NIHR BioResource
Rare Diseases

BRIDGE

Genomics
england

Rare Diseases and the NHS 100,000 Genomes Project

Willem H Ouwehand MD PhD FMedSci

Professor of Experimental Haematology

Director NIHR BioResource – Rare Diseases

IRDiRC
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DISEASES
RESEARCH
CONSORTIUM

wellcome trust
sanger
institute

NHS
Blood and Transplant

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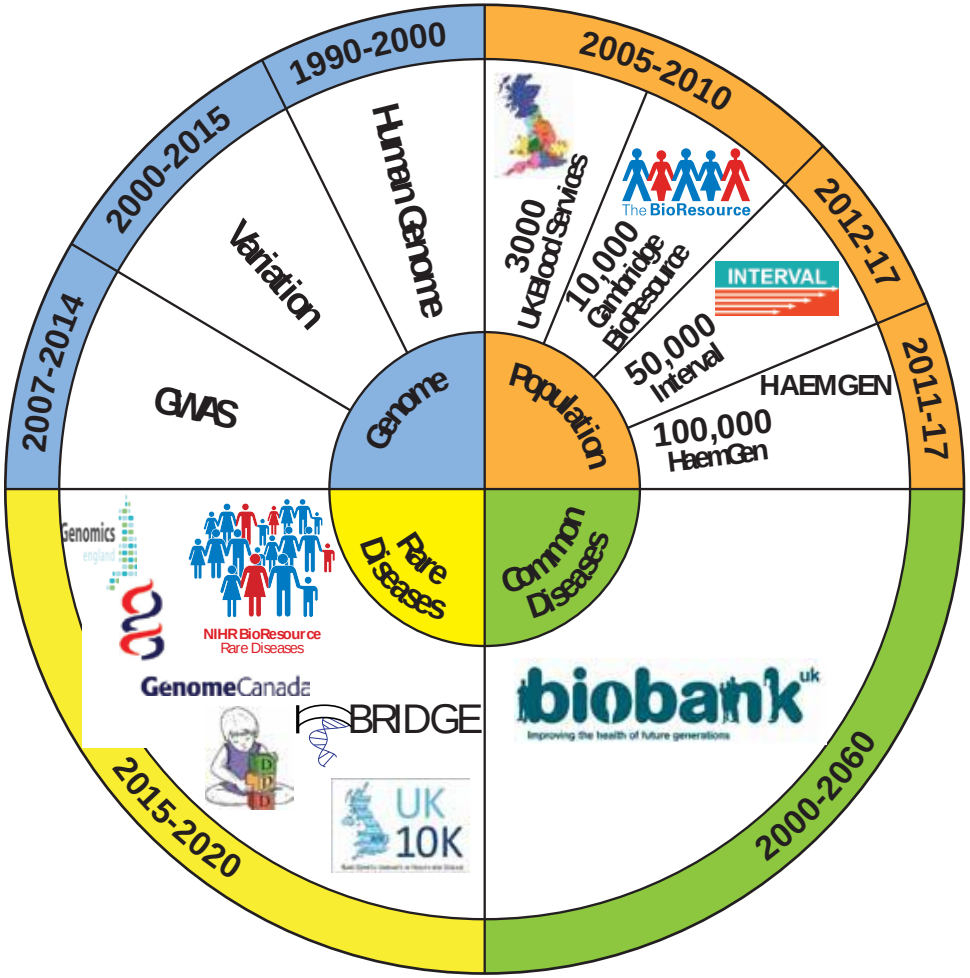
1990-2000
2000-2015
2007-2014
2005-2010
2012-17
2011-17
2015-2020
2000-2060
Human Genome
Variation
GWAS
Genome
3000 UK Blood Services
10,000 Cambridge BioResource
The BioResource
INTERVAL
50,000 Interval
HAEMGEN
100,000 HaemGen
Population
Rare Diseases
Common Diseases
Genomics
NIHR BioResource
Rare Diseases
GenomeCanada
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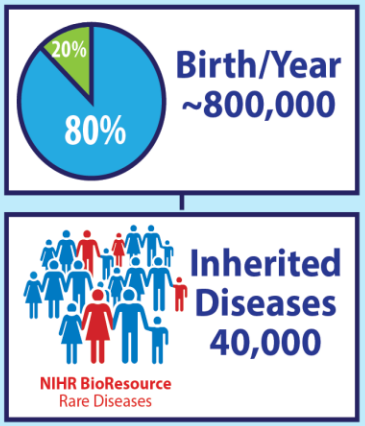
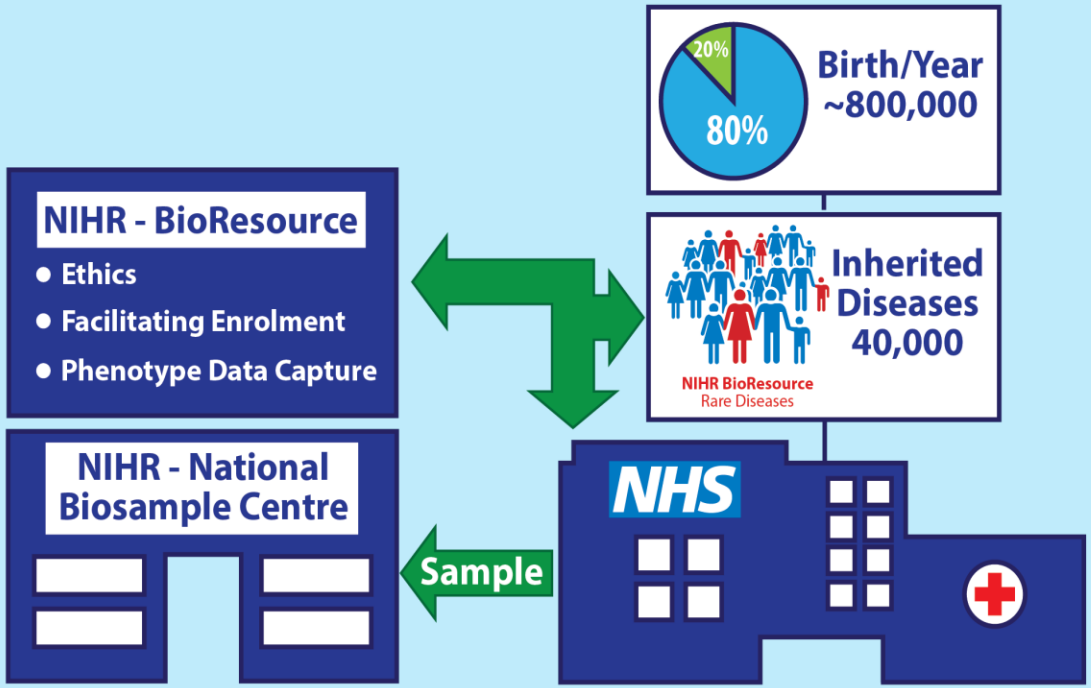
Improving the health of future generations

