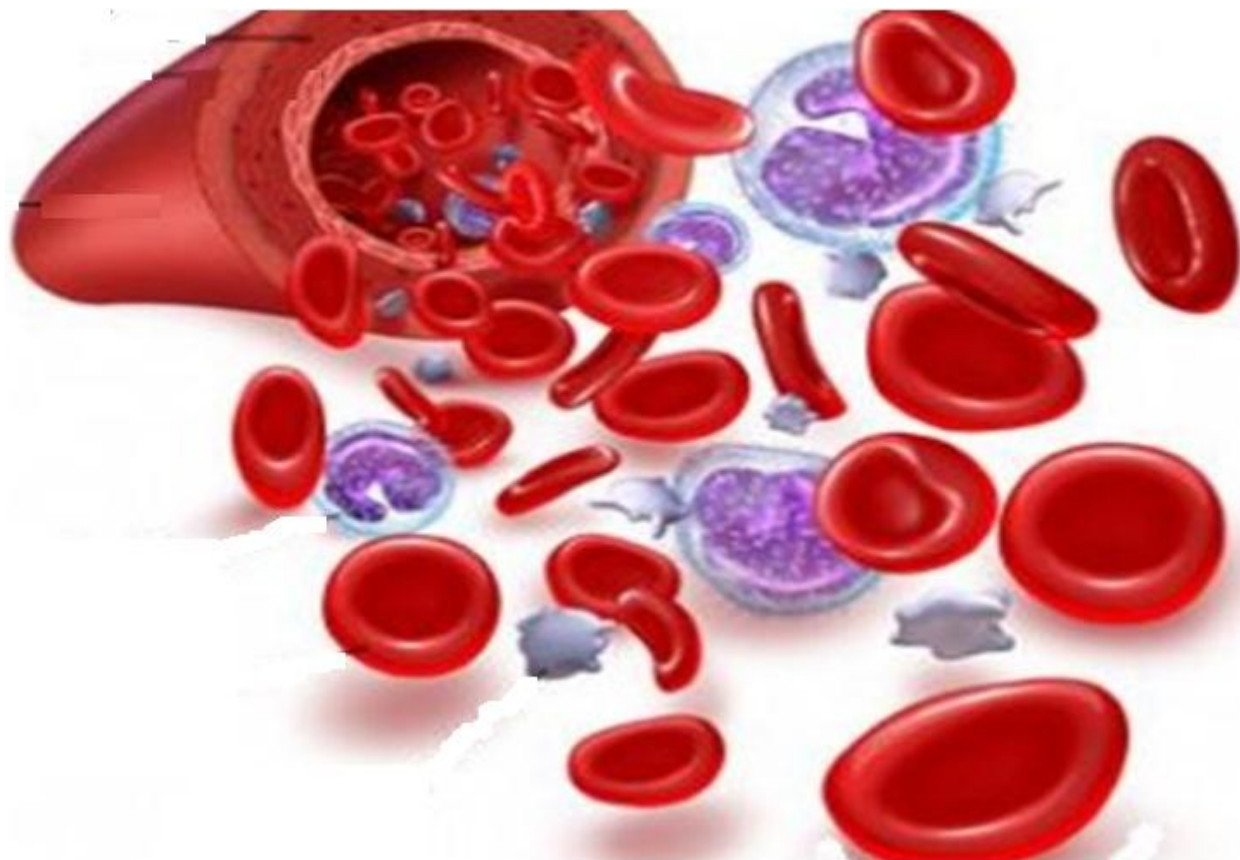


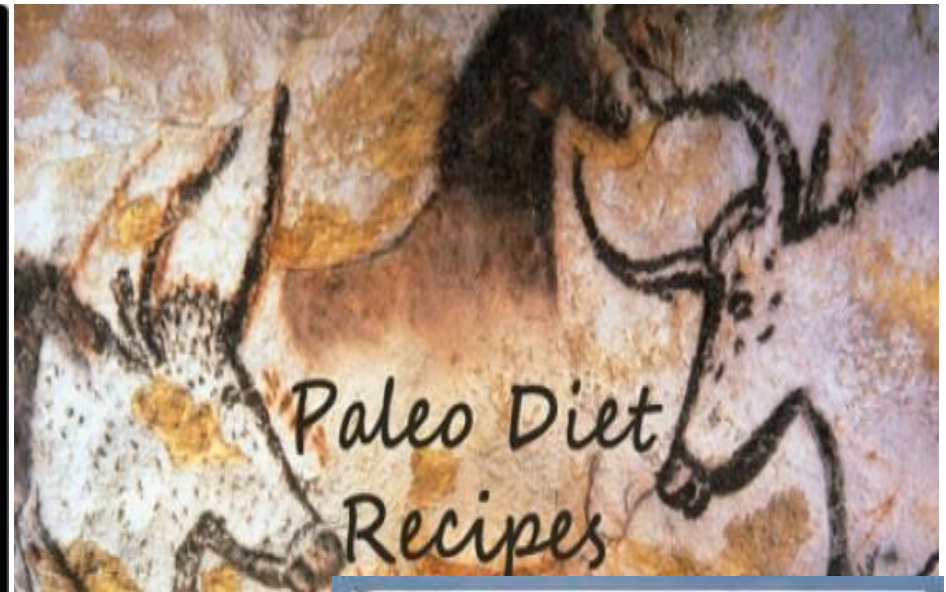
A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium



Nicole Soranzo, Spector TD, Mangino M, et al.

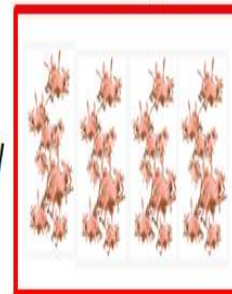
The HaemGen Consortium

	Paleolithic (Ancient) Diet	Modern Diet
PROTEIN	Very lean	Fatty
CARBOHYDRATES	Vegetables	Grains/refined sugars
FATS	Balanced intake	Pro-inflammatory
ANIMAL/FISH	65% of diet	15% of diet
VEGETABLES/FRUIT	100 different plants	Small selection
FIBER	100 grams/day	20 grams/day
VITAMINS/MINERALS	High intake	Low intake
GRAINS	None	Substantial
Glucose & Gluten intolerance		
DAIRY	None	Substantial
Lactose intolerance		
PRESSED OILS	None	Substantial
Lipid intolerance		
TRANS FATTY ACIDS	Negligible	Substantial
Lipid intolerance		
ALCOHOL	None	3% of overall calories
Alcohol intolerance		



Large

Many

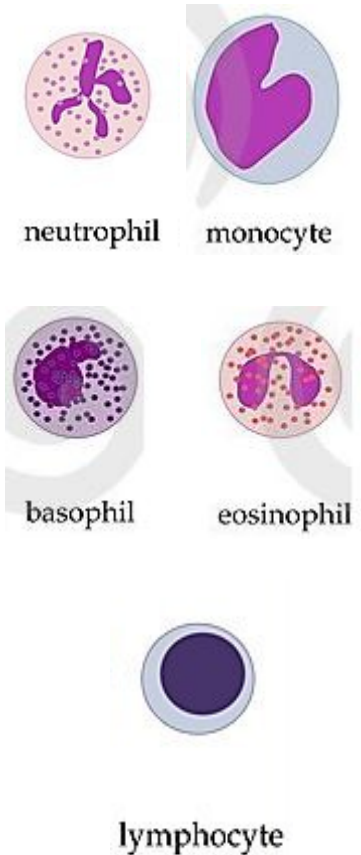
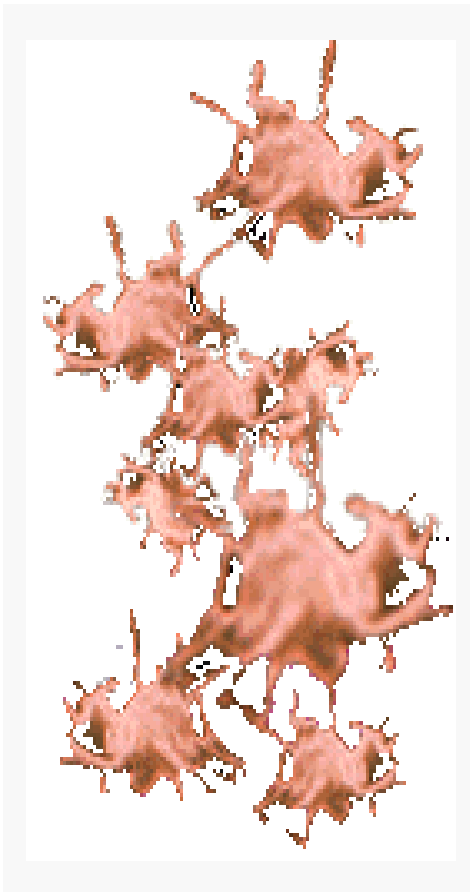


A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium

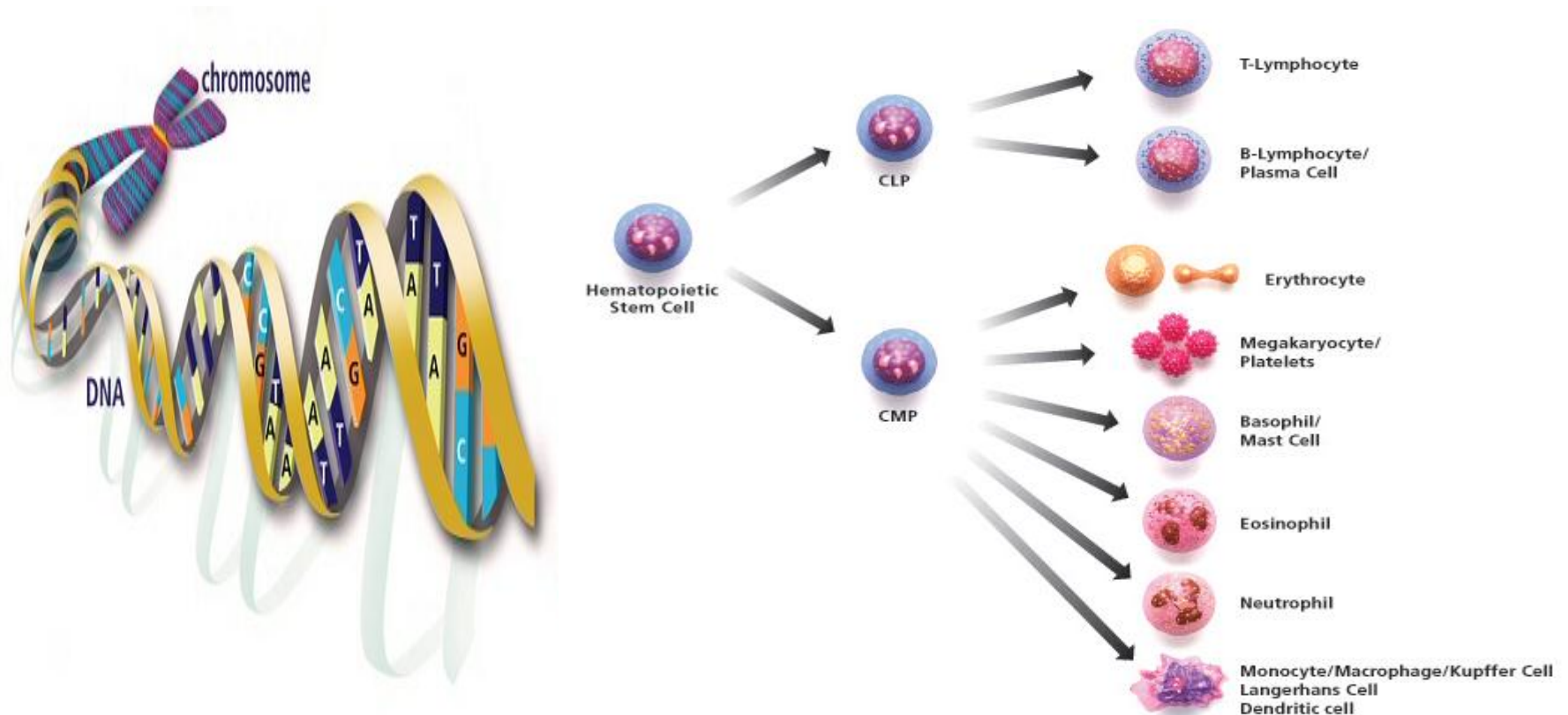
Nicole Soranzo^{1,2,45*}, Tim D Spector^{2,45}, Massimo Mangino^{2,45}, Brigitte Kühnel³, Augusto Rendon⁴, Alexander Teumer⁵, Christina Willenborg^{6,7}, Benjamin Wright⁸, Li Chen⁹, Mingyao Li¹⁰, Perttu Salo^{11,12}, Benjamin F Voight^{13,14}, Philippa Burns⁴, Roman A Laskowski¹⁵, Yali Xue¹, Stephan Menzel¹⁶, David Altshuler^{13,14,17-19}, John R Bradley²⁰, Suzannah Bumpstead¹, Mary-Susan Burnett²¹, Joseph Devaney²¹, Angela Döring³, Roberto Elosua²², Stephen E Epstein²¹, Wendy Erber²³, Mario Falchi^{2,24}, Stephen F Garner⁴, Mohammed J R Ghorri¹, Alison H Goodall²⁵, Rhian Gwilliam¹, Hakon H Hakonarson²⁶, Alistair S Hall²⁷, Naomi Hammond¹, Christian Hengstenberg²⁸, Thomas Illig³, Inke R König⁶, Christopher W Knouff²⁹, Ruth McPherson⁹, Olle Melander³⁰, Vincent Mooser²⁹, Matthias Nauck³¹, Markku S Nieminen³², Christopher J O'Donnell^{18,33}, Leena Peltonen^{11,12}, Simon C Potter¹, Holger Prokisch^{34,35}, Daniel J Rader^{36,37}, Catherine M Rice¹, Robert Roberts⁹, Veikko Salomaa^{11,12}, Jennifer Sambrook⁴, Stefan Schreiber³⁸, Heribert Schunkert⁷, Stephen M Schwartz^{39,40}, Jovana Serbanovic-Canic⁴, Juha Sinisalo³², David S Siscovick^{39,40}, Klaus Stark²⁸, Ida Surakka¹², Jonathan Stephens⁴, John R Thompson⁸, Uwe Völker⁵, Henry Völzke⁴¹, Nicholas A Watkins⁴, George A Wells⁹, H-Erich Wichmann^{3,42}, David A Van Heel⁴³, Chris Tyler-Smith¹, Swee Lay Thein¹⁶, Sekar Kathiresan^{18,33}, Markus Perola^{11,12}, Muredach P Reilly^{36,37}, Alexandre F R Stewart⁹, Jeanette Erdmann⁷, Nilesh J Samani²⁵, Christa Meisinger³, Andreas Greinacher⁴⁴, Panos Deloukas^{1,45}, Willem H Ouwehand^{1,4,45} & Christian Gieger^{3,45}

