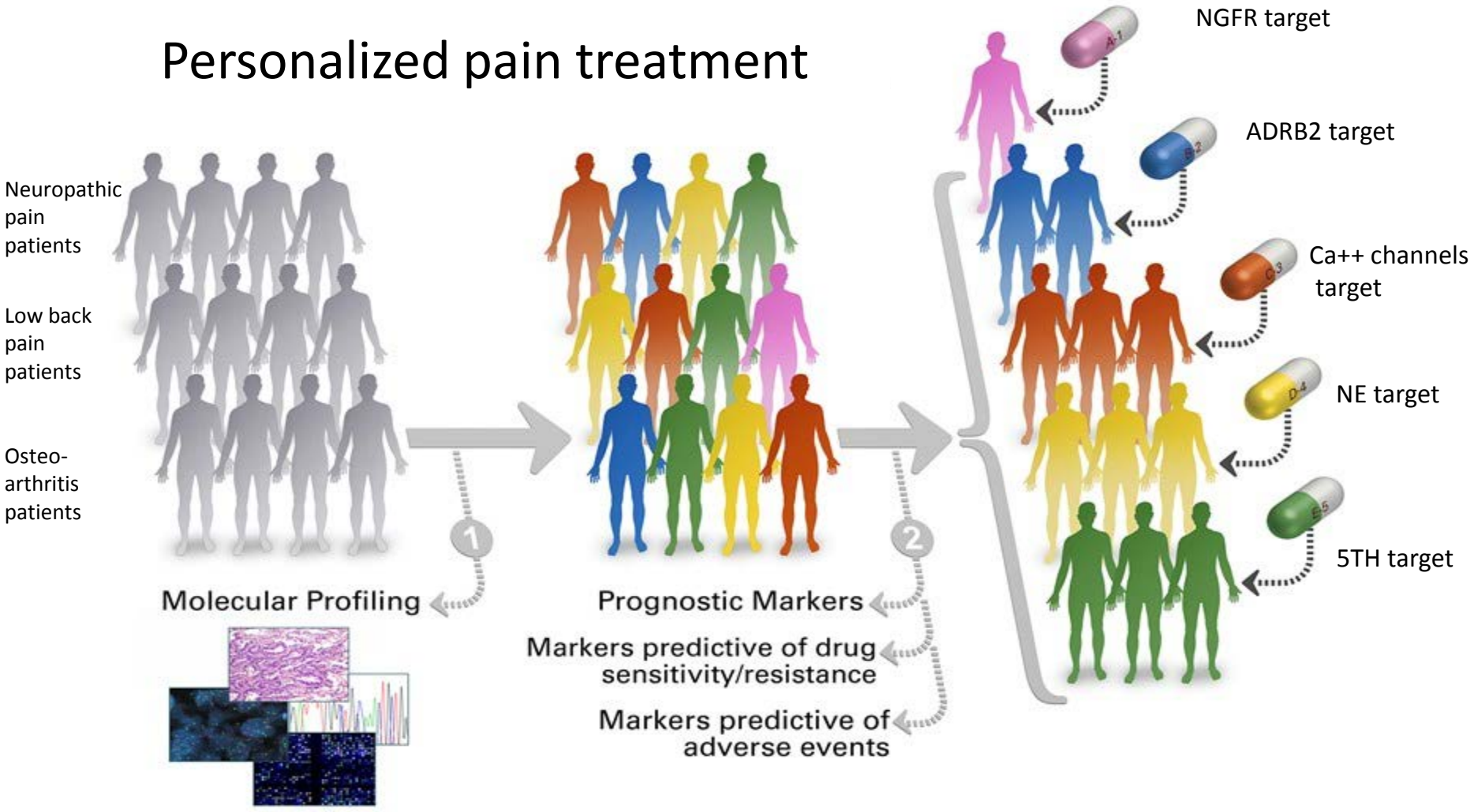
Human Pain Genetics Lab

Meloto et al, Pain, Submitted

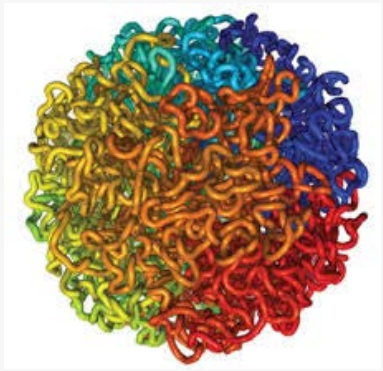
Non-organ specific approach to treatment cancer

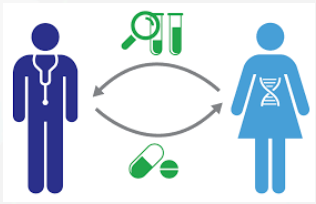


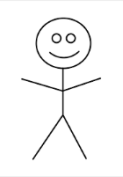
Non-organ specific approach to treatment pain

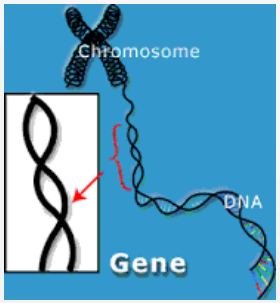


SUMMARY OF STEPS IN GLOBAL GENETIC PAIN TARGETS DEVELOPMENT PROGRAM









McGill

Welcome to the Human Pain Genetics Lab

McGill


Thank You