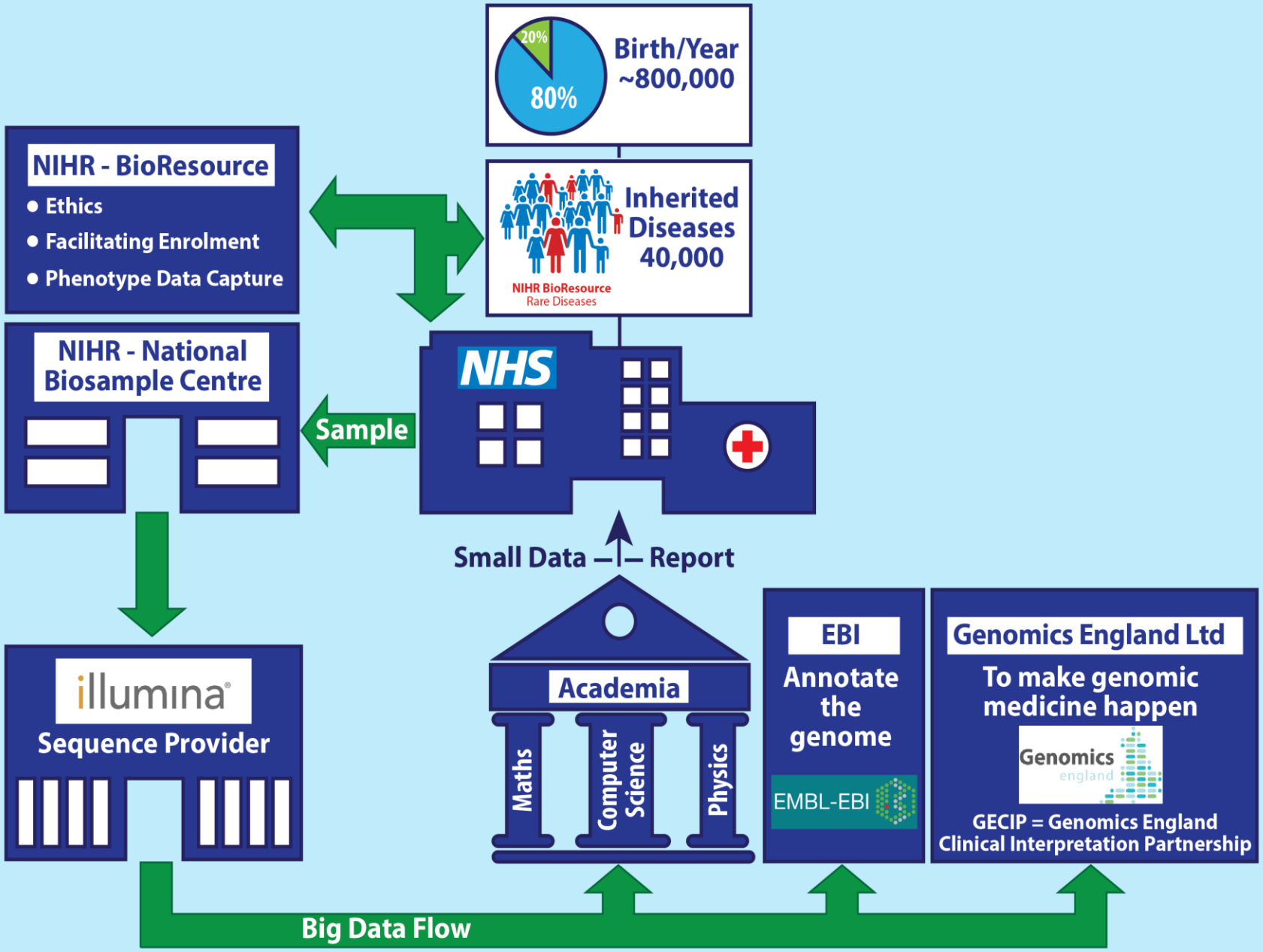
The NHS 100,000 Genome Project



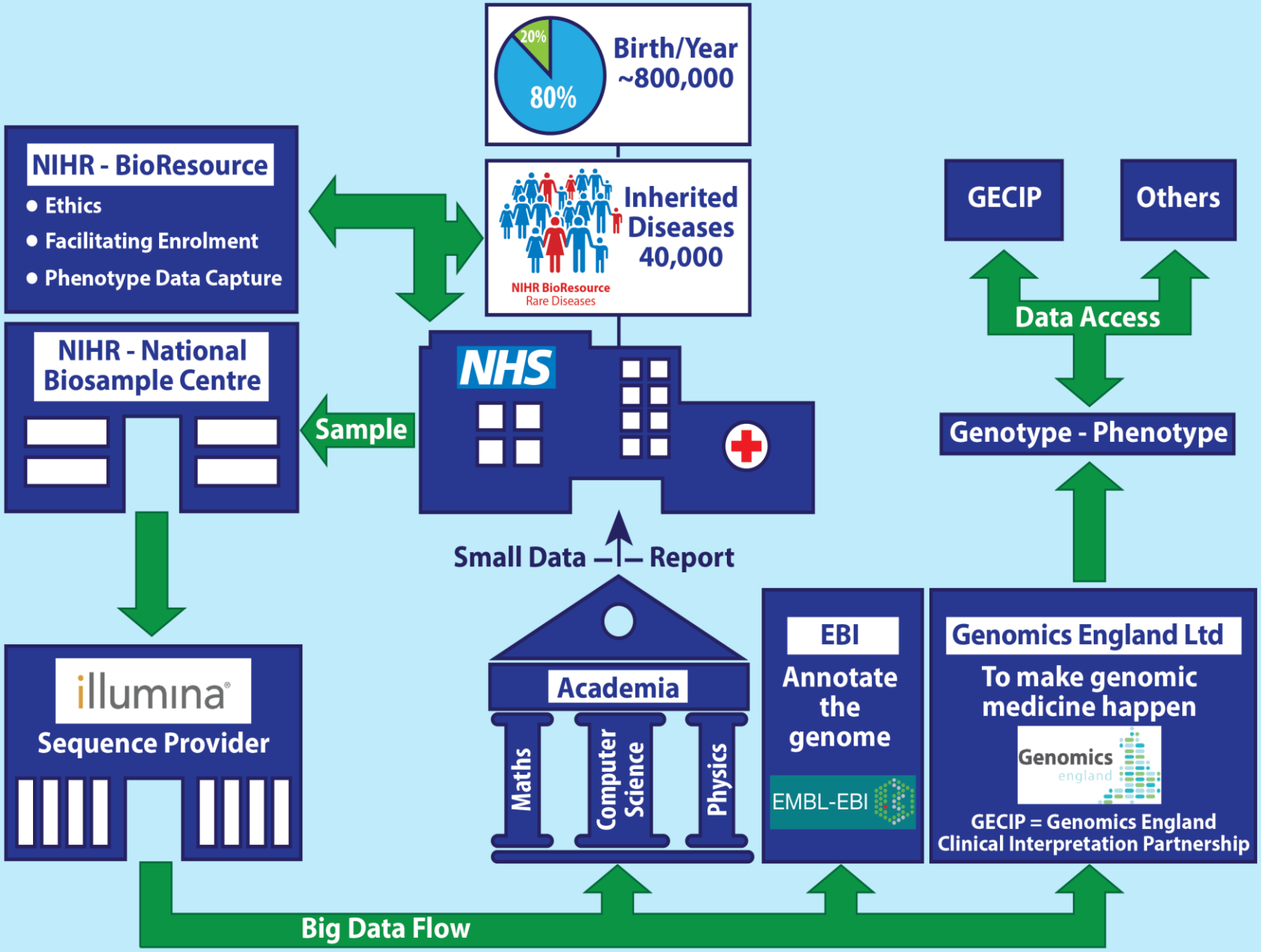
The NHS 100,000 Genome Project



The NHS 100,000 Genome Project



The NHS 100,000 Genome Project



The NIHR National Biosample Centre

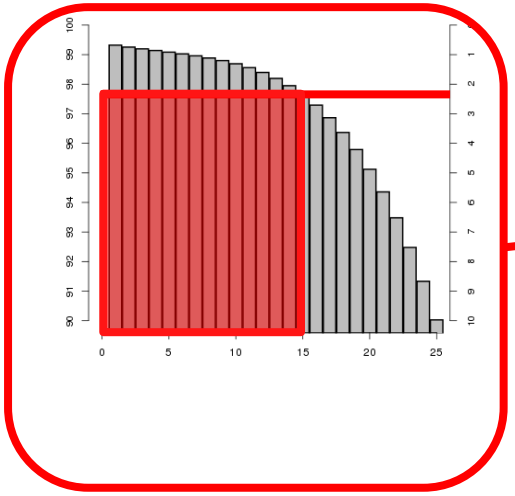
a highly automated and scalable sample handling, testing and archiving facility

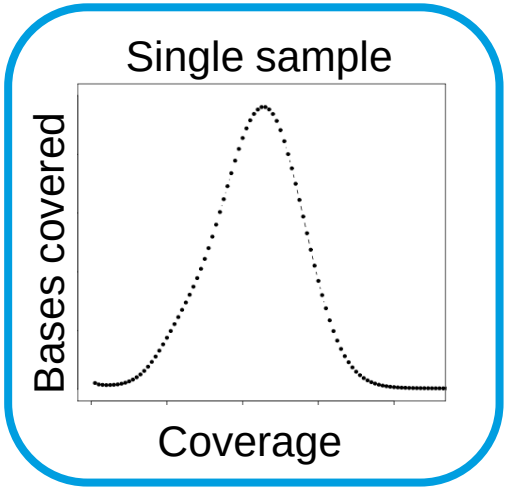
Whole Genome Sequencing (WGS) results

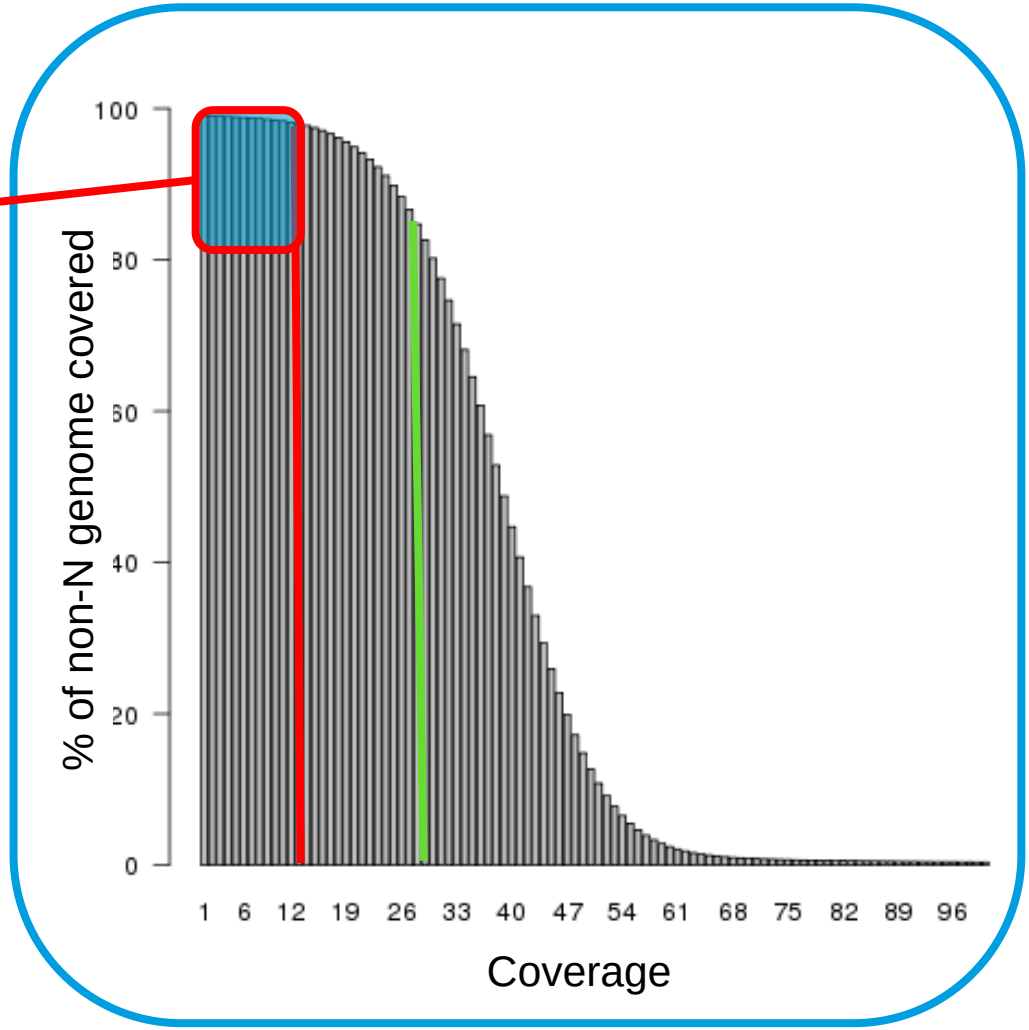
mean minimum percentage of genome covered

~2% covered <15x

1,789 samples



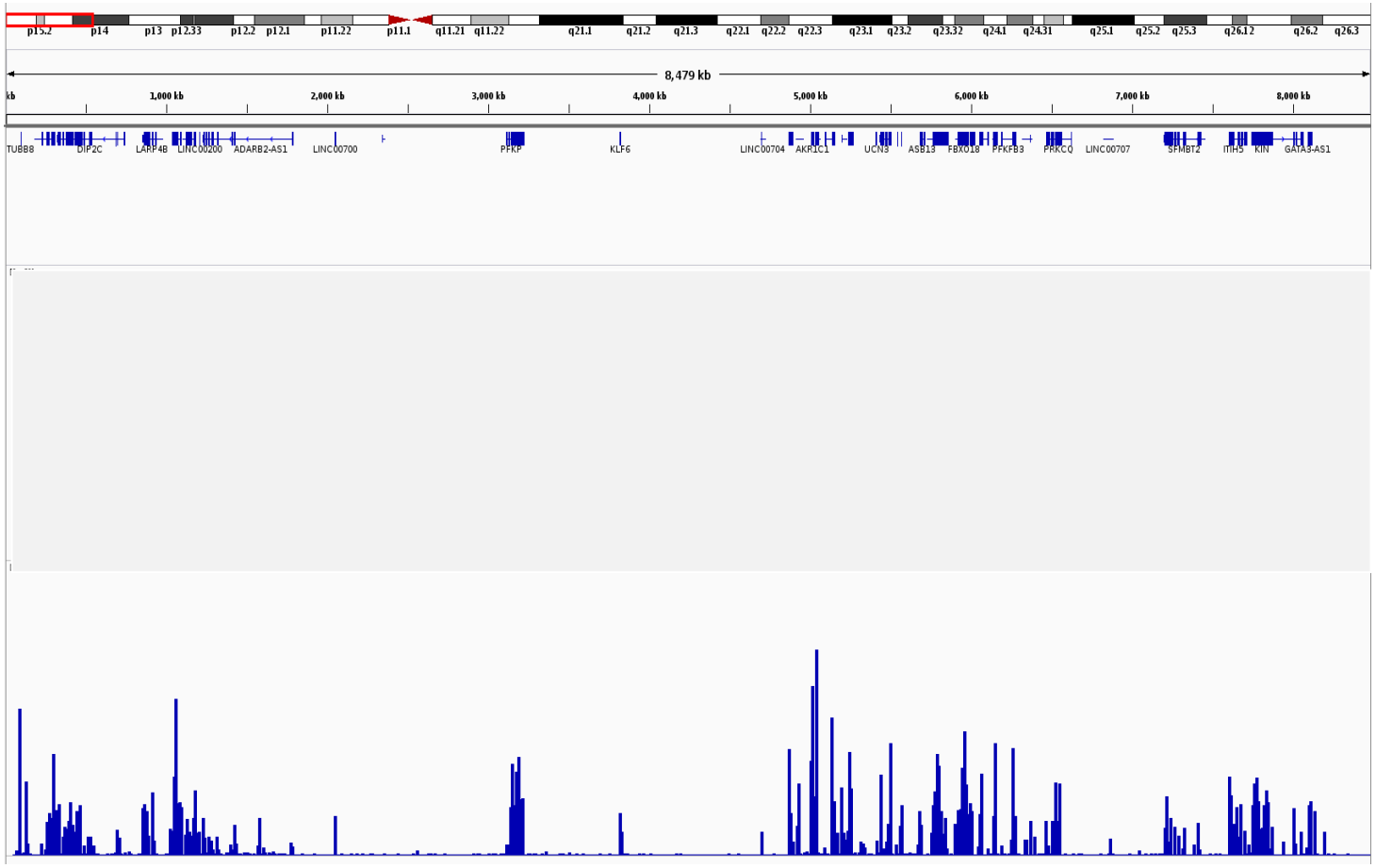




Whole Genome (WGS) vs Whole Exome Sequencing (WES)

first 10 Mb of chromosome 10

Coverage



WES

Whole Genome (WGS) vs Whole Exome Sequencing (WES)