The HaemGen Consortium

The **number and volume** of cells in the blood affect a wide range of disorders including cancer and **cardiovascular**, metabolic, infectious and immune conditions.

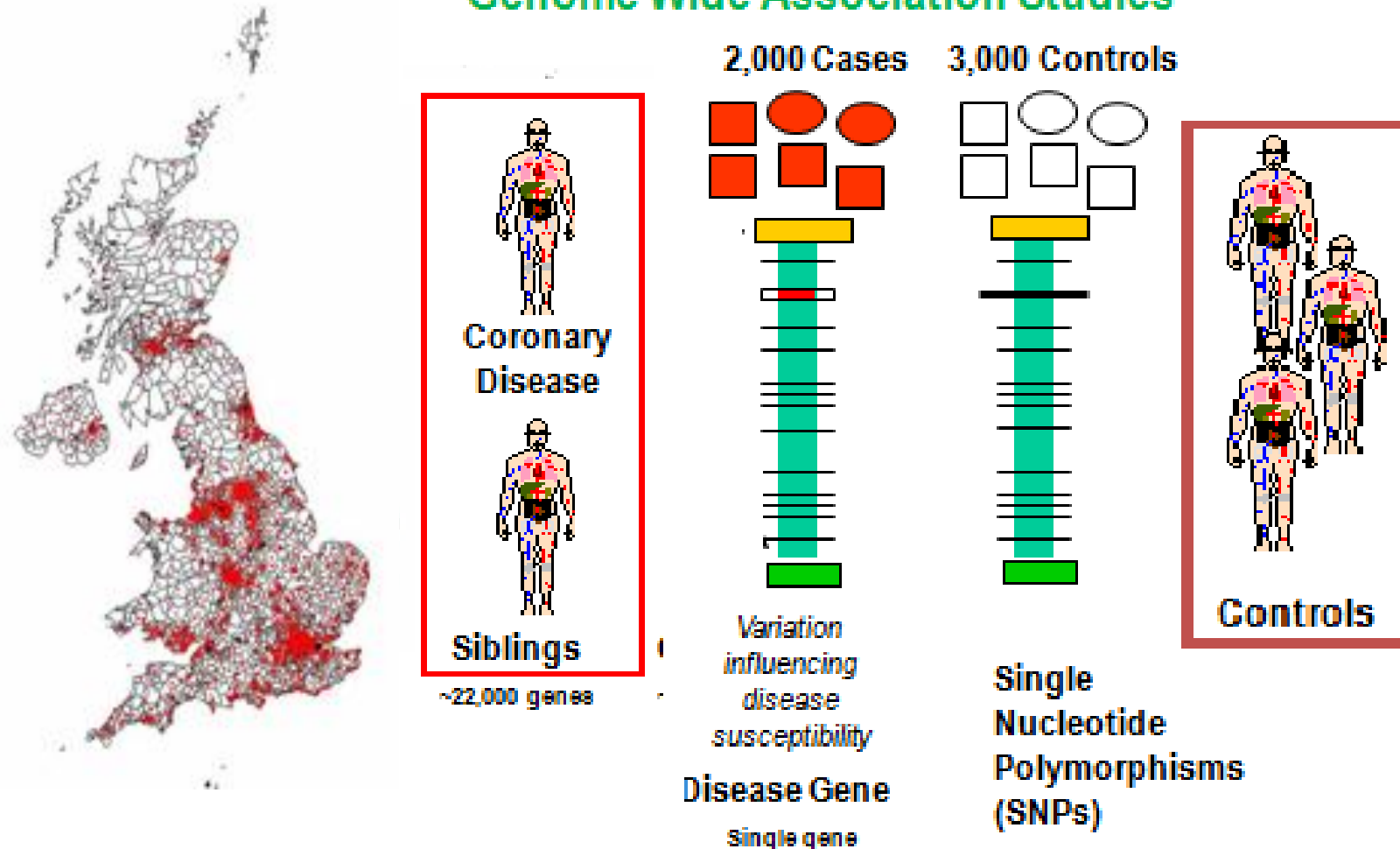


The HaemGen Consortium



“to search for genetic loci contributing to variation in haematological parameters and to assess the potential correlation of these loci with disease”

Genome Wide Association Studies



Genetic variation in 8 clinically relevant haematological parameters, including haemoglobin levels, red and white blood cell counts and **platelet counts and volume.**

Red blood cell



Hb

MCH

MCHC

MCV

RBC

Platelet

MPV

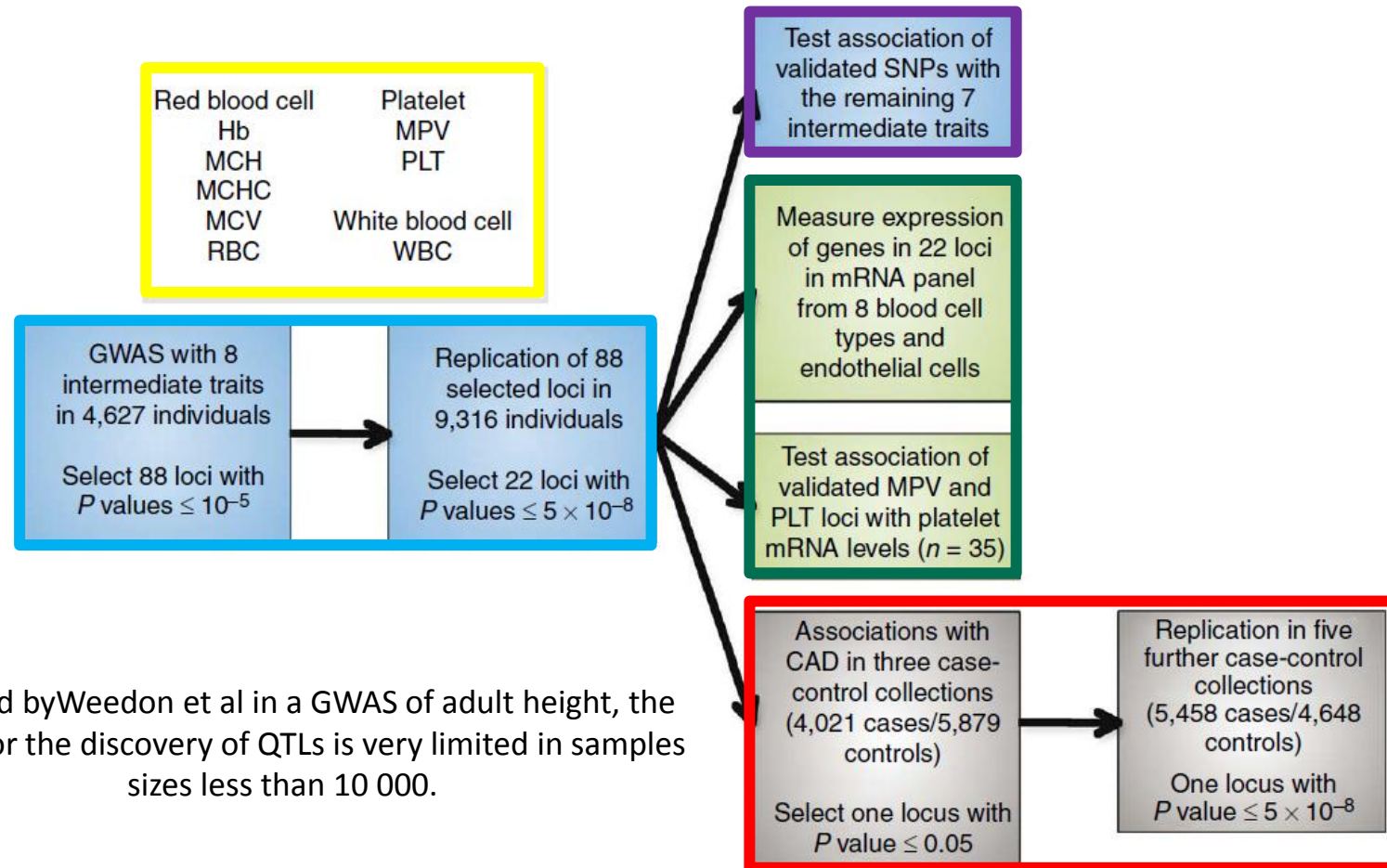
PLT



White blood cell

WBC





As noted by Weedon et al in a GWAS of adult height, the power for the discovery of QTLs is very limited in samples sizes less than 10 000.

Figure 1 Summary of the study design.

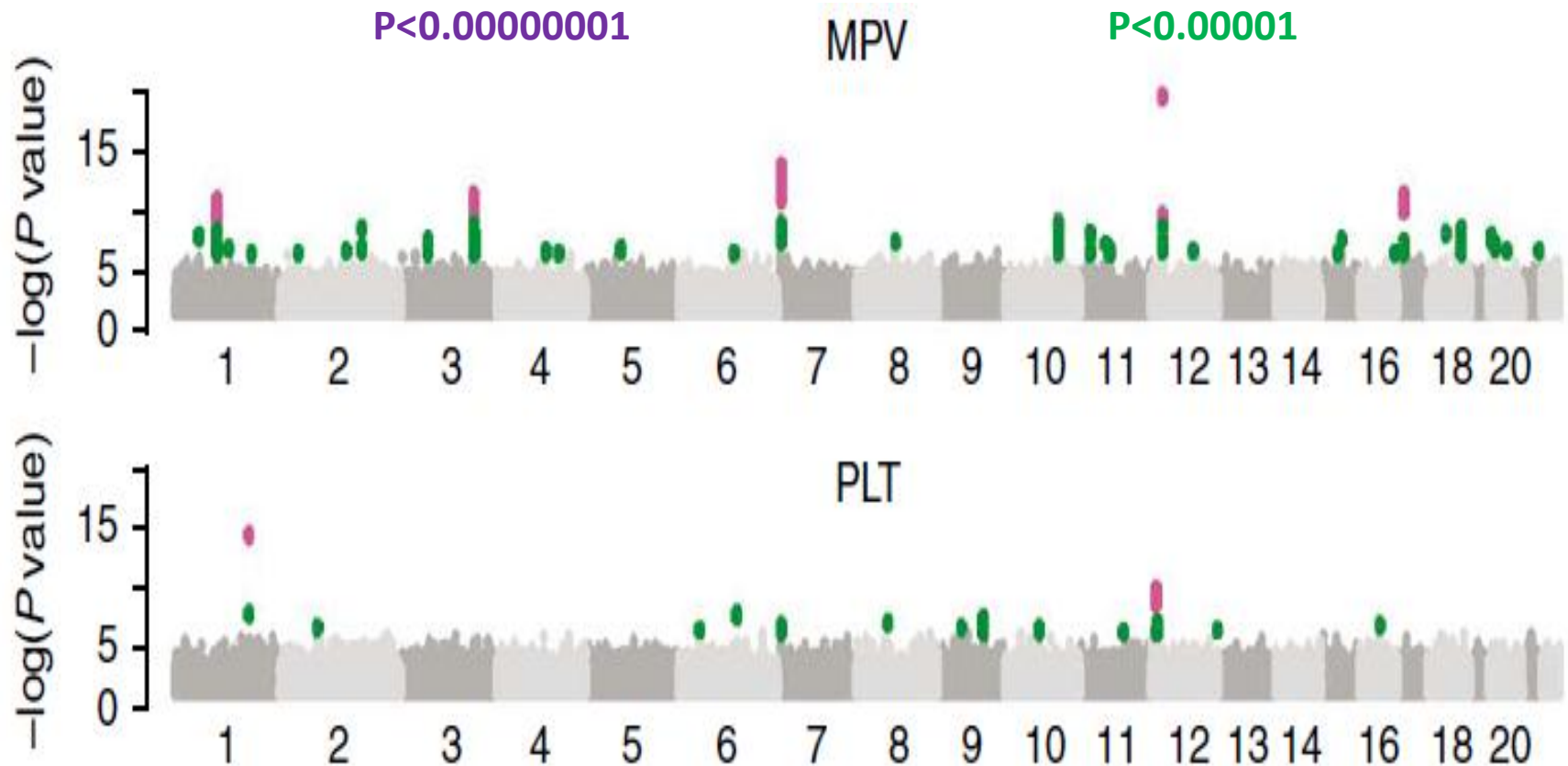
The HaemGen Consortium

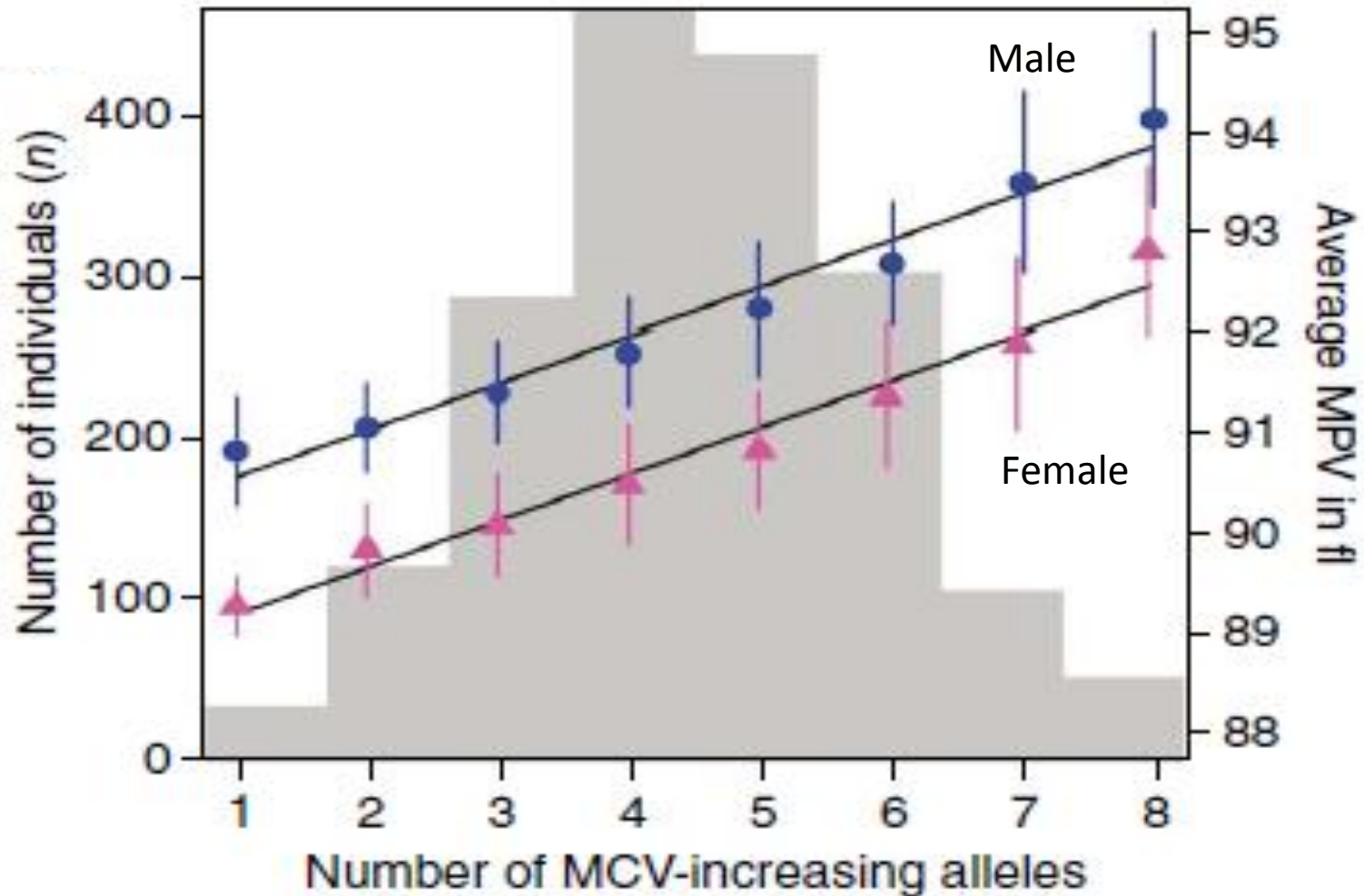
nature
genetics

22 genetic loci reproducibly associated with these haematological parameters
13,943 samples from six European population-based studies



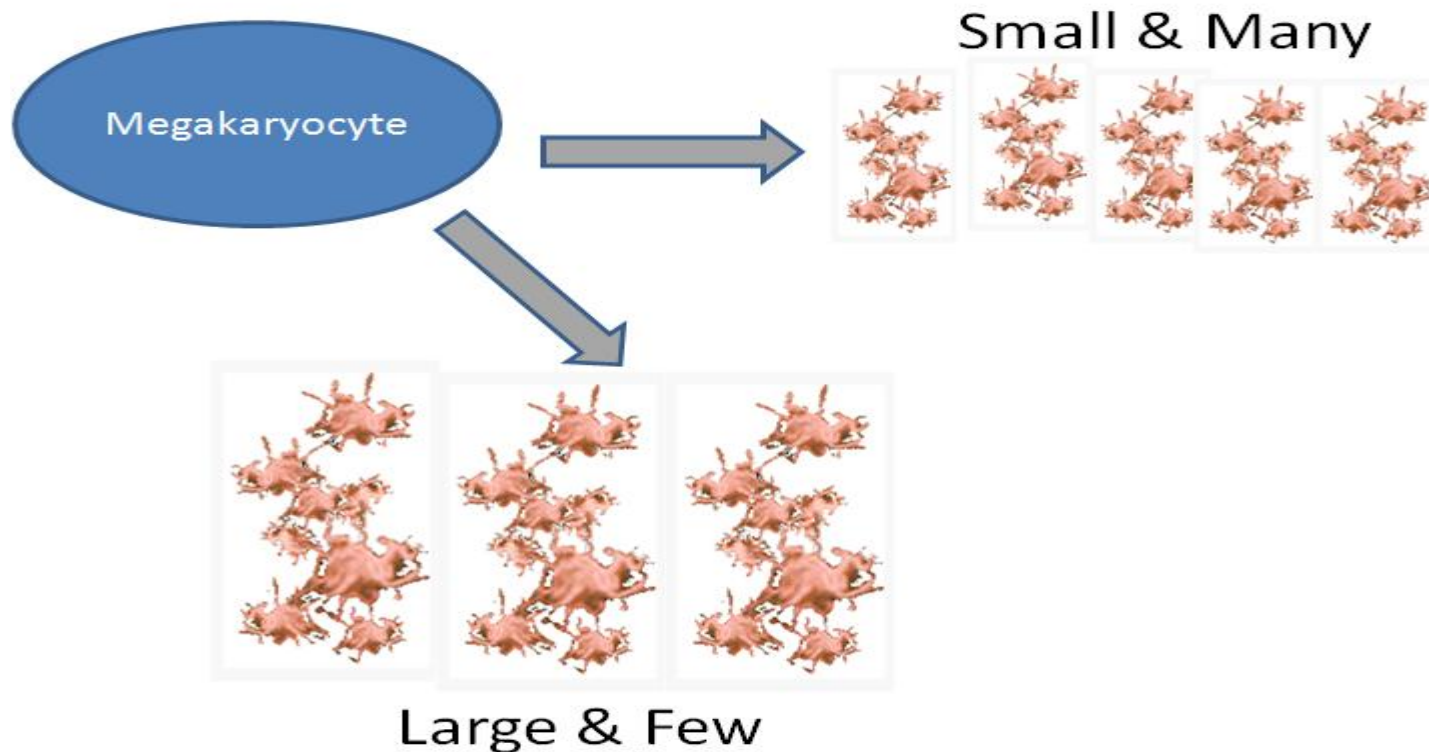
15 loci associated with platelet parameters





9 loci for MVP (mean platelet volume) also associated with PLT (platelet number)

Loci for **HIGH MVP** associated with **LOW PLT** in **ALL** cases

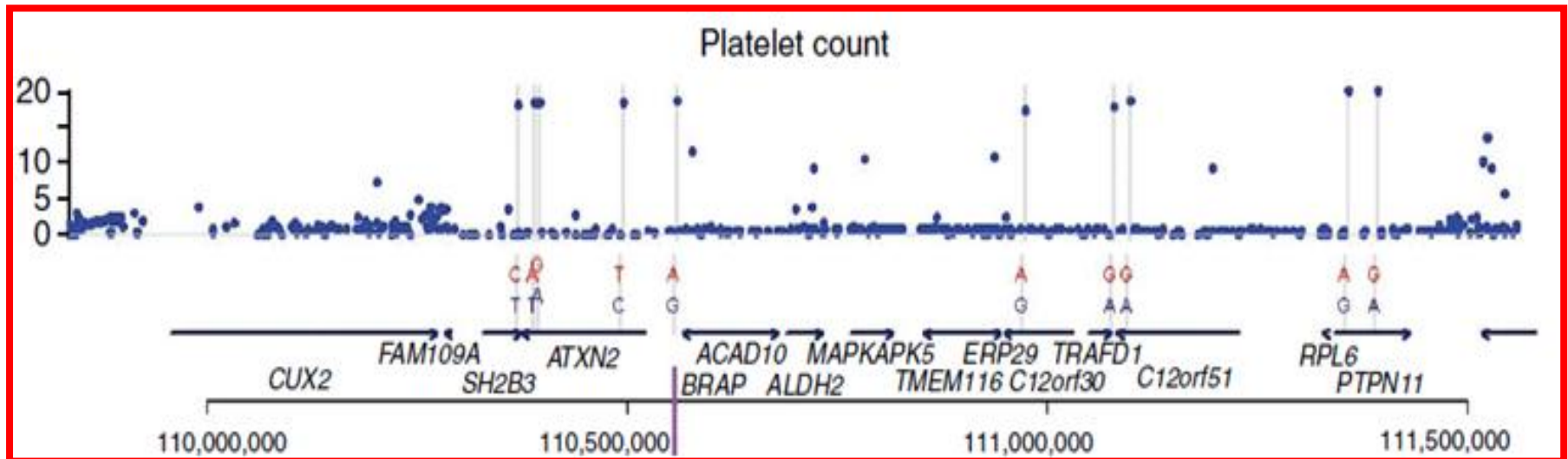


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the first 3 loci associated with platelet count.