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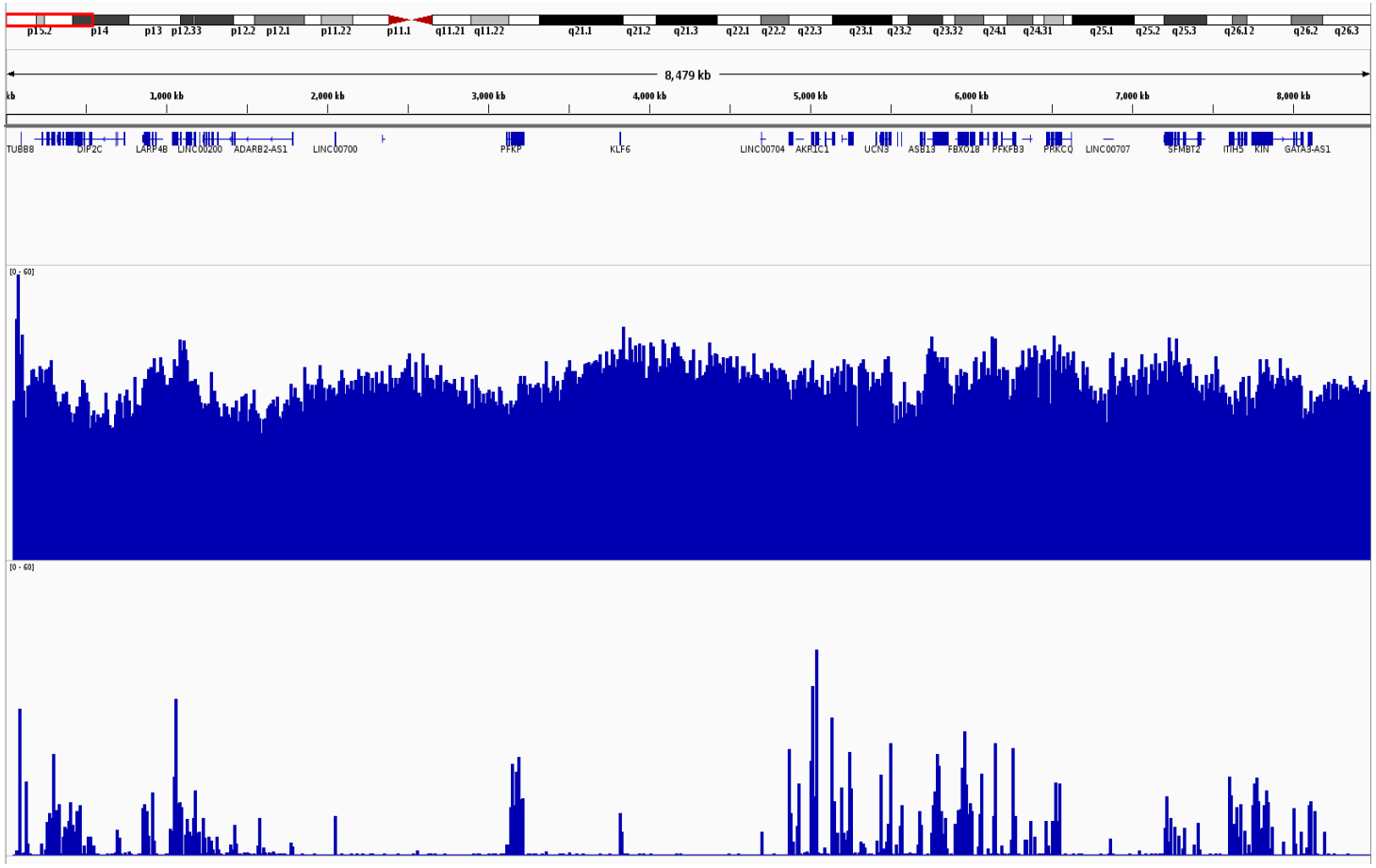
Coverage



WGS

WES

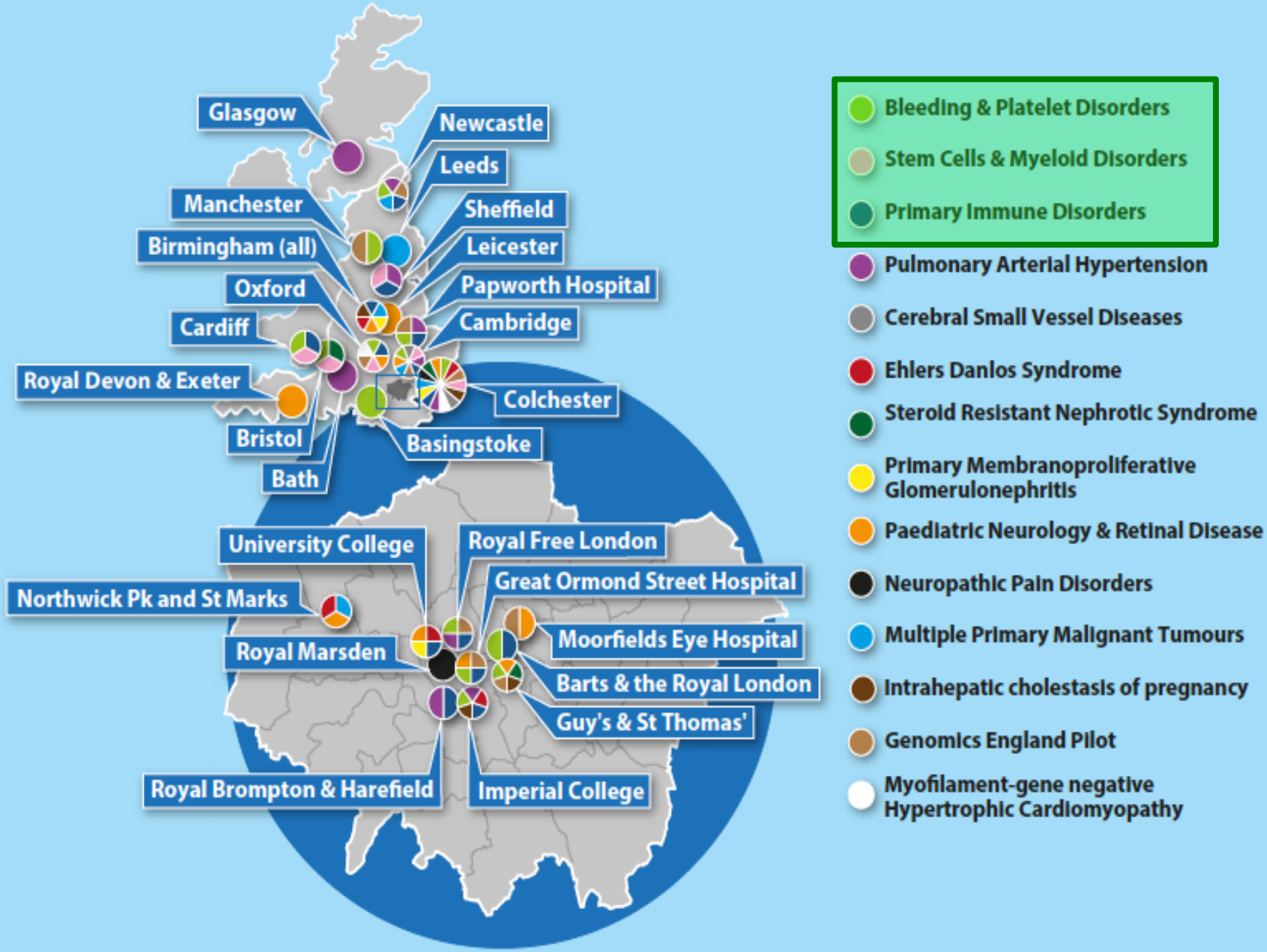
WES vs WGS

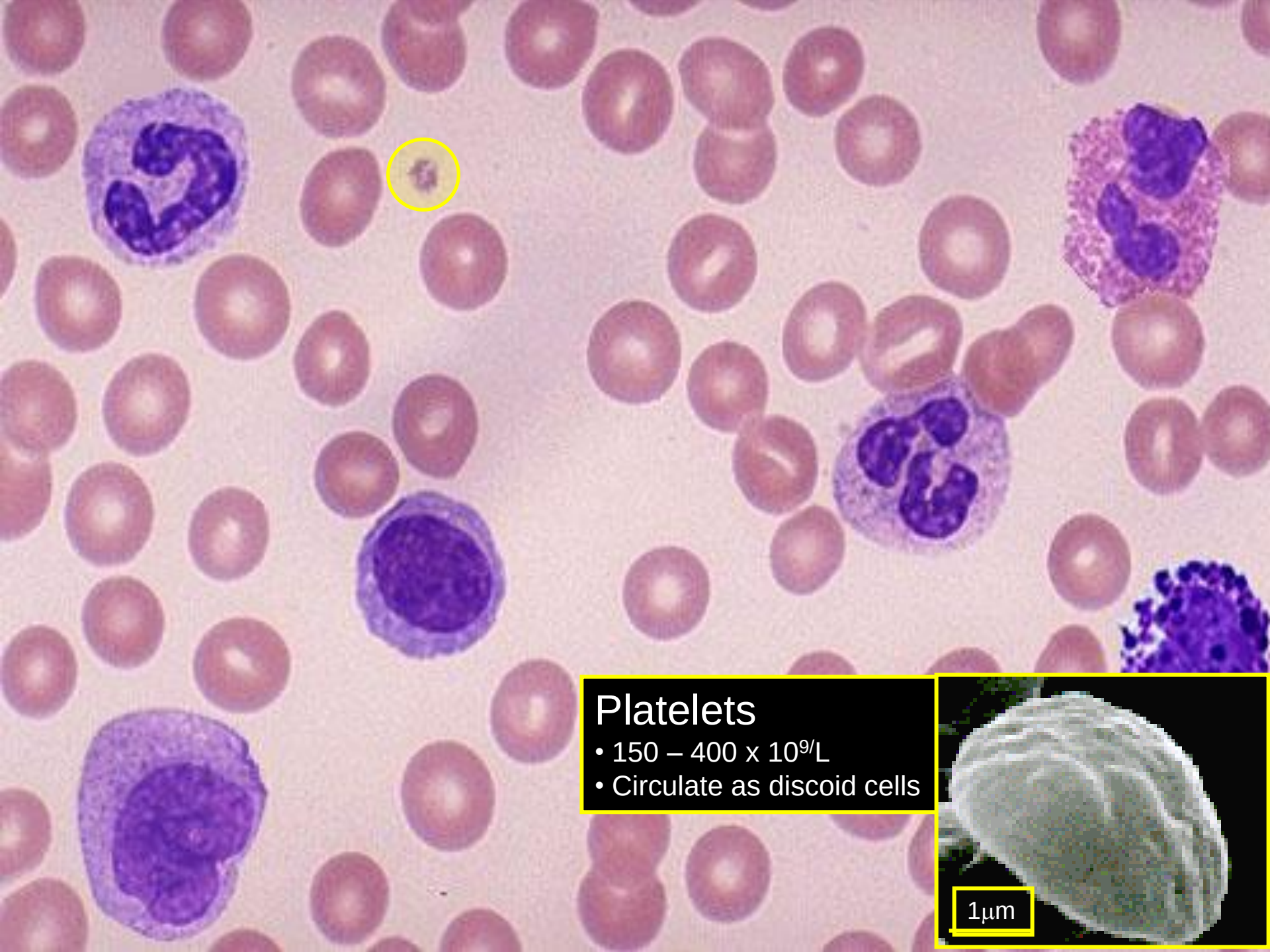
comparison of results in Rare Diseases pilot