Platelet Count

Trait	SNP	Pos (build 36)	Cytoband	Locus	Minor allele	MAF CEU	A1/ A2 ^a	Discovery (n = 4,627)			Replication (n = 9,316)				Combined (n = 13,943)		
								Beta (s.e.m.)	P	r ² (%)	Beta (s.e.m.)	P	r ² (%)	% variance	Beta (s.e.m.)	P	r ² (%)
PLT	rs11065987	110,556,807	12q24	ATXN2	G	0.34	G/A	7.521 (1.305)	8.3 × 10 ⁻⁹	0	4.118 (0.815)	4.4 × 10 ⁻⁷	0	0.23	5.073 (0.692)	2.2 × 10 ⁻¹³	31
	rs11066301	111,355,755	12q24	PTPN11	G	0.35	G/A	7.479 (1.251)	2.3 × 10 ⁻⁹	0	3.467 (0.809)	1.8 × 10 ⁻⁵	0	0.16	4.650 (0.680)	7.7 × 10 ⁻¹²	45
	rs210135	33,648,670	6p21.3	BAK1	T	0.32	A/T	6.908 (1.342)	2.6 × 10 ⁻⁷	0	4.380 (1.138)	1.2 × 10 ⁻⁴	0	0.19	5.438 (0.868)	3.7 × 10 ⁻¹⁰	0
	rs385893	4,753,176	9p24.1 -p24.3	AK3	T	0.44	C/T	6.951 (1.389)	5.6 × 10 ⁻⁷	47	5.979 (0.895)	2.4 × 10 ⁻¹¹	24	0.33	6.264 (0.753)	8.5 × 10 ⁻¹⁷	26



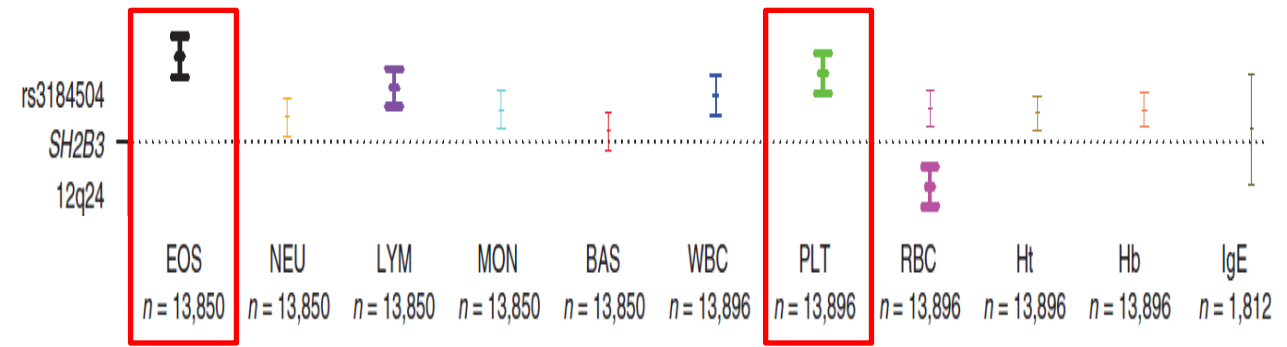
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- CUX2
- FAM109A
- SH2B3**
- ATXN2
- BRAP
- ACAD10
- ALDH2
- MAPKAPK5
- TMEM116
- ERP29
- C12orf30
- TRAFD1
- C12orf51
- RPL6
- PTPN11

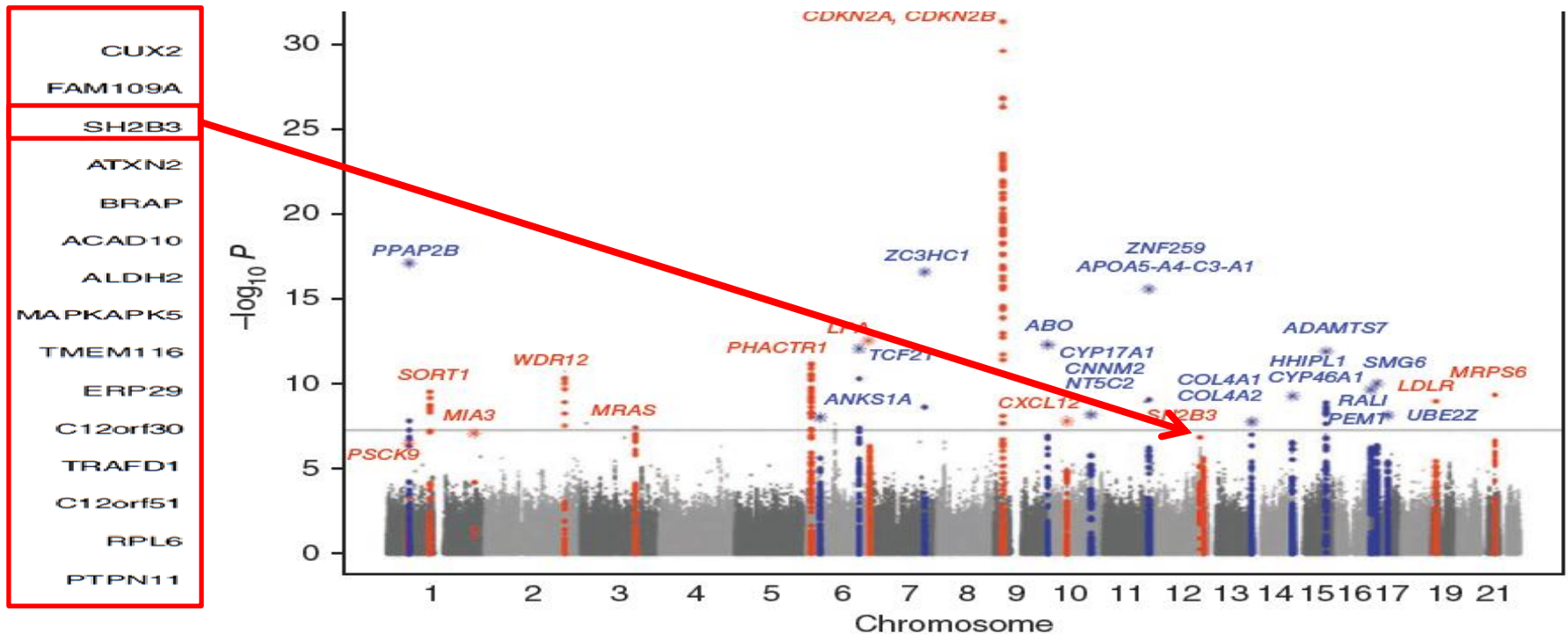
Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction

Daniel F Gudbjartsson^{*1}, Unnur S Bjornsdottir^{1,2}, Eva Halapi¹, Anna Helgadóttir¹, Patrick Sulem¹,

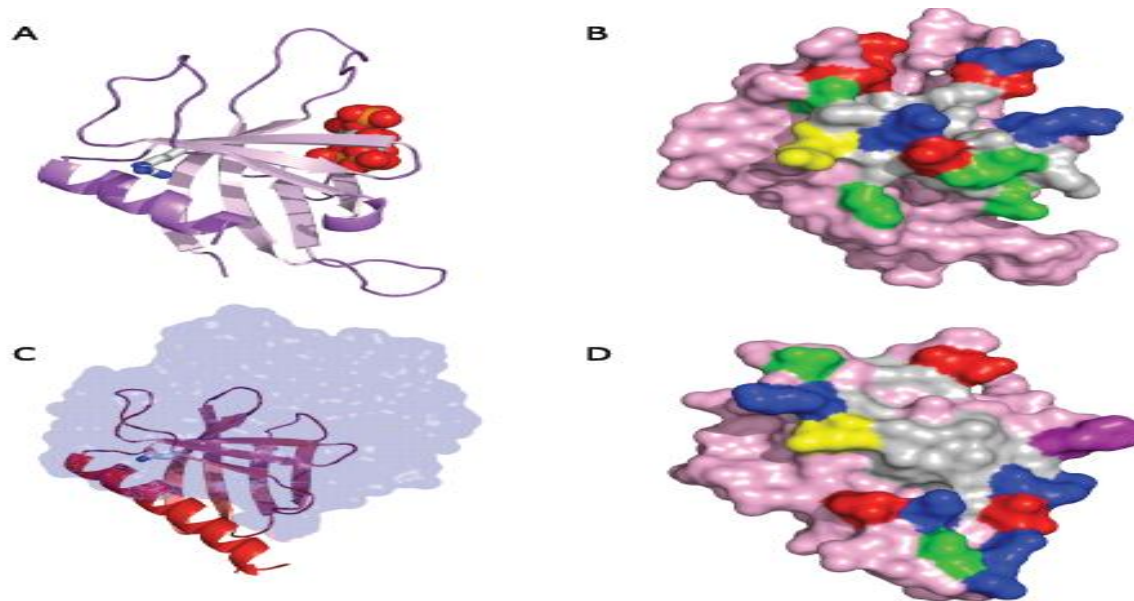


We also found that a nonsynonymous SNP at 12q24, in *SH2B3*, associated significantly ($P = 8.6 \times 10^{-8}$) with myocardial infarction in six different populations (6,650 cases and 40,621 controls).

Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease

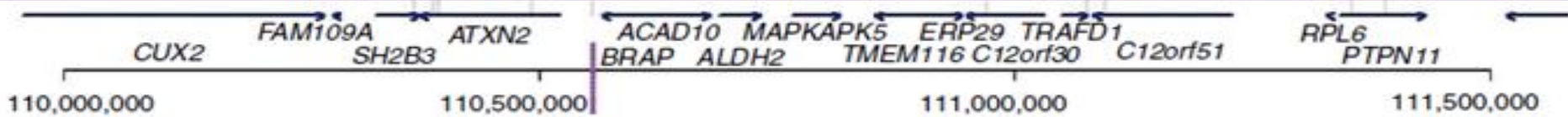


SH2B3 Homology Models (Arg262 Mutation)



Trait and location	Gene Name	Links to gene function and correlations with hematopoiesis	Effect of common variants and inherited disorder in humans	Model Organism	Gene Expression (this study)
PLT (12q24)	<i>SH2B3</i> (10019) SH2B adapter protein 3	<i>SH2B3</i> encodes the intracellular protein LNK, implicated in the intracellular signalling cascade leading to the differentiation of embryonic hemopoiesis. LNK is a negative regulator of intracellular signalling downstream of activatory membrane receptors, such as the T-cell receptor and MPL and the receptor for TPO on MKs	Sequence variation in <i>SH2B3</i> locus is associated with Associated with type 1 diabetes and susceptibility to celiac disease	Lnk ^{-/-} mice show extramedullary hematopoiesis with increased numbers of CD41+ MKs as well as EBs ⁹³	Ubiquitously transcribed in all blood cells.

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- CUX2
- FAM109A
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- ACAD10
- ALDH2
- MAPKAPK5
- TMEM116
- ERP29
- C12orf30
- TRAFD1
- C12orf51
- RPL6
- PTPN11

SNPs in *BRAP* associated with risk of myocardial infarction in Asian populations

Kouichi Ozaki¹, Hiroshi Sato², Katsumi Inoue³, Tatsuhiko Tsunoda⁴, Yasuhiko Sakata², Hiroya Mizuno², Tsung-Hsien Lin^{5,6}, Yoshinari Miyamoto⁷, Asako Aoki¹, Yoshihiro Onouchi¹, Sheng-Hsiung Sheu^{5,6}, Shiro Ikegawa⁷, Keita Odashiro³, Masakiyo Nobuyoshi³, Suh-Hang H Joo⁸⁻¹⁰, Masatsugu Hori², Yusuke Nakamura¹¹ & Toshihiro Tanaka¹

ORIGINAL ARTICLE

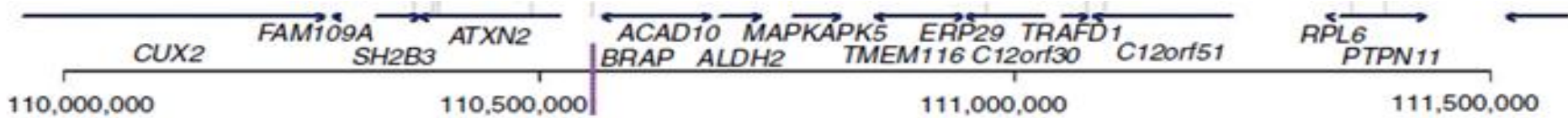
Validation of eight genetic risk factors in East Asian populations replicated the association of *BRAP* with coronary artery disease

Kunihiko Hinohara^{1,2}, Hitoshi Ohtani^{1,2}, Toshiaki Nakajima^{1,2}, Taishi Sasaoka³, Motoji Sawabe⁴, Bok-Soo Lee⁵, Jimin Ban⁵, Jeong-Euy Park⁵, Tohru Izumi³ and Akinori Kimura^{1,2}

Journal of Human Genetics (2009) 54, 642-646

conceivable that a higher expression of *BRAP* with an minor allele of intron 3 (G allele) might enhance the degree of inflammation

The HaemGen Consortium



- CUX2
- FAM109A
- SH2B3
- ATXN2
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- C12orf51
- RPL6
- PTPN11

Diabetologia (2010) 53:1349–1353
DOI 10.1007/s00125-010-1695-y

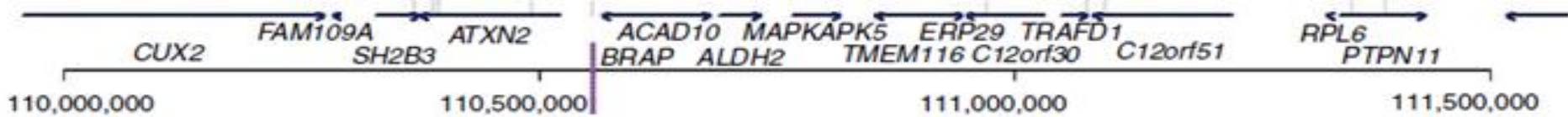
ARTICLE

Variants in *ACAD10* are associated with type 2 diabetes, insulin resistance and lipid oxidation in Pima Indians

L. Bian • R. L. Hanson • Y. L. Muller • L. Ma • MAGIC Investigators • S. Kobes • W. C. Knowler • C. Bogardus • L. J. Baier

Conclusions/interpretation We propose that *ACAD10* variation may increase type 2 diabetes susceptibility by impairing insulin sensitivity via abnormal lipid oxidation.

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- CUX2
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- TRAFD1
- C12orf51
- RPL6
- PTPN11**

Noonan Syndrome (PTPN11)

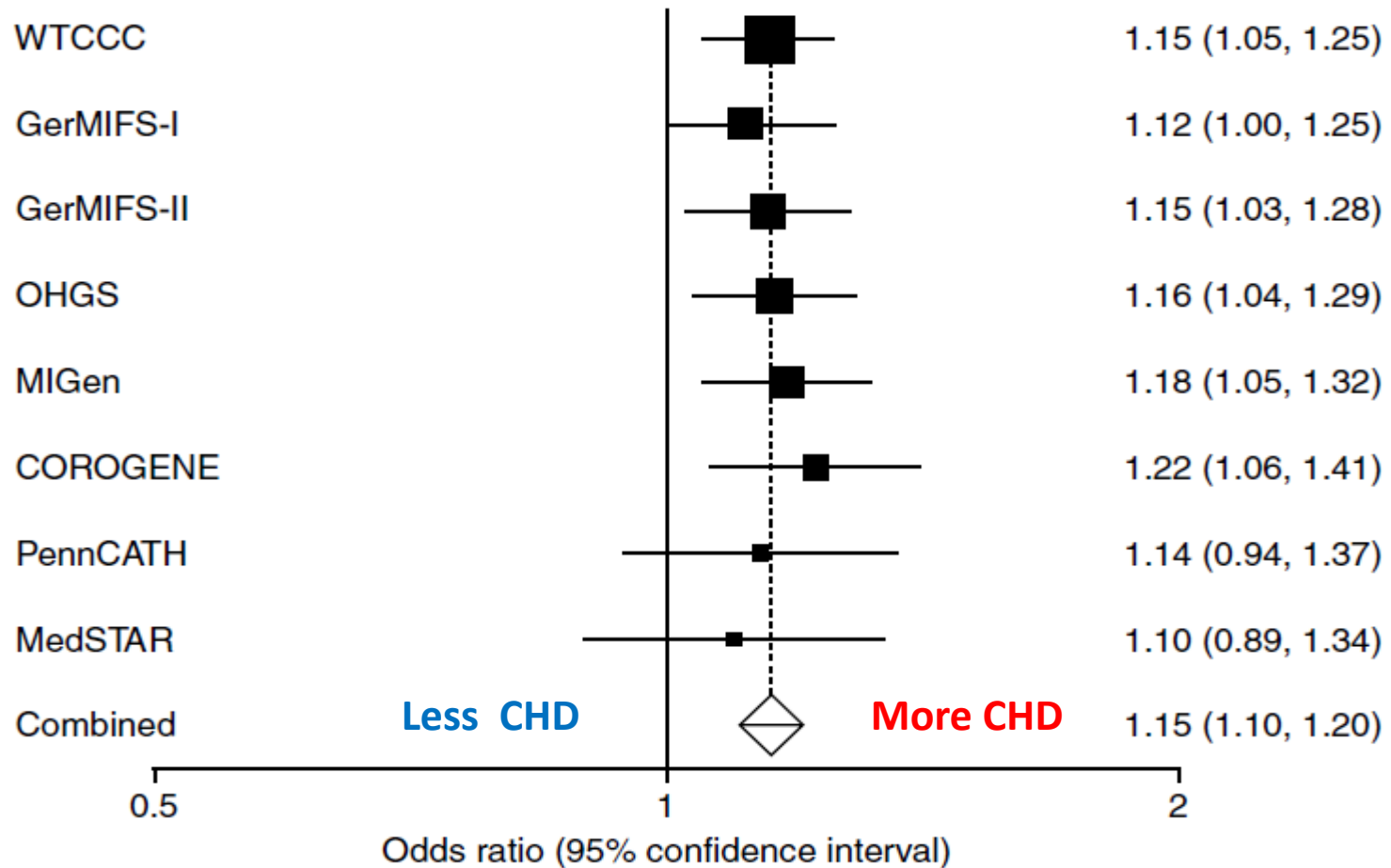
Noonan Syndrome (NS), which occurs at an incidence of about 1:1,000 – 1:2,500 live births. In about 50% of cases, NS is associated with autosomal dominant gain-of-function mutations in the gene *PTPN11*.

Abnormalities Observed in NS (26)

Craniofacial	hypertelorism with down-slanting palpebral fissures and ptosis, vivid blue or blue-green irides, low-set posteriorly angulated ears with thickened helices, low posterior hairline, webbed neck, excess nuchal skin
Growth	proportionate short stature, delayed and prolonged growth
Skeletal	superior pectus carinatum with inferior pectus excavatum, spinal deformities, cubitus valgus
Heart	pulmonary valve stenosis, hypertrophic cardiomyopathy, atrial and ventricular septal defects, branch pulmonary artery stenosis, tetralogy of Fallot, coarctation of aorta, coronary aneurysms
Genitorurinary	cryptorchidism (in males), delayed puberty, dilatation of renal pelvis
Developmental	mild retardation
Ocular	strabismus, refractive errors, amblyopia, nystagmus
Hematological	coagulation-factor (especially factor XI) deficiency, abnormalities of platelet count and function, increased risk of JMML
Lymphatic	postnatal dorsal lymphedema
Pigmentation	pigmented nevi, café-au-lait spots
Other	feeding difficulties in infancy, hepatosplenomegaly, malignant hyperthermia

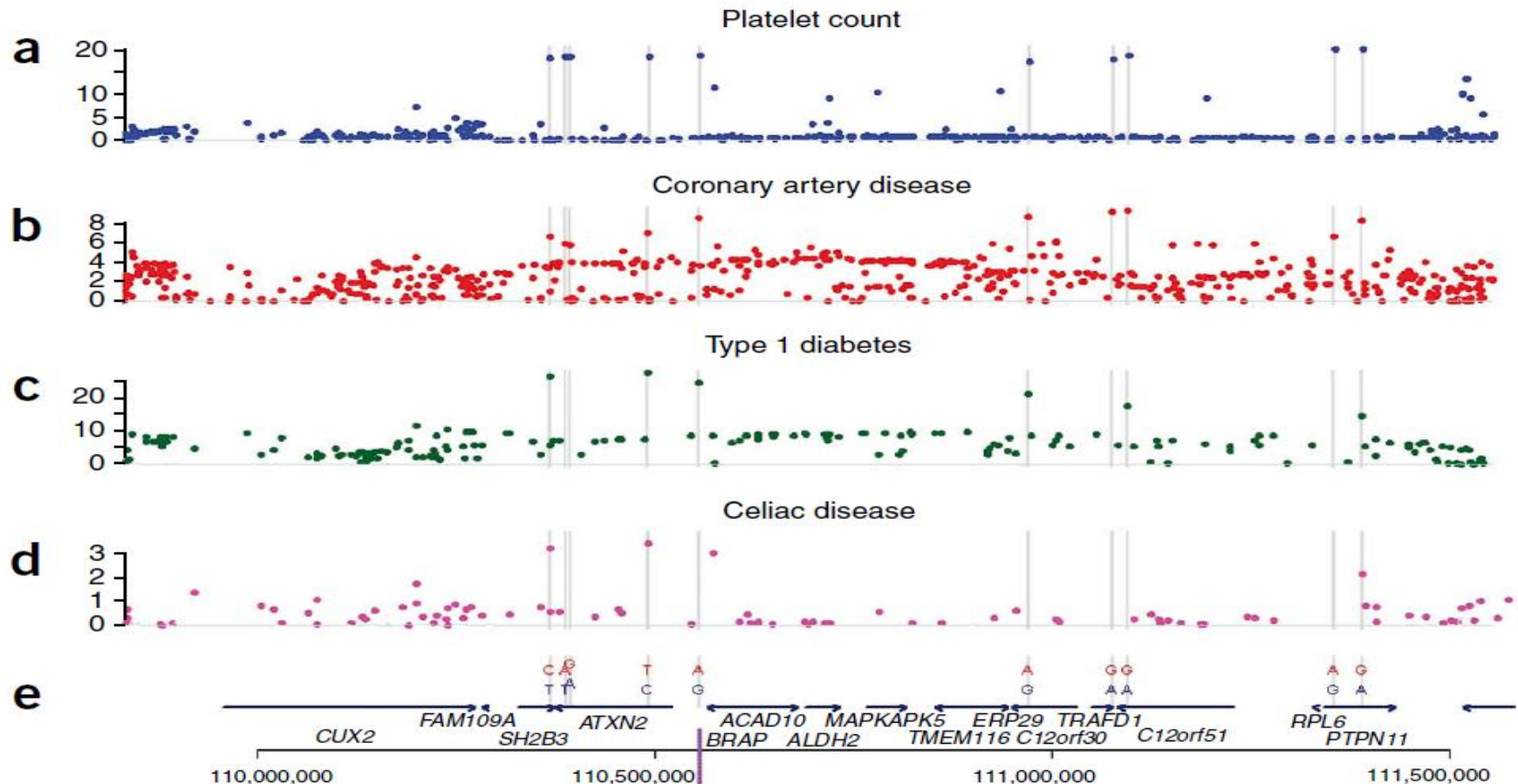
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We further identified a long-range haplotype at 12q24 associated with **coronary artery disease and myocardial infarction** in 9,479 cases and 10,527 controls.