Genotyping Method	Number of of Samples	All variants (in M)	Rare coding variants <1:1000 *	% increase in sensitivity
WES	737	3.3	129,394	100
WGS	736	45.3	176,592	136

* Calculated over 64 Mb of coding space

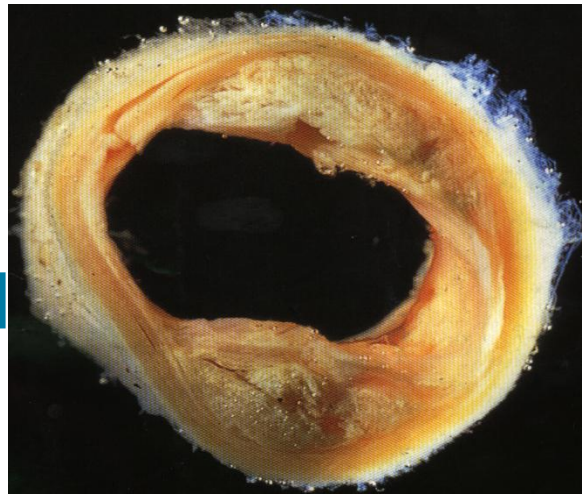
Biomedical Research Centres/Units & NHS Foundation Trusts Supporting the NIHR BioResource – Rare Diseases

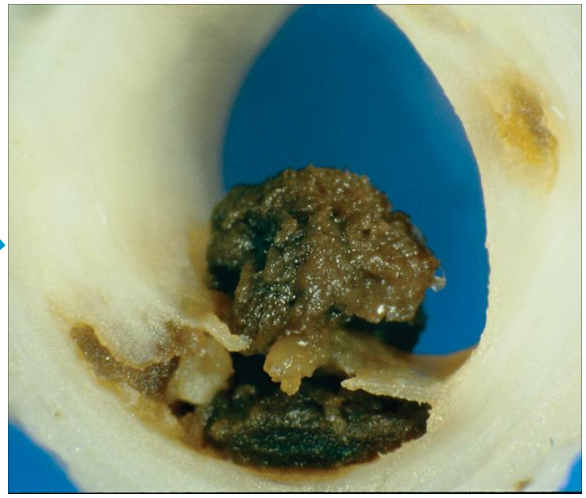


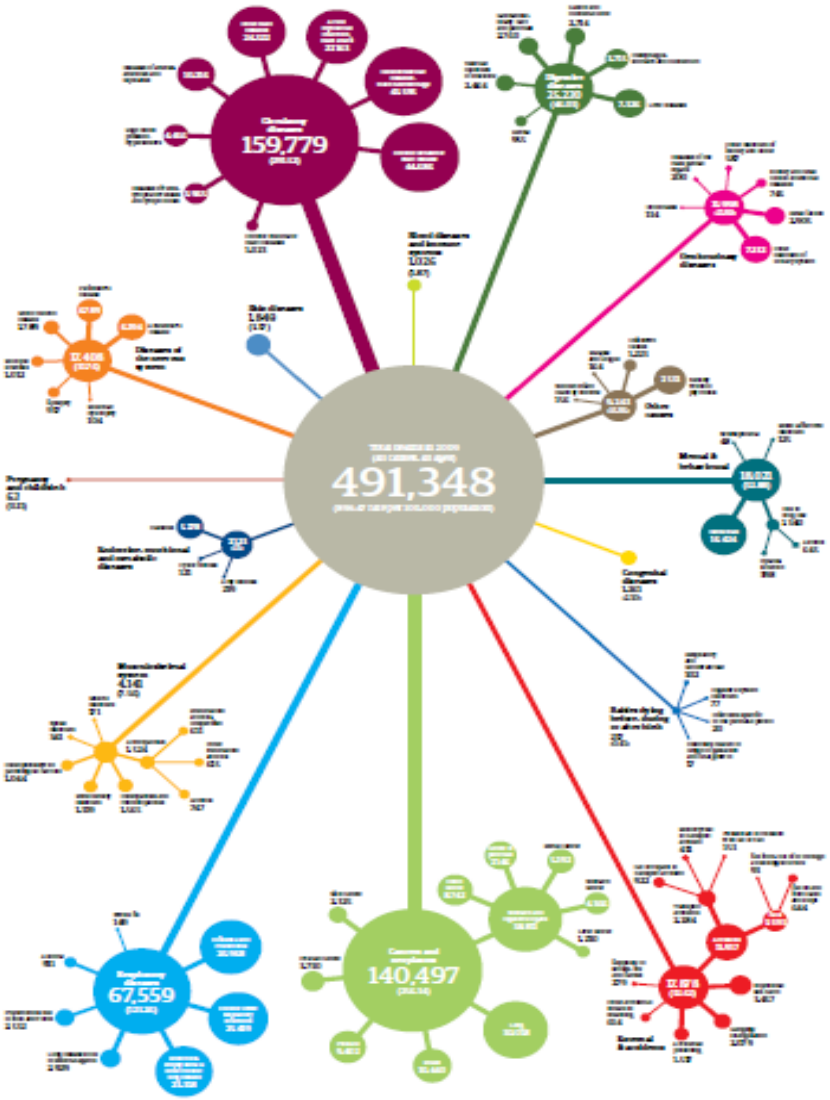

Platelets
• 150 – 400 x 10⁹/L
• Circulate as discoid cells
1μm

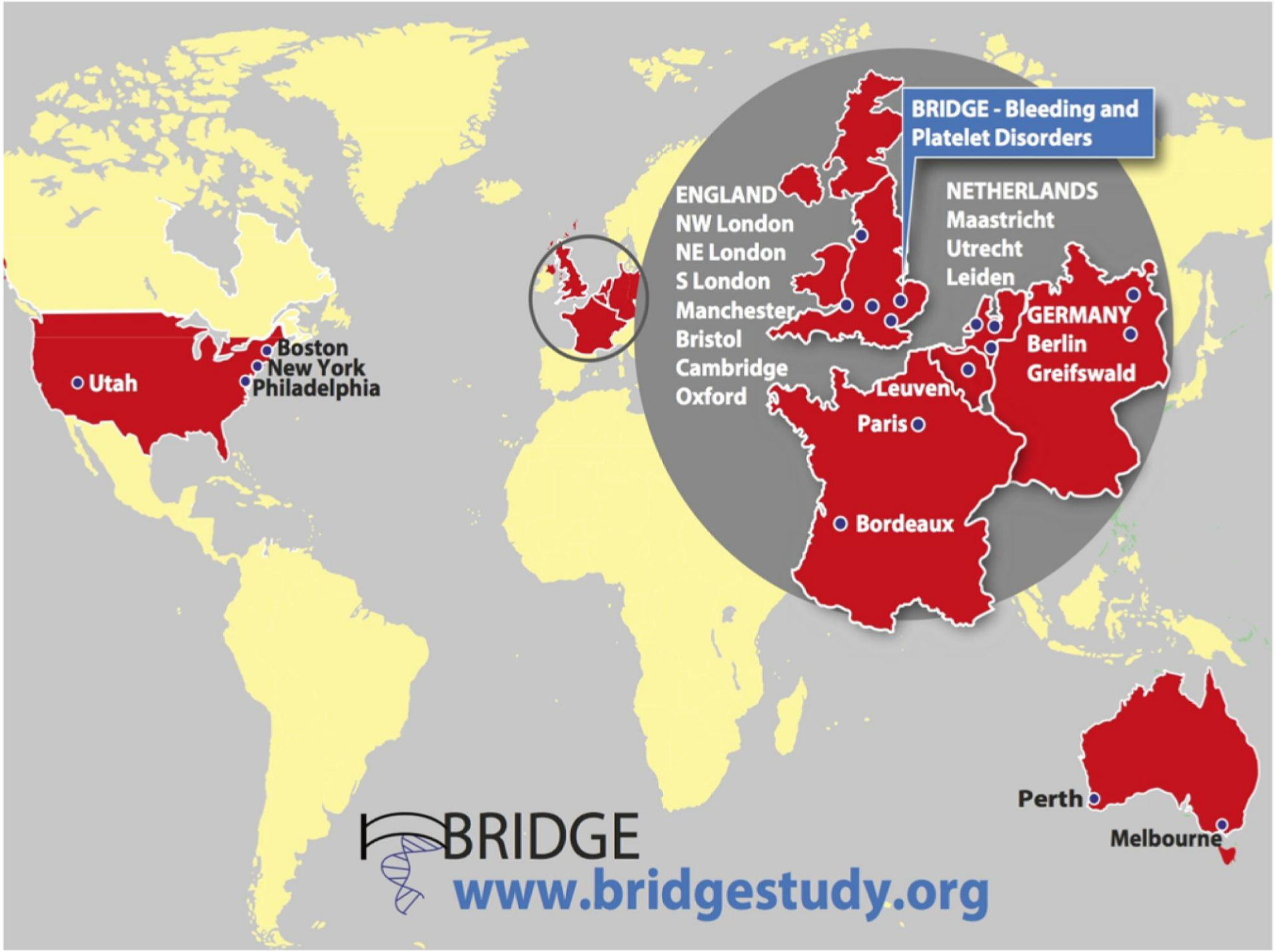
Imbalance between damage and repair

is the Number 1 killer in Western society








BRIDGE - Bleeding and Platelet Disorders
ENGLAND
NW London
NE London
S London
Manchester
Bristol
Cambridge
Oxford
NETHERLANDS
Maastricht
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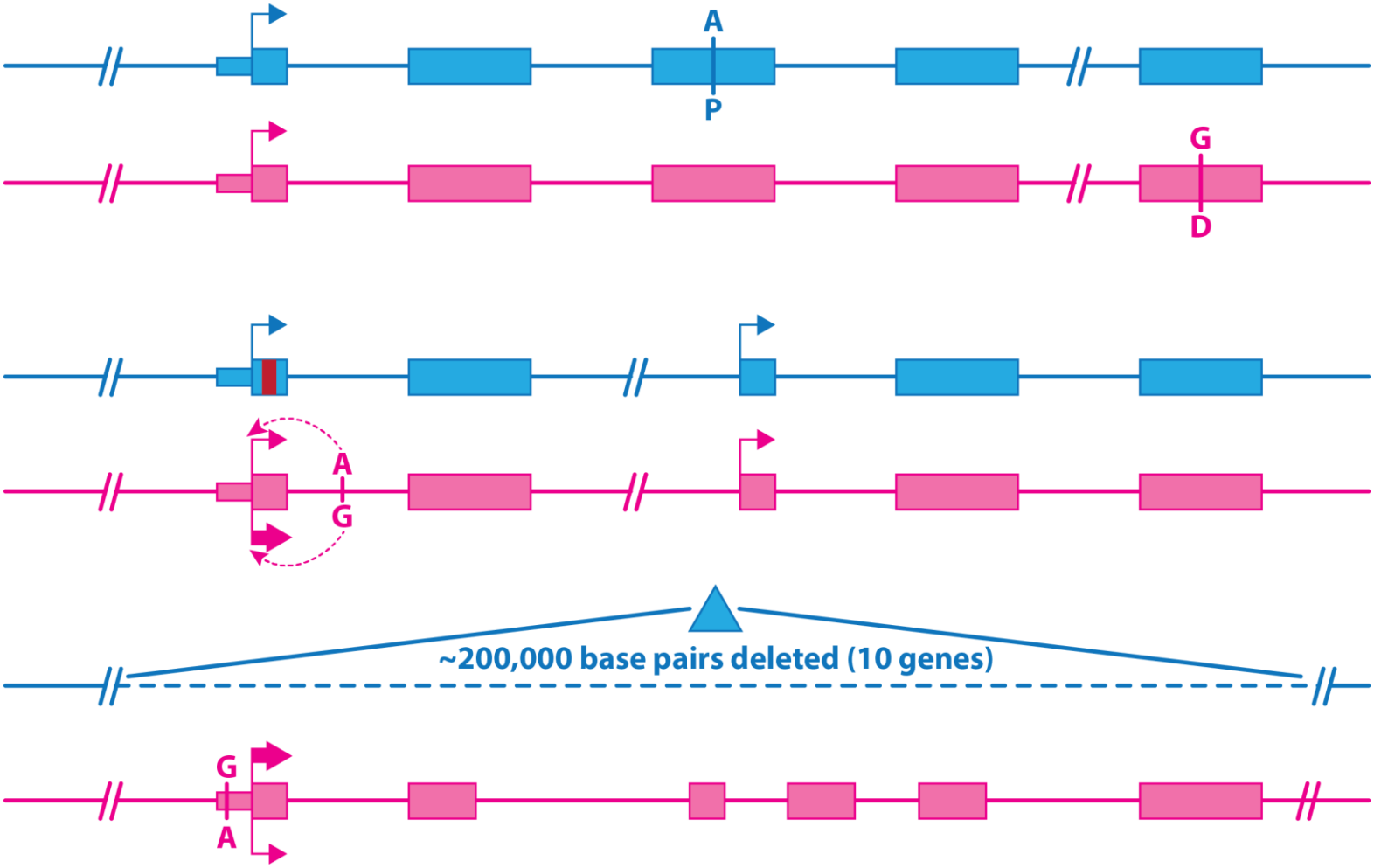
Three gene discovery stories

with three new messages, one about biology and two about genetic architecture



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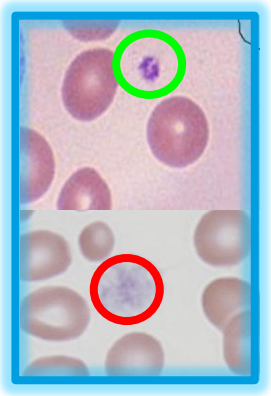
NIHR BioResource
Rare Diseases