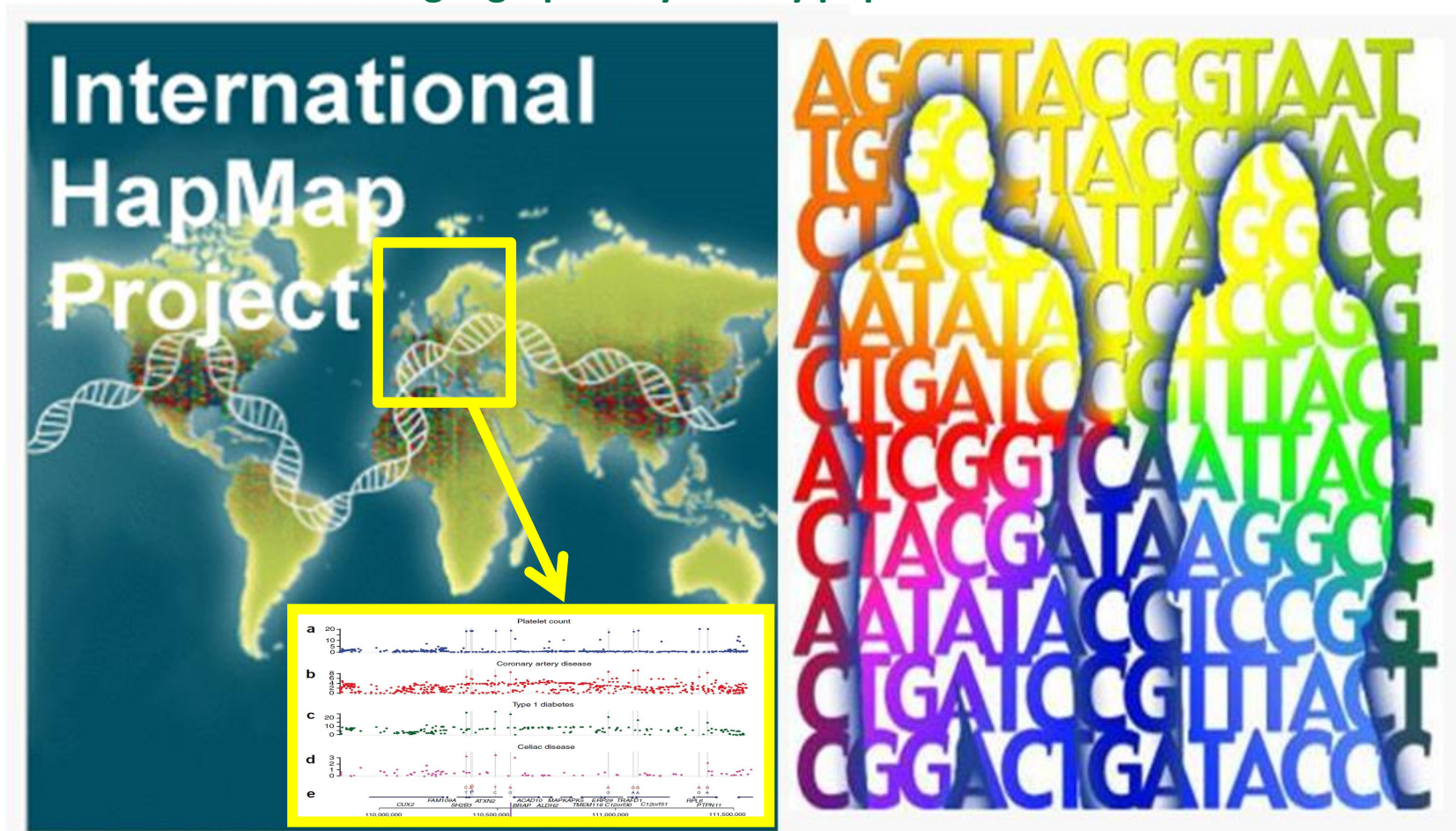
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Chromosome 12 haplotype demonstrates extensive disease pleiotropy, as it contains known risk loci for **type 1 diabetes**, **hypertension** and **celiac disease**



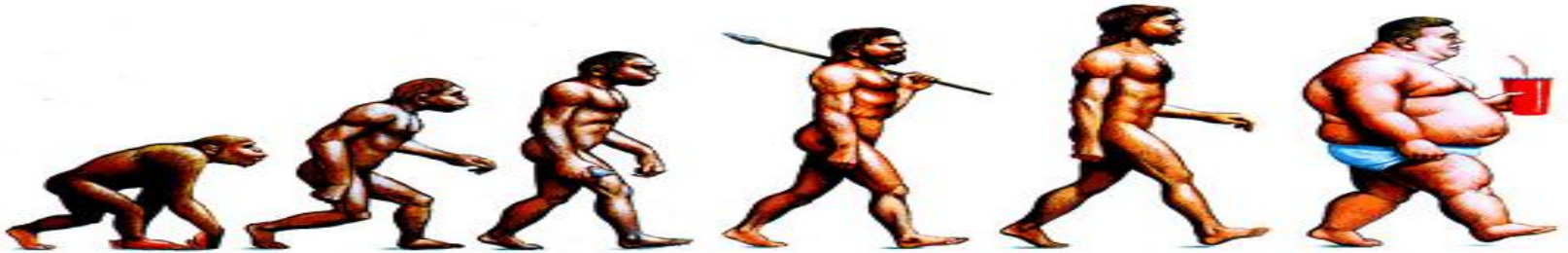
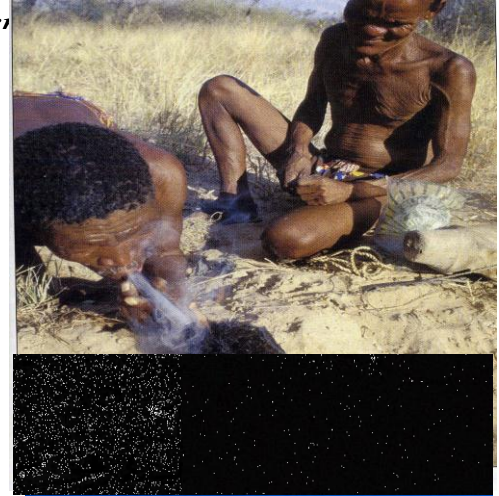
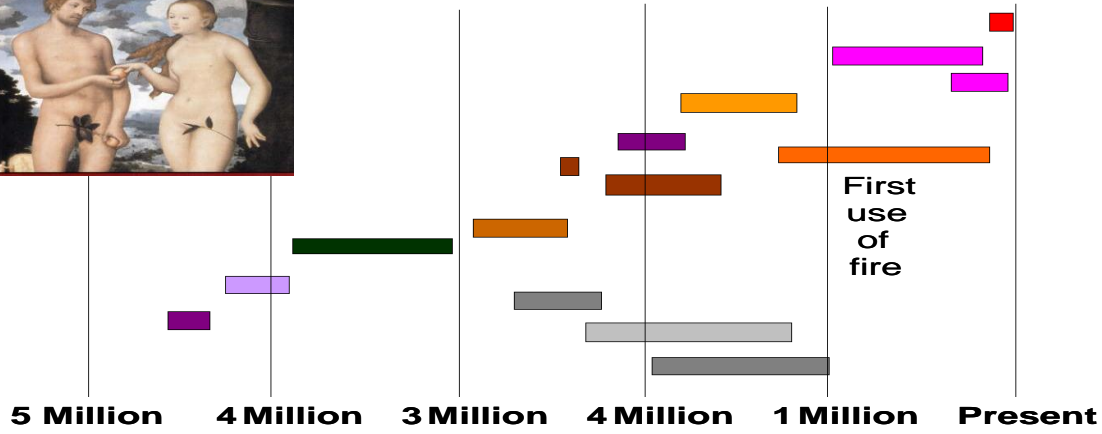
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Has been spread by a selective sweep specific to **European** and geographically nearby populations.





Homo Sapien

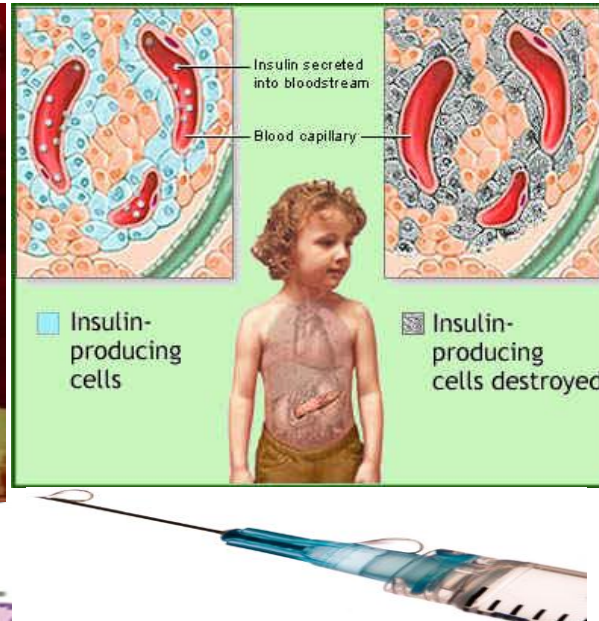


Celiacs Disease



*“in the light of evolution
cow milk and wheat gluten
appeared late”*

Type-1 Diabetes Mellitus



*“antiviral response gene called
IFIH1 improve its ability to
protect against enterovirus
infection also increase a
carrier's risk for type-1
diabetes”*

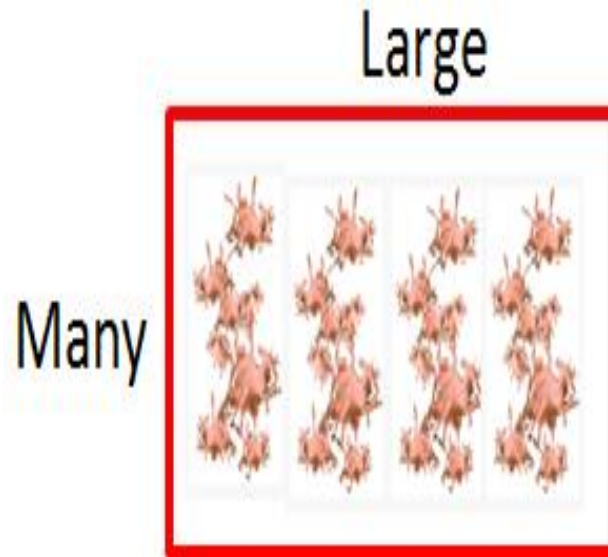
Hypertension



*The sodium hypothesis
exemplifies the ideas
and principles of
darwinian medicine*



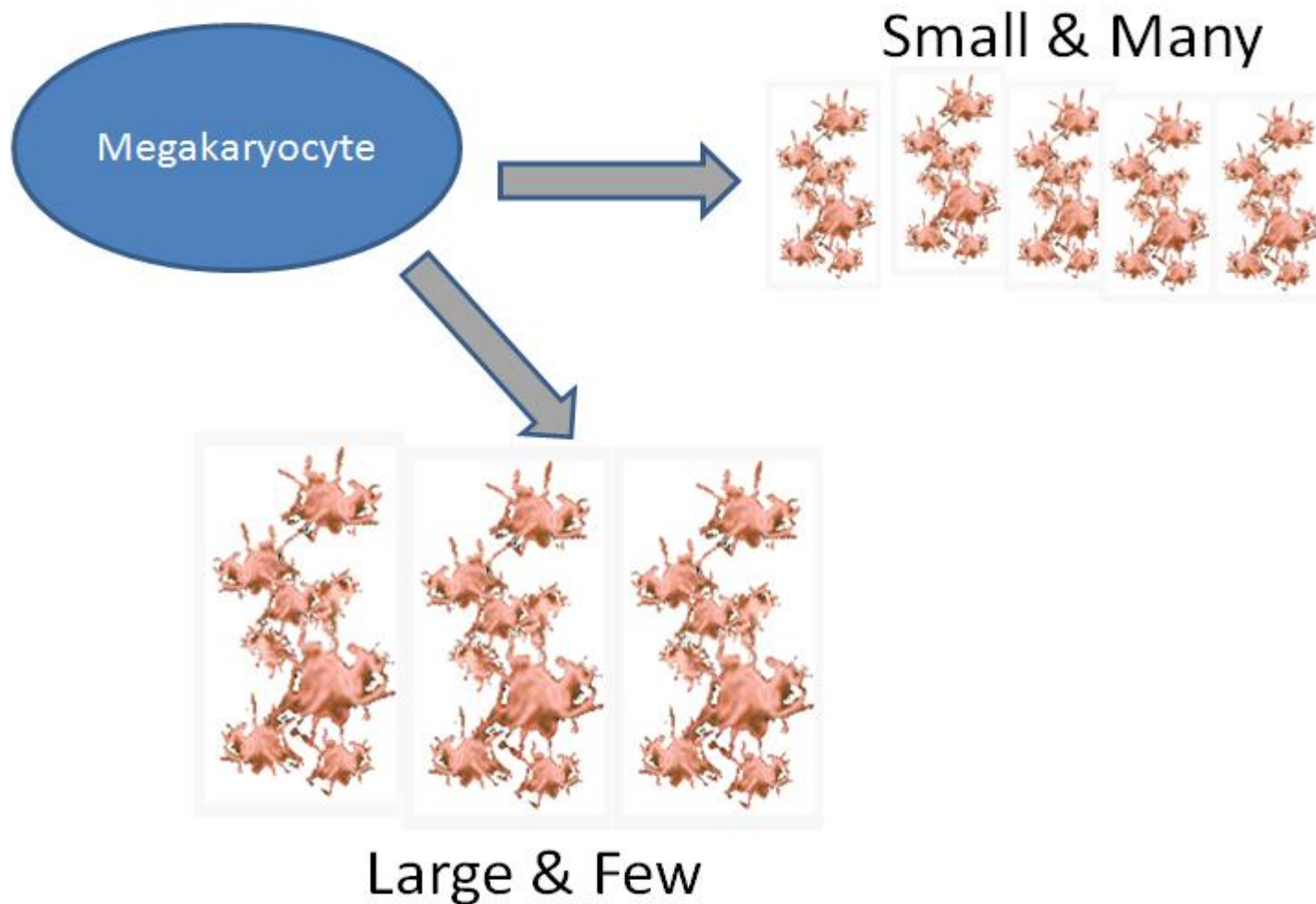
Trauma....
Hookworm

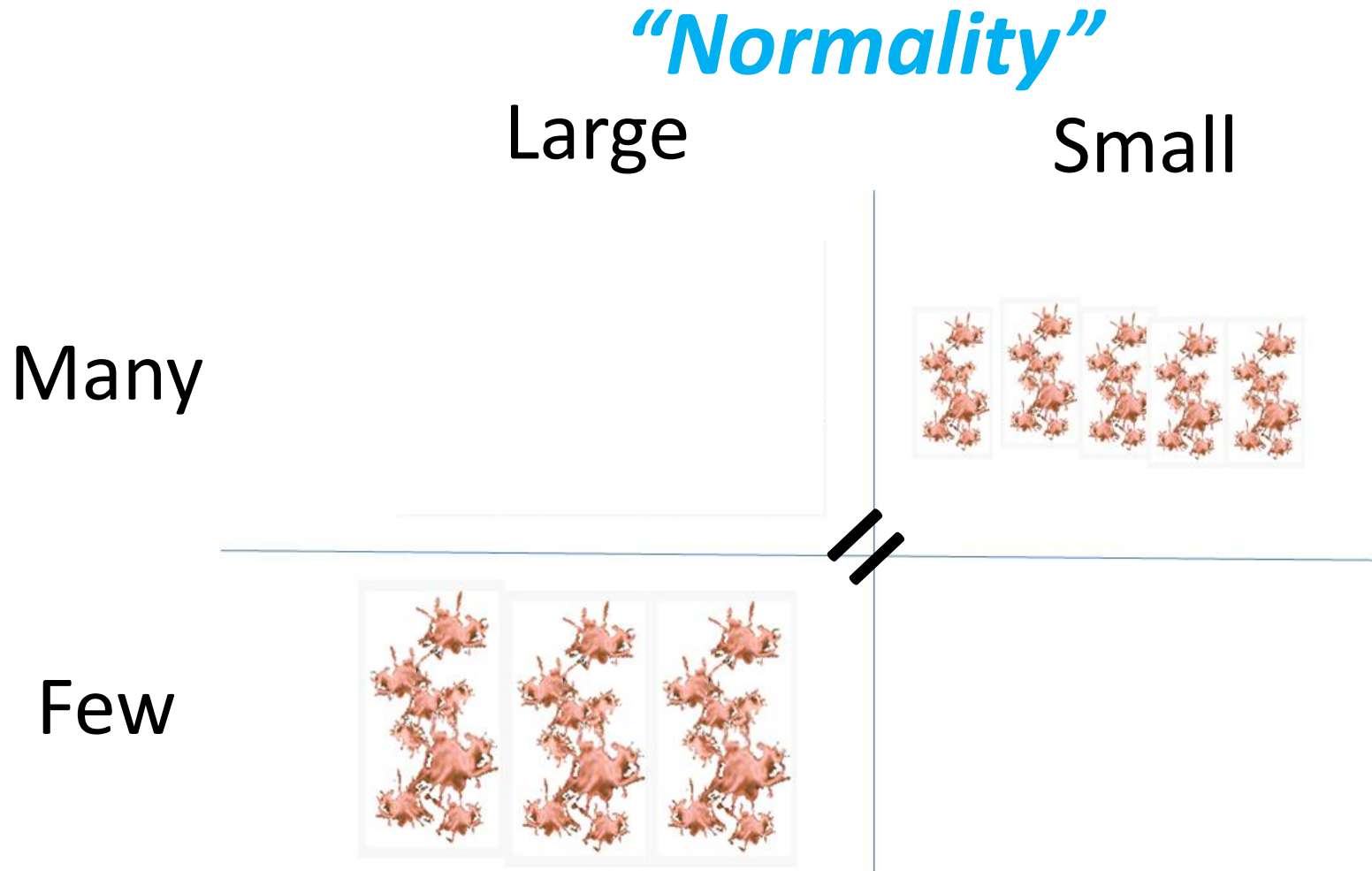


Platelets



Thrombosis

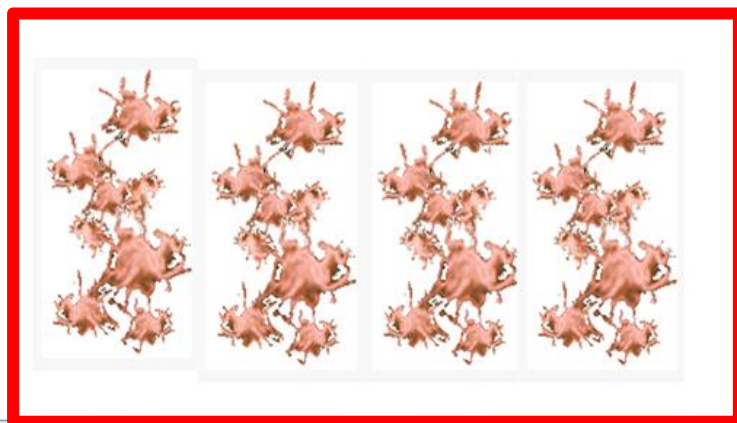




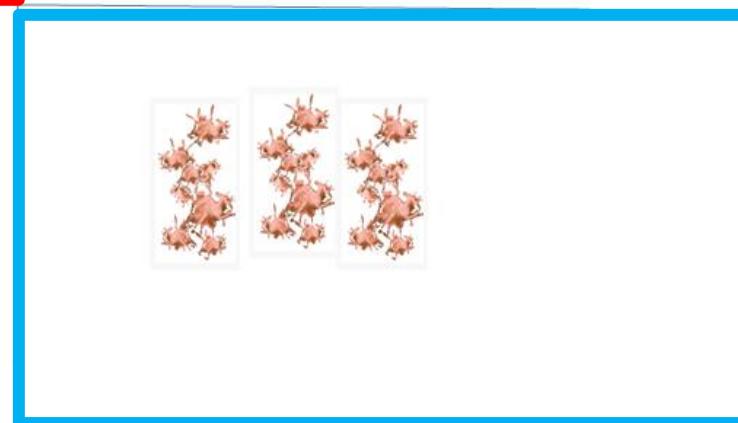
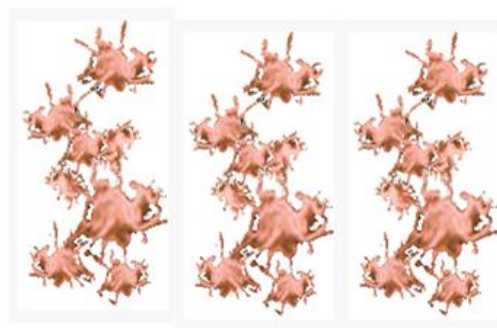
Large

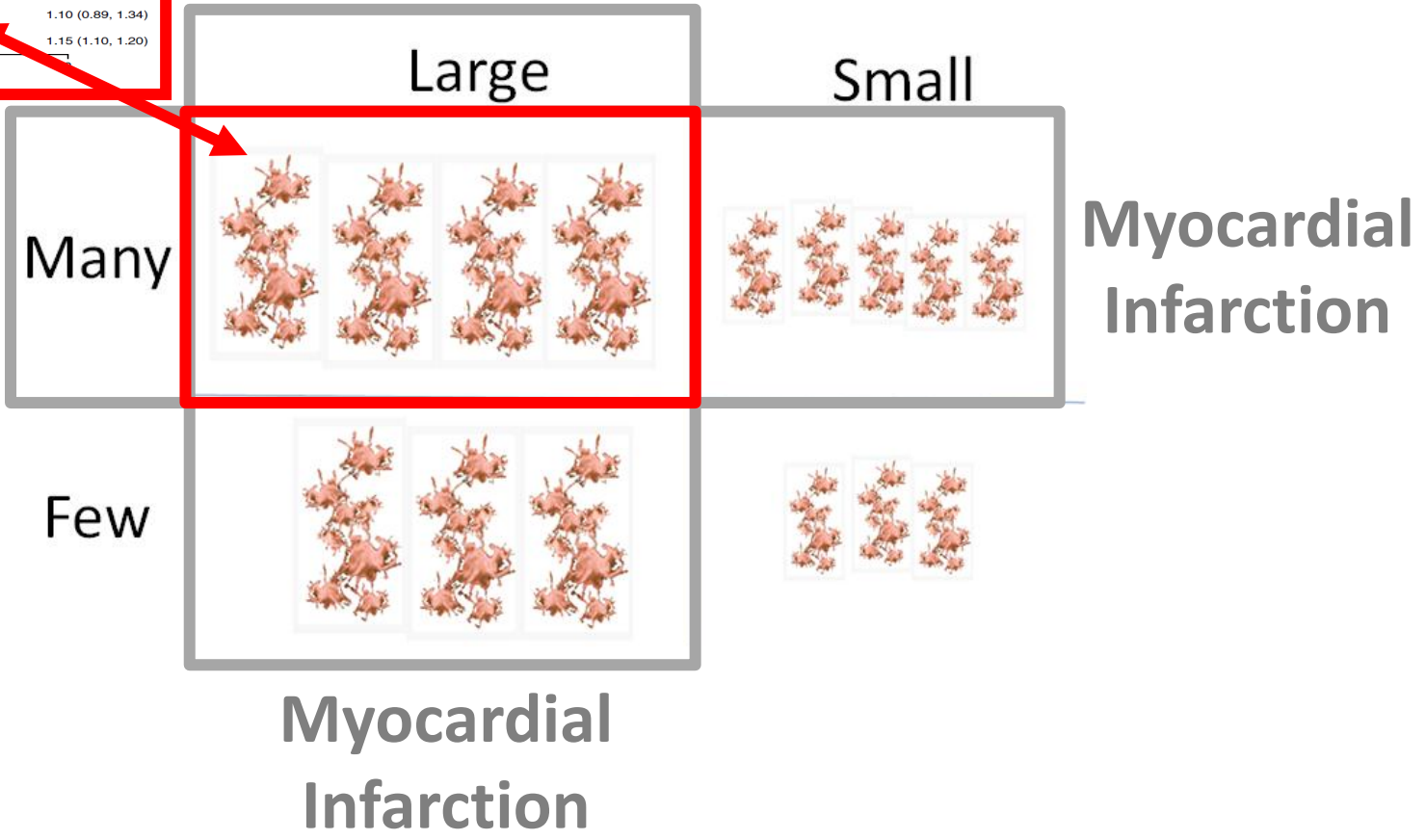
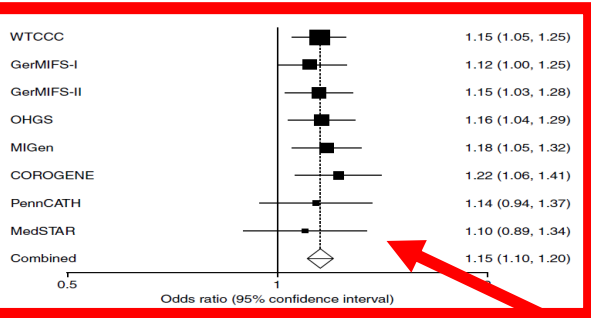
Small