A mutation from both parents

Grey Platelets &
defective alpha granules
NBEAL2
Albers, *Nat Genet* 2011

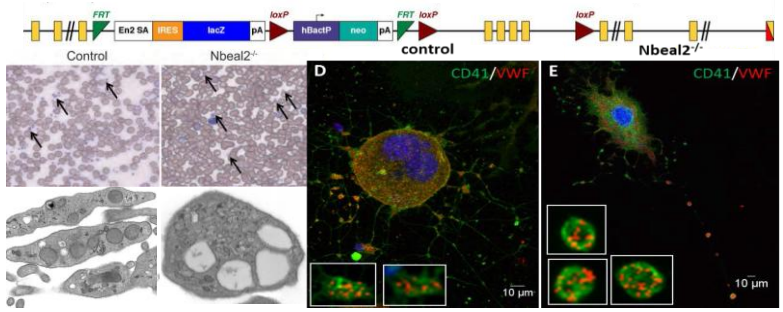


- Known **since 1970**
- **~50 cases** worldwide
- **Moderate** bleeding
- **Large and low number** of platelets
- **Absence of α-granules** in platelets

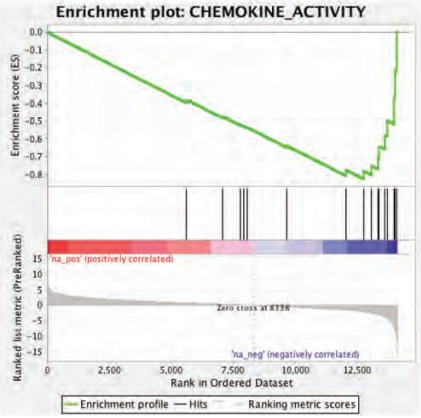
Studies in Grey Platelet Syndrome (GPS) mice

shows roles of platelets outside their classic territory of blood clot formation

Faithful phenocopy



Scarring of the blood stem cell niche and a pro-inflammatory state



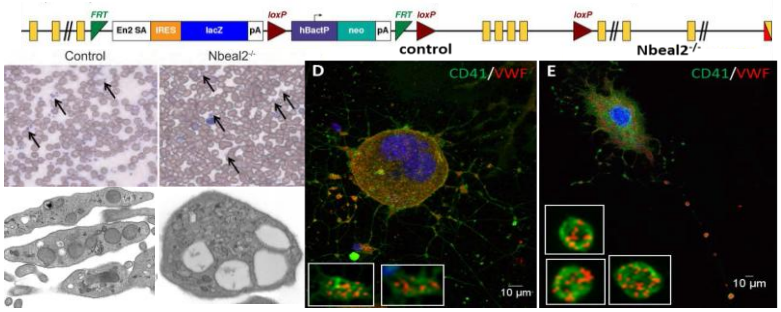
Genes contributing to the enrichment	
Gene Symbol	Running ES
Ccl27	-0.7813
Ccl7	-0.7501
Cklf	-0.7060
Cxcl10	-0.6428
Cxcl1	-0.5790
Cxcl2	-0.4973
Cxcl16	-0.3675
Ccl3	-0.2109
Ccl4	0.0016

Guerrero *et al. Blood 2014*

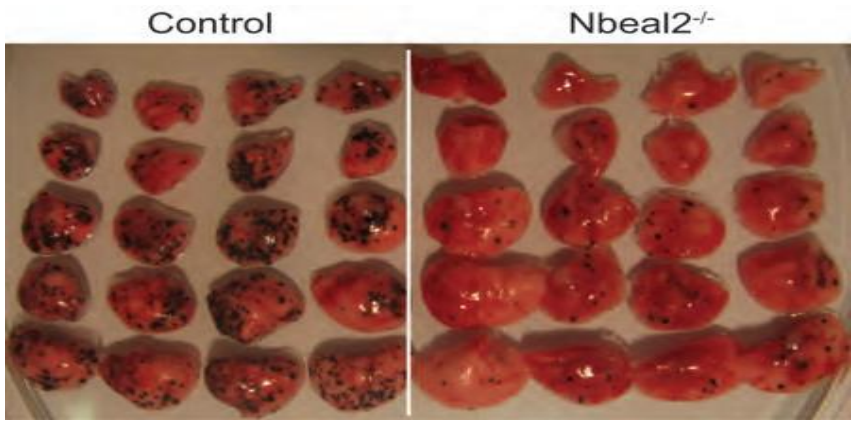
Studies in Grey Platelet Syndrome (GPS) mice

shows roles of platelets outside their classic territory of blood clot formation

Faithful phenocopy



No metastasis of melanoma cells to the lungs



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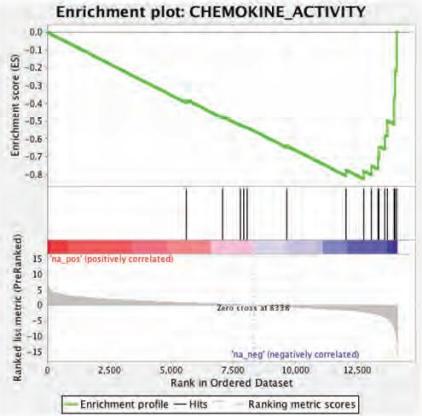

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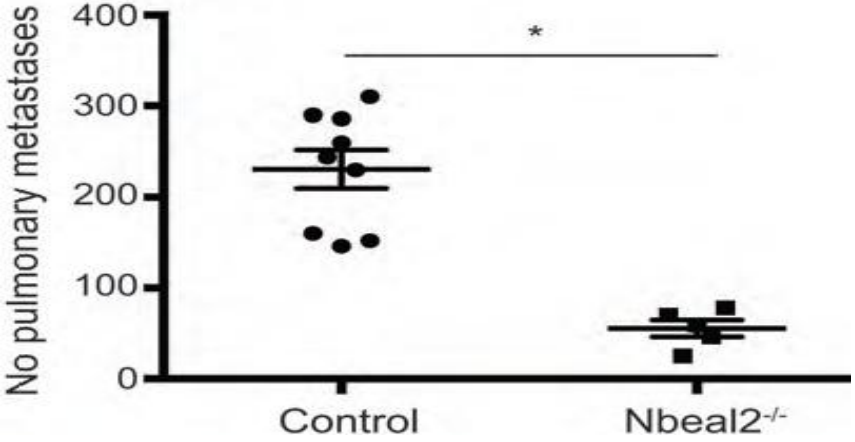
Cxcl16	-0.3675
Ccl3	-0.2109
Ccl4	0.0016

Lack of α-granules has the most profound effect ever observed in this model



Guerrero *et al. Blood 2014*

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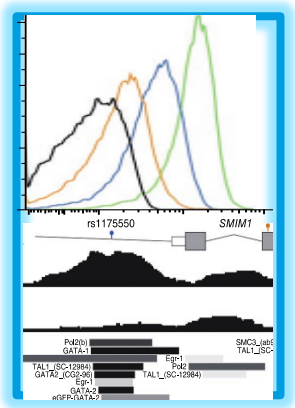
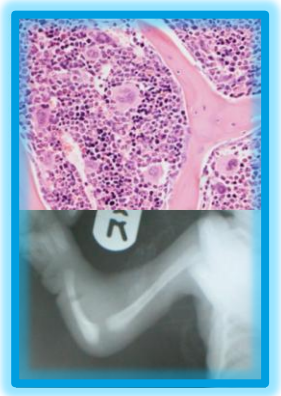
Rare Diseases