Many



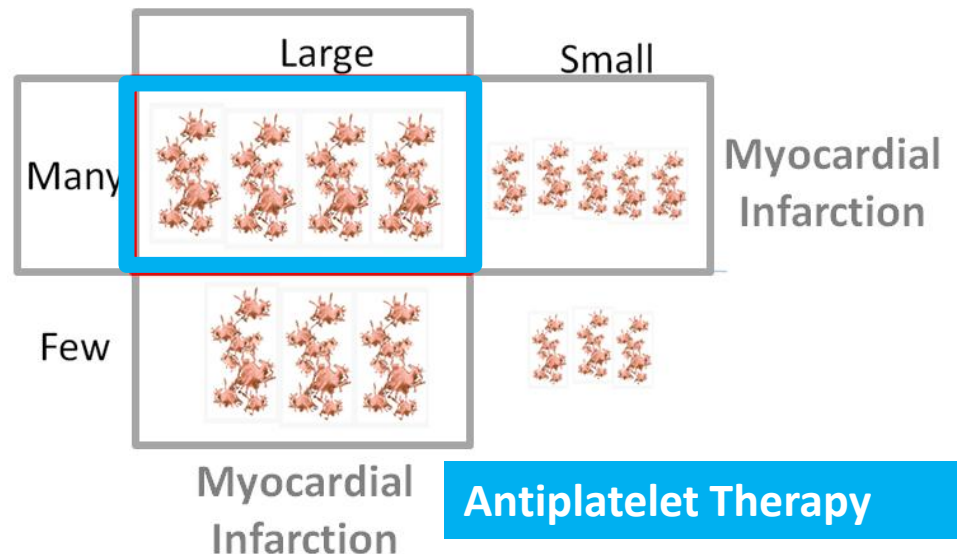
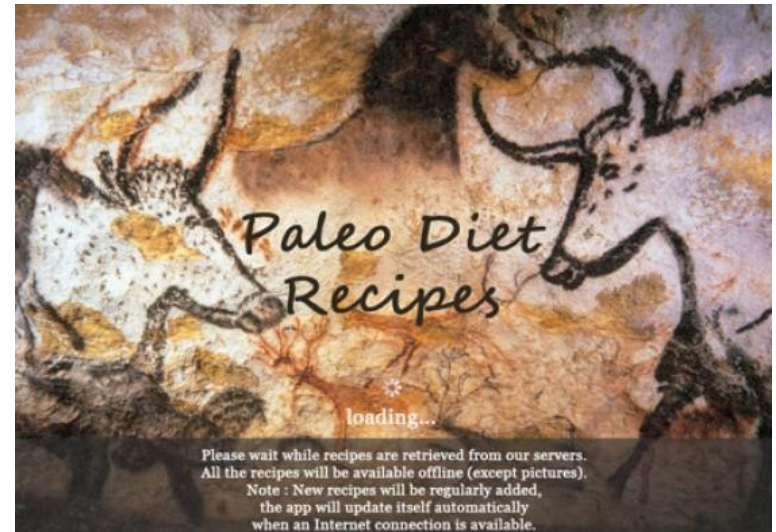
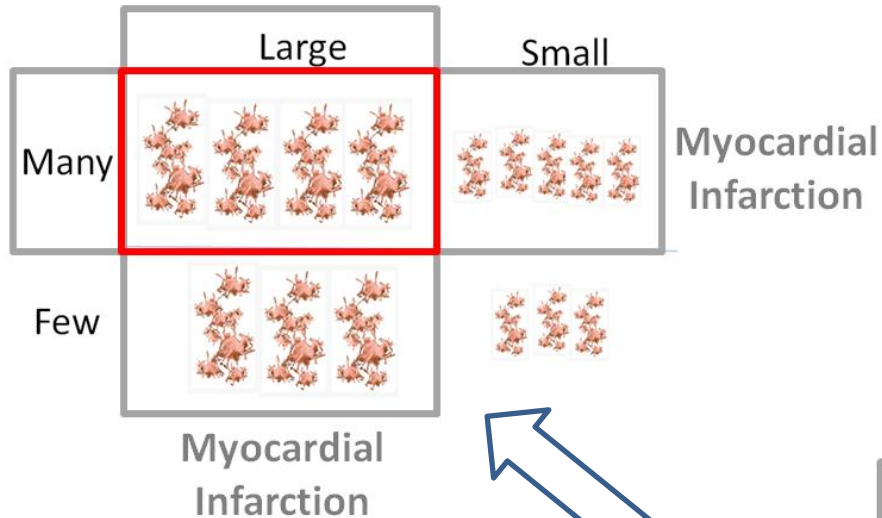
Few



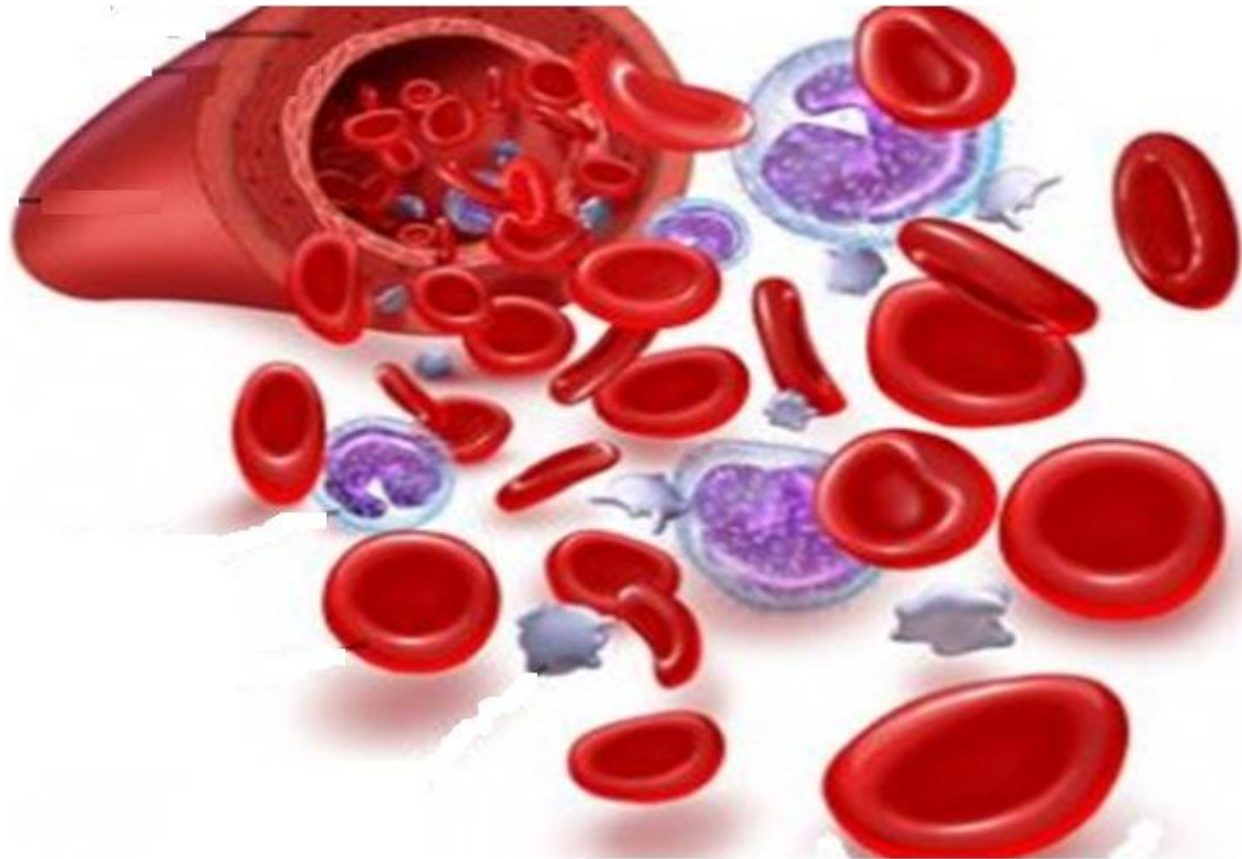


The HaemGen Consortium

Thrombotic Stimulus



A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium



blood

The genetics of normal platelet reactivity

Thomas J. Kunicki and Diane J. Nugent

Gene	Protein function	SNP*	Cytoband	Functional trait			
				PA	FA	PC	FC
<i>GP6</i>	Platelet glycoprotein VI	rs1613662	19q13.4	✓	—	✓	✓
<i>FCER1G</i>	Adapter protein for agonist receptor	rs3557	1q23.3	—	—	✓	✓
<i>PEAR1</i>	Platelet surface receptor PEAR1	rs3737224	1q23.1	—	—	✓	✓
		rs11264579		✓	✓	—	—
<i>RAF1</i>	Protein kinase	rs3729931	3p25.1	—	✓	✓	✓
<i>JAK2</i>	Protein kinase	rs10429491	9p24.1	✓	✓	—	—
<i>P2RY12</i>	Purinogenic (ADP) receptor P2Y12	rs1472122	3q25.1	✓	✓	✓	—
<i>GNAZ</i>	Adapter protein for agonist receptor	rs3788337	22q11.22	✓	—	—	—
<i>VAV3</i>	Intracellular signaling molecule	rs17229705	1p13.3	✓	✓	✓	—
<i>CD36</i>	Platelet surface receptor	rs1049654	7q21.11	—	—	✓	✓
<i>MAP2K2</i>	Protein kinase	rs350916	19p13.3	—	✓	—	—
<i>ITGA2</i>	Integrin subunit- α 2	rs41305896	5q11.2	✓	✓	—	—
<i>AKT2</i>	Protein kinase	rs41275750	19q13.2	—	—	✓	✓
<i>MAPK14</i>	Protein kinase	rs851007	6p21.31	✓	✓	✓	—
<i>MAP2K4</i>	Protein kinase	rs41307923	17p12	—	—	✓	✓
<i>ITPR1</i>	Intracellular signaling molecule	rs17786144	3p26.2	✓	✓	—	—

PA indicates P-selectin expression in response to ADP; FA, fibrinogen binding in response to ADP; PC, P-selectin expression in response to CRP-XL; and FC, fibrinogen binding in response to CRP-XL.

Data from Jones et al² with permission.

*SNP exhibiting lowest *P* value.