A deletion from one parent & not-so-rare regulatory SNP from the other parent

VEL group &
new genetic mechanism
SMIM1
Cvejic, *Nat Genet* 2013

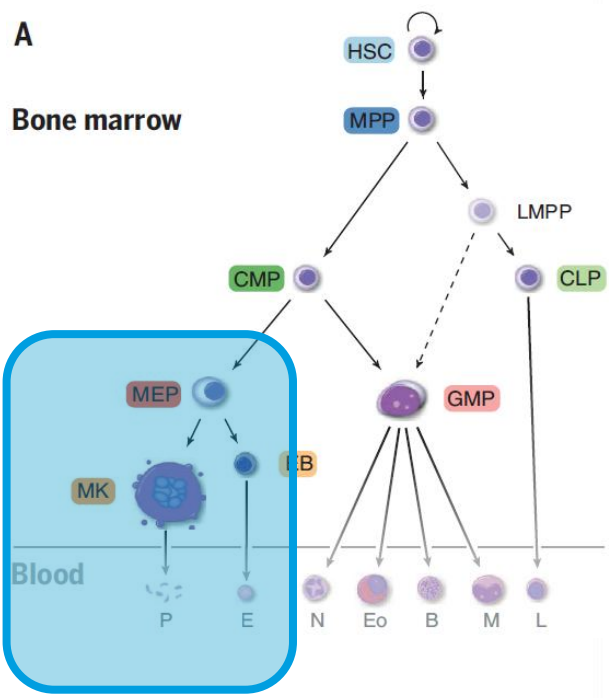


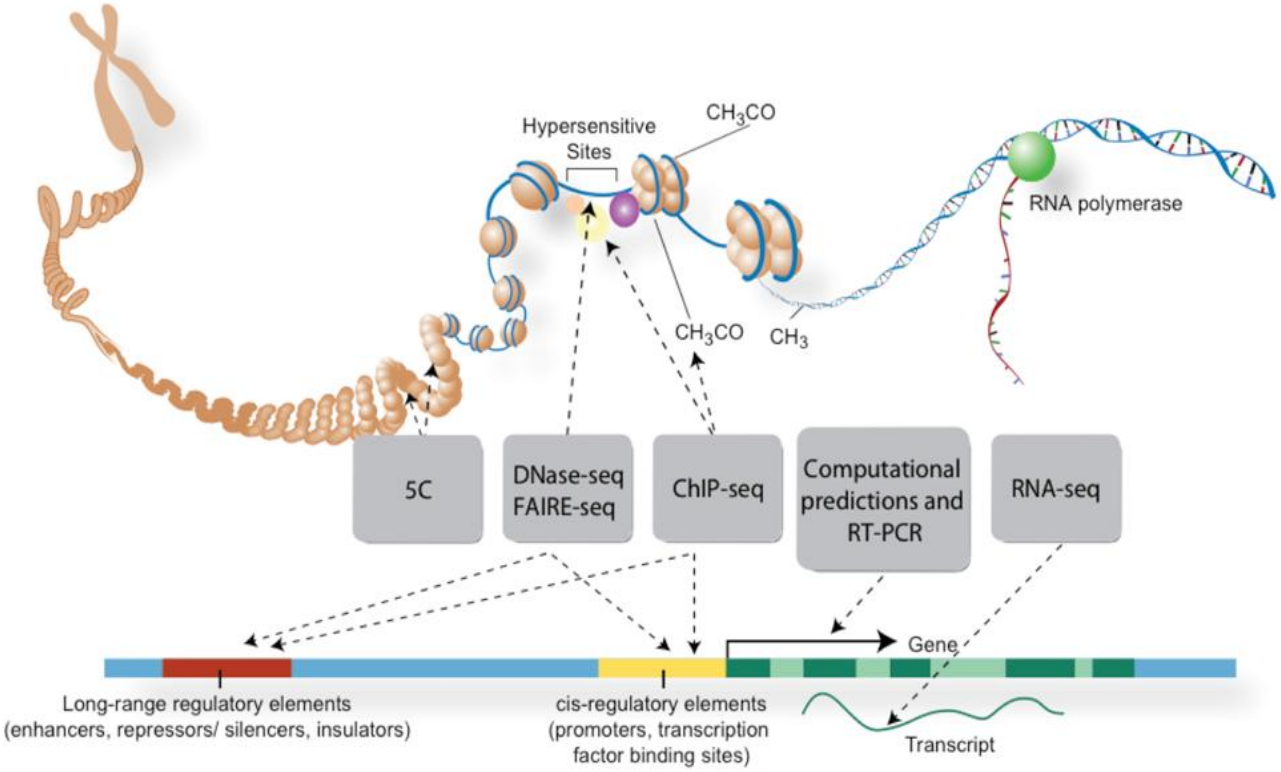
TAR &
new genetic mechanism
RBM8A
Albers, *Nat Genet* 2012
Albers, *Curr Op Gen* 2013



Chromatin marks and epigenetic regions

drive differentiation programs and confer cellular identity and functional phenotypes





UNIVERSITY OF CAMBRIDGE

BLUEPRINT epigenome

BLUEPRINT epigenome

High Impact Project
funded by EC-FP7 Health Directorate

SEVENTH FRAMEWORK PROGRAMME

IMMUNOLOGY

Metabolic shift may train immune cells

BLUEPRINT project studies epigenetics of various blood cells

RESEARCH ARTICLE

IMMUNOGENETICS

mTOR- and HIF-1α–mediated aerobic glycolysis as metabolic basis for trained immunity

Shih-Chin Cheng,[1] Jessica Quintin,[1] Robert A. Cramer,[2] Kelly M. Shepardson,[2] Sadia Saeed,[3] Vinod Kumar,[4] Evangelos J. Giamarellos-Bourboulis,[5] Joost H. A. Martens,[3] Nagesha Appukudige Rao,[3] Ali Aghajanirefah,[3] Ganesh R. Manjeri,[6] Yang Li,[4] Daniela C. Ifrim,[1] Rob J. W. Arts,[1] Brian M. J. W. van der Meer,[4] Peter M. T. Deen,[7] Colin Logie,[3] Luke A. O'Neill,[8] Peter Willems,[6] Frank L. van de Veerdonk,[1] Jos W. M. van der Meer,[1] Aylwin Ng,[9,10] Leo A. B. Joosten,[1] Cisca Wijmenga,[4] Hendrik G. Stunnenberg,[4] Ramnik J. Xavier,[9,10] Mihai G. Netea[1*]

IMMUNOGENETICS

Transcriptional diversity during lineage commitment of human blood progenitors

Lu Chen,[1,2,3*] Myrto Kostadima,[2,4,3*] Joost H. A. Martens,[5*] Giovanni Canu,[2,3] Sara P. Garcia,[2,3] Ernest Turro,[2,3] Kate Downes,[2,3] Iain C. Macaulay,[6] Ewa Bielczyk-Maczynska,[2,3] Sophia Coe,[2,3] Samantha Farrow,[2,3] Pawan Poudel,[2,3] Frances Burden,[2,3] Sjoert B. G. Jansen,[2,3] William J. Astle,[2,3,7] Antony Attwood,[2,3] Tadbir Bariana,[8,9] Bernard de Bono,[10,11] Alessandra Breschi,[12] John C. Chambers,[13,14] BRIDGE Consortium,† Fizzah A. Choudry,[2,3] Laura Clarke,[4] Paul Coupland,[1] Martijn van der Ent,[5] Wendy N. Erber,[15] Joop H. Jansen,[16] Rémi Favier,[17] Matthew E. Fenech,[18] Nicola Foad,[2,3] Kathleen Freson,[19] Chris van Geet,[19] Keith Gomez,[9] Roderic Guigo,[12] Daniel Hampshire,[2,3] Anne M. Kelly,[2,3,20] Hindrik H. D. Kerstens,[5] Jaspal S. Kooner,[13,14] Michael Laffan,[21] Claire Lentaigne,[21] Charlotte Labalette,[2,3] Tiphaine Martin,[2,3,22]‡ Stuart Meacham,[2,3] Andrew Mumford,[23] Sylvia Nürnberg,[2,3]§ Emilio Palumbo,[12] Bert A. van der Reijden,[16] David Richardson,[4] Stephen J. Sammut,[24,25] Greg Slodkowicz,[4] Asif U. Tamuri,[4] Louella Vasquez,[3] Katrin Voss,[2,3]¶ Stephen Watt,[3] Sarah Westbury,[26] Paul Flicek,[4,1] Remco Loos,[4] Nick Goldman,[4] Paul Bertone,[4,27,28] Randy J. Read,[29] Sylvia Richardson,[7] Ana Cvejic,[2,1] Nicole Soranzo,[1,2*] Willem H. Ouwehand,[2,3,1*] Hendrik G. Stunnenberg,[5*] Mattia Frontini,[2,3*]|| Augusto Rendon[2,3,7*]||

RESEARCH ARTICLE

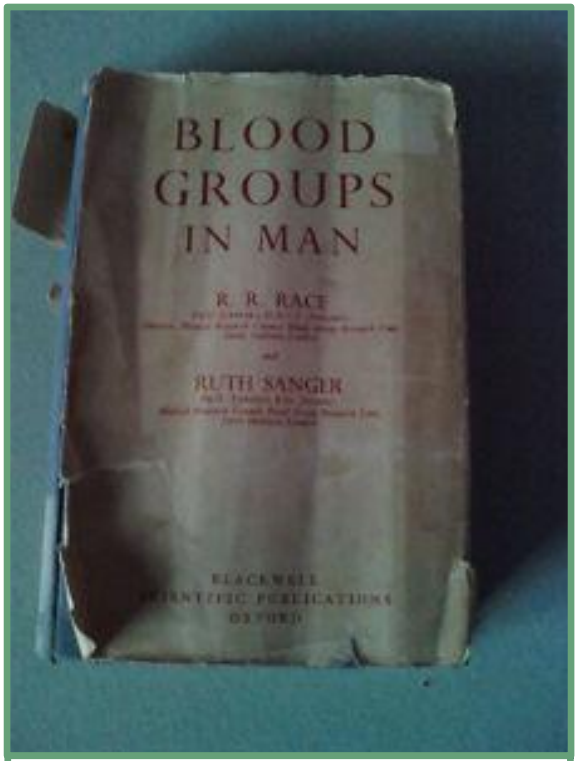
IMMUNOGENETICS

Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity

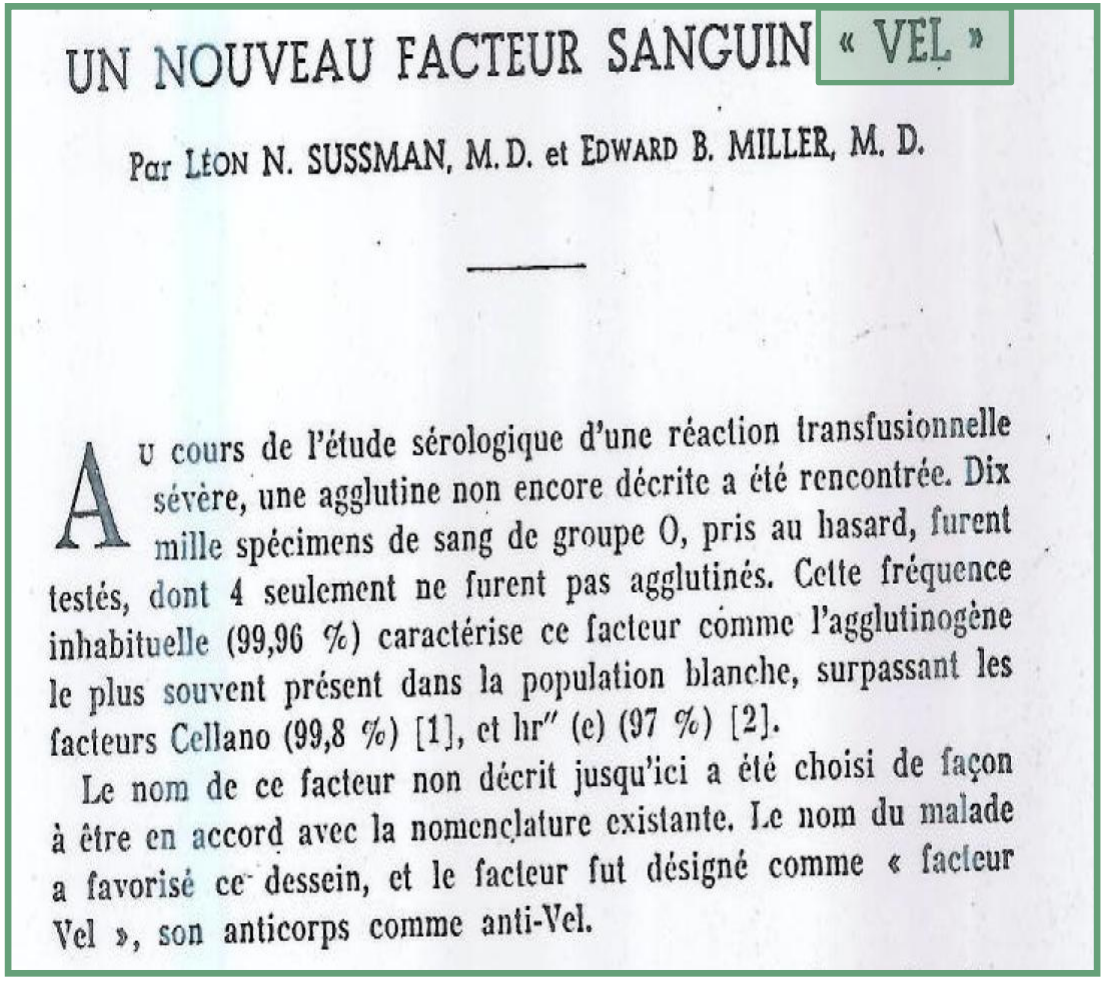
Sadia Saeed,[1*] Jessica Quintin,[2*] Hindrik H. D. Kerstens,[1*] Nagesha A. Rao,[1*] Ali Aghajanirefah,[1*] Filomena Matarese,[1] Shih-Chin Cheng,[2] Jacqueline Ratter,[2] Kim Berentsen,[1] Martijn A. van der Ent,[1] Nilofar Sharifi,[1] Eva M. Janssen-Megens,[1] Menno Ter Huurne,[1] Amit Mandoli,[1] Tom van Schaik,[1] Aylwin Ng,[3,4] Frances Burden,[5,6] Kate Downes,[5,6] Mattia Frontini,[5,6] Vinod Kumar,[7] Evangelos J. Giamarellos-Bourboulis,[8] Willem H. Ouwehand,[5,6] Jos W. M. van der Meer,[2] Leo A. B. Joosten,[2] Cisca Wijmenga,[7] Joost H. A. Martens,[1] Ramnik J. Xavier,[3,4] Colin Logie,[1]† Mihai G. Netea,[2]† Hendrik G. Stunnenberg[1]†

The genetic basis of all blood groups has been resolved

except for one rare group which is absent in 1 in 4000 individuals



There are 32 red cell blood group systems of man



UN NOUVEAU FACTEUR SANGUIN « VEL »

Par LÉON N. SUSSMAN, M. D. et EDWARD B. MILLER, M. D.

Au cours de l'étude sérologique d'une réaction transfusionnelle sévère, une agglutine non encore décrite a été rencontrée. Dix mille spécimens de sang de groupe O, pris au hasard, furent testés, dont 4 seulement ne furent pas agglutinés. Cette fréquence inhabituelle (99,96 %) caractérise ce facteur comme l'agglutinogène le plus souvent présent dans la population blanche, surpassant les facteurs Cellano (99,8 %) [1], et hr″ (e) (97 %) [2].

Le nom de ce facteur non décrit jusqu'ici a été choisi de façon à être en accord avec la nomenclature existante. Le nom du malade a favorisé ce dessein, et le facteur fut désigné comme « facteur Vel », son anticorps comme anti-Vel.

The genetic basis of all blood groups has been resolved

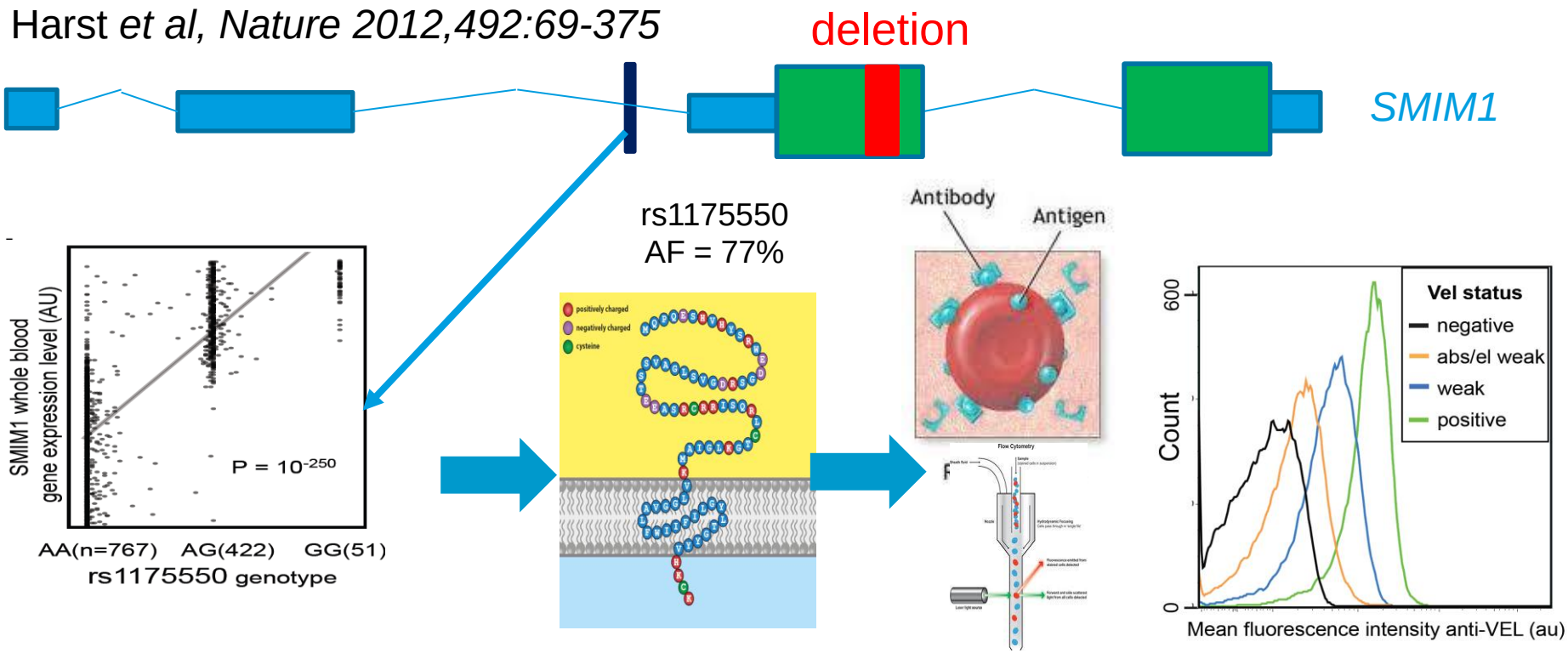
except for one rare group which is absent in 1 in 4000 individuals

ARTICLE

doi:10.1038/nature11677

Seventy-five genetic loci influencing the human red blood cell

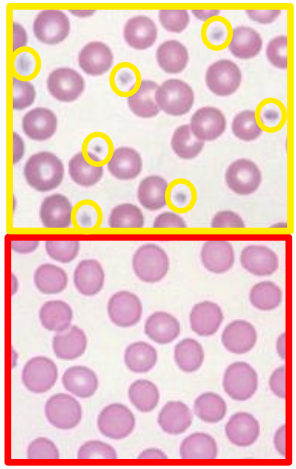
Harst *et al, Nature 2012,492:69-375*



Cvejic *et al, Nat Genetics, 2013*

Thrombocytopenia with Absent Radii (TAR)

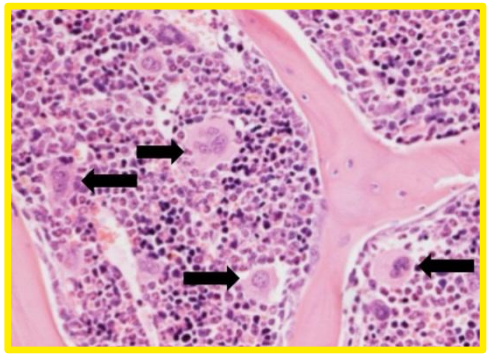
selective block of platelet formation and skeletal abnormalities



Platelets Yes

Platelets No

Platelet progenitors in bone marrow

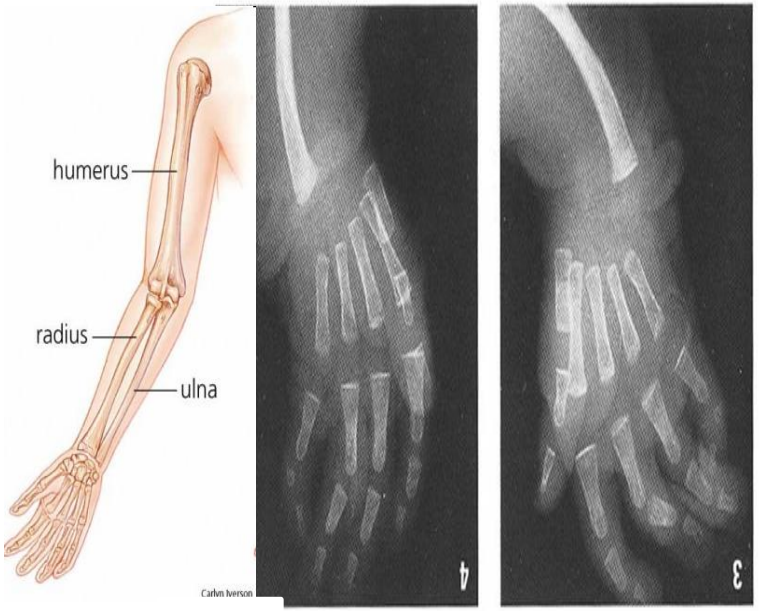


Bleeding because of low platelets

Missing radii and club hands

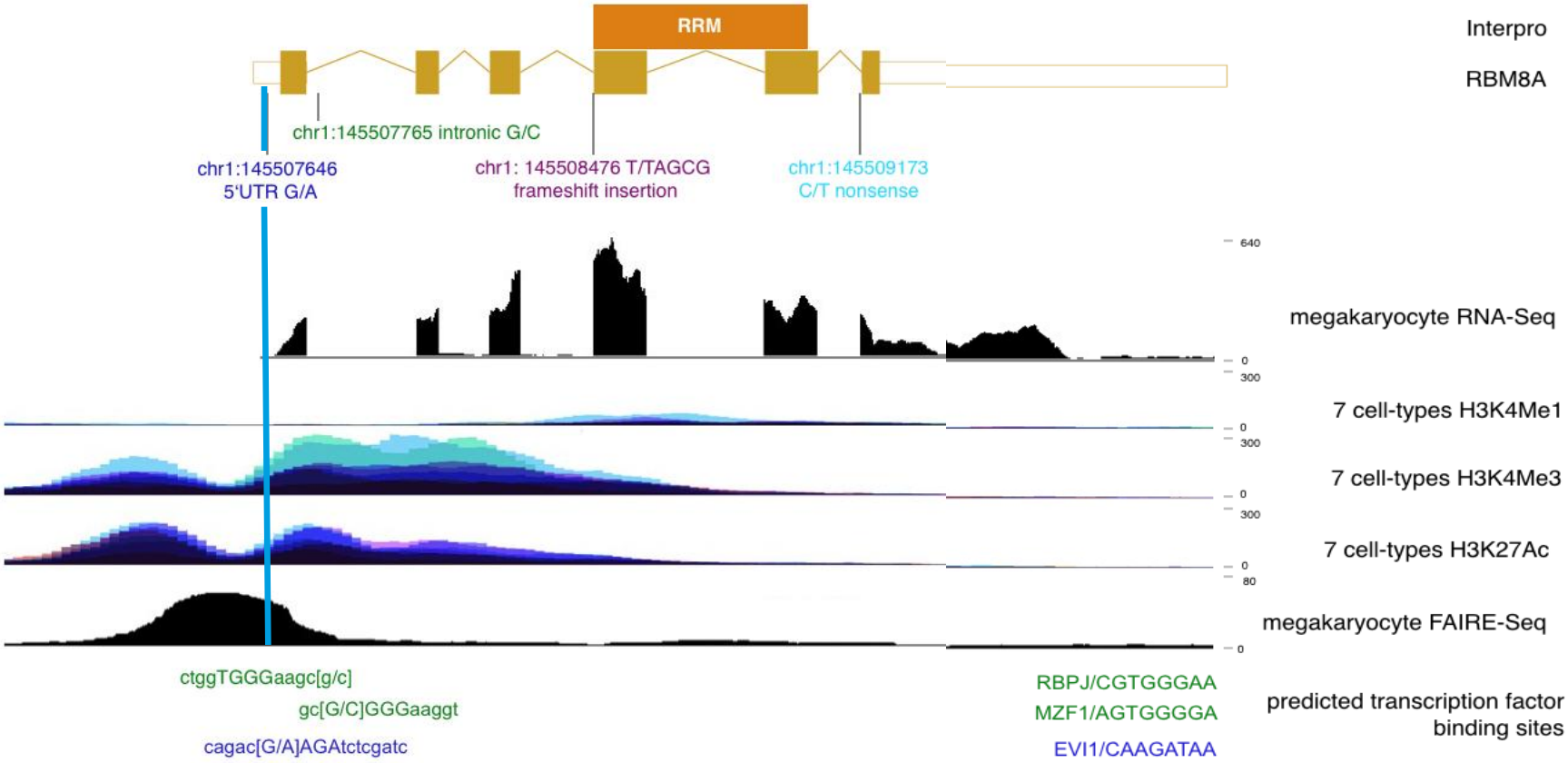
Shortened humerus and ulnae

Small shoulder girdle



TAR – deletion of ~12 genes on one haplotype and

a rather common (1 in 30) regulatory SNP on the other haplotype



The 5'UTR SNP and the intronic SNP lie in a regulatory element active in megakaryocytes and modify transcription factor binding

Albers *et al, Nat Genetics, 2012*

Inherited bleeding and platelet disorders (BPD)

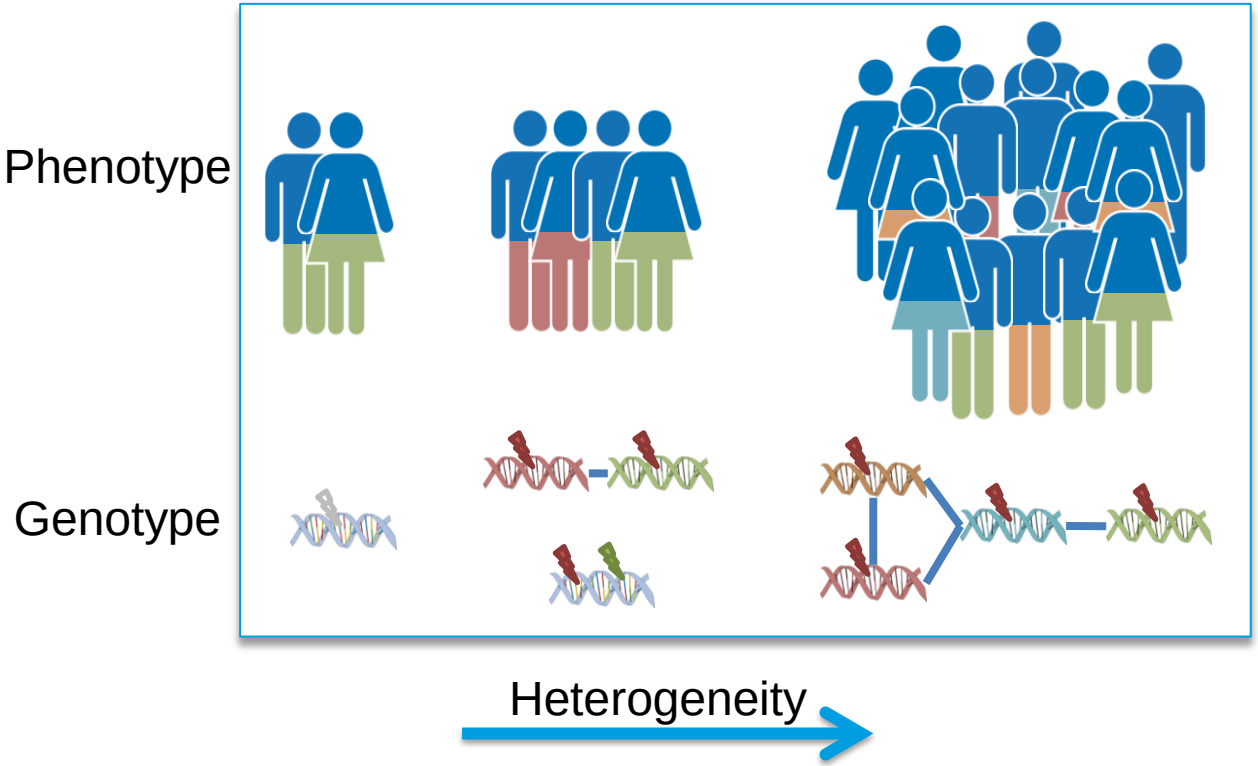
864 rare cases enrolled across 12 clinical referral centres

Inclusion

- Abnormality of platelet
  - count / volume
  - morphology
  - function
- Bleeding of unknown aetiology
- Likelihood of being genetic

Exclusion

- Acquired causes
- Known inherited disorders



The need to phenotype deeply

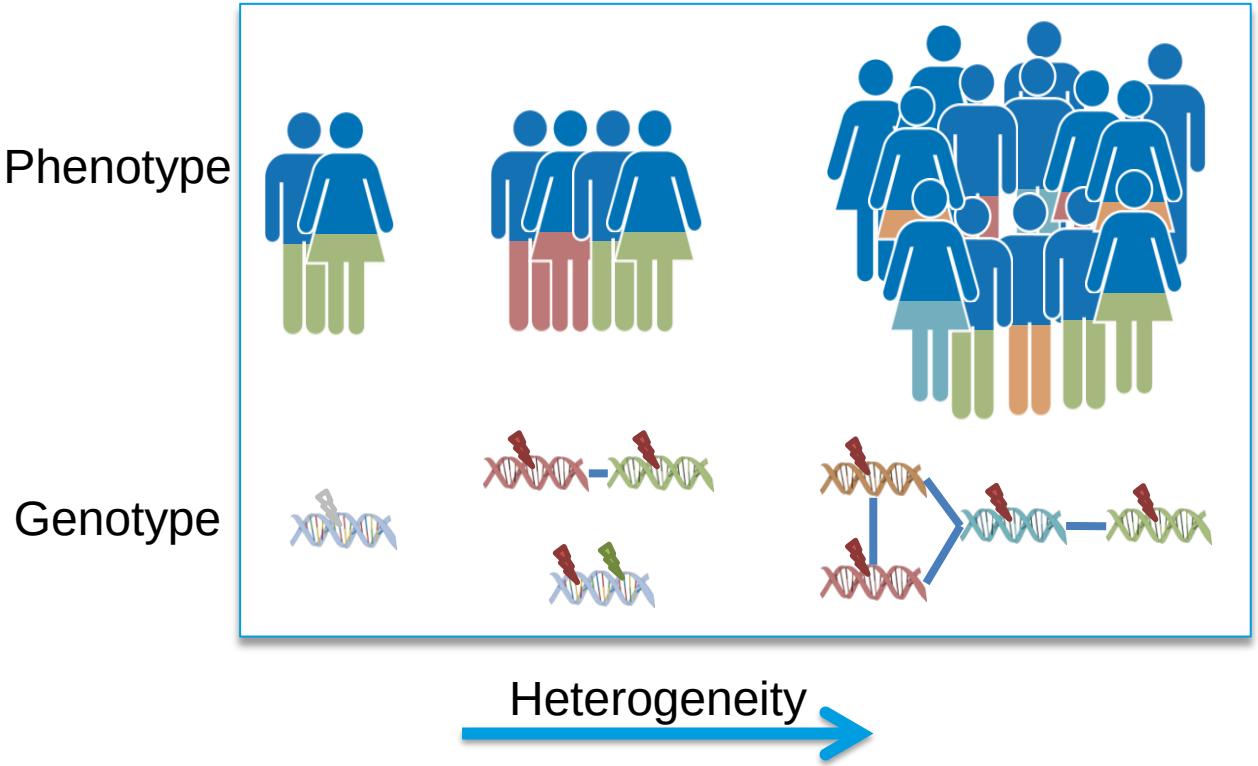
in order to reduce case heterogeneity and maintain power

Inclusion

- Abnormality of platelet
  - count / volume
  - morphology
  - function
- Bleeding of unknown aetiology
- Likelihood of being genetic

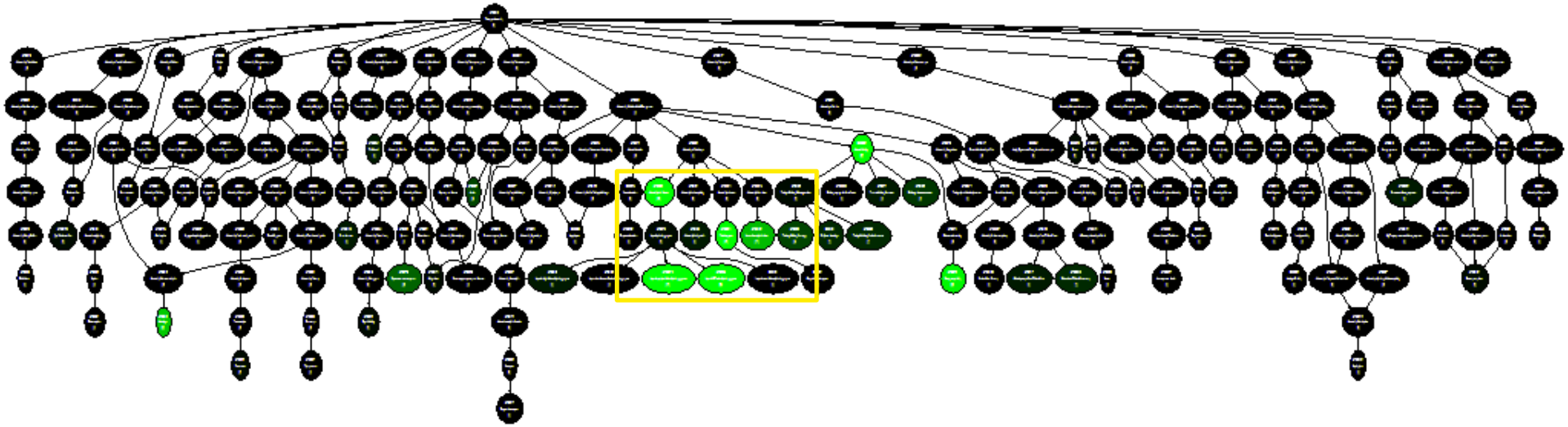
Exclusion

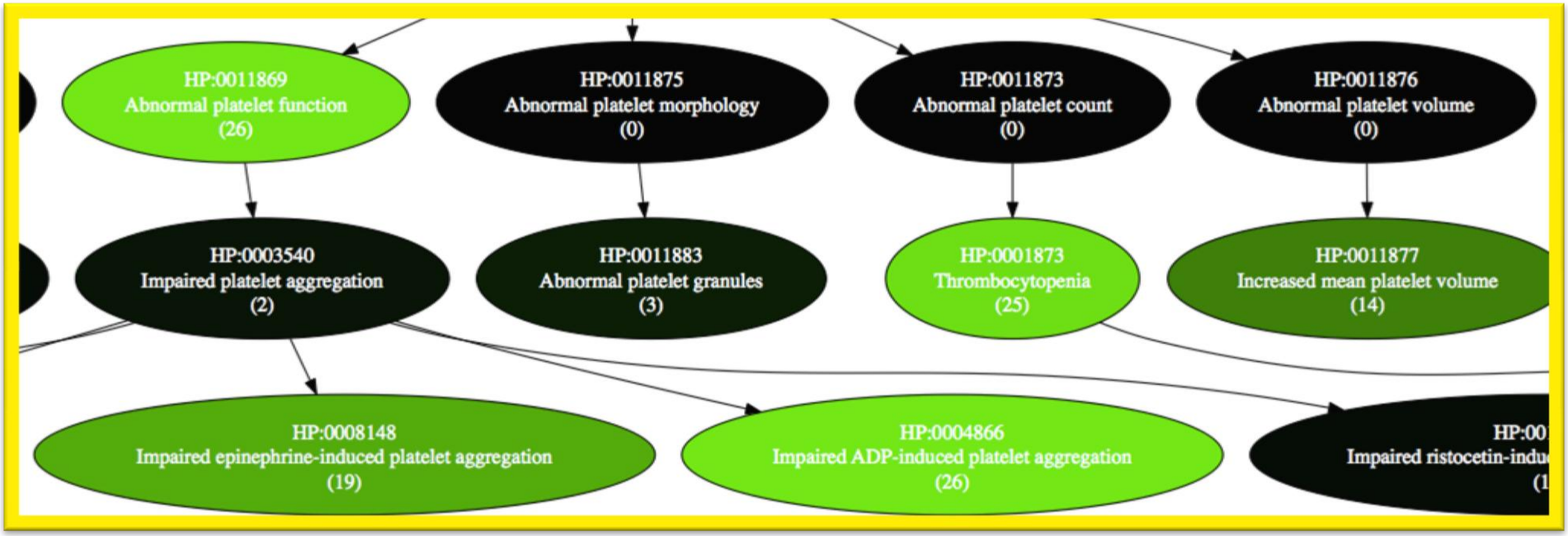
- Acquired causes
- Known inherited disorders



Human Phenotype Ontology annotation to cluster cases

cases have been HPO coded by 12 clinical centres in the UK and overseas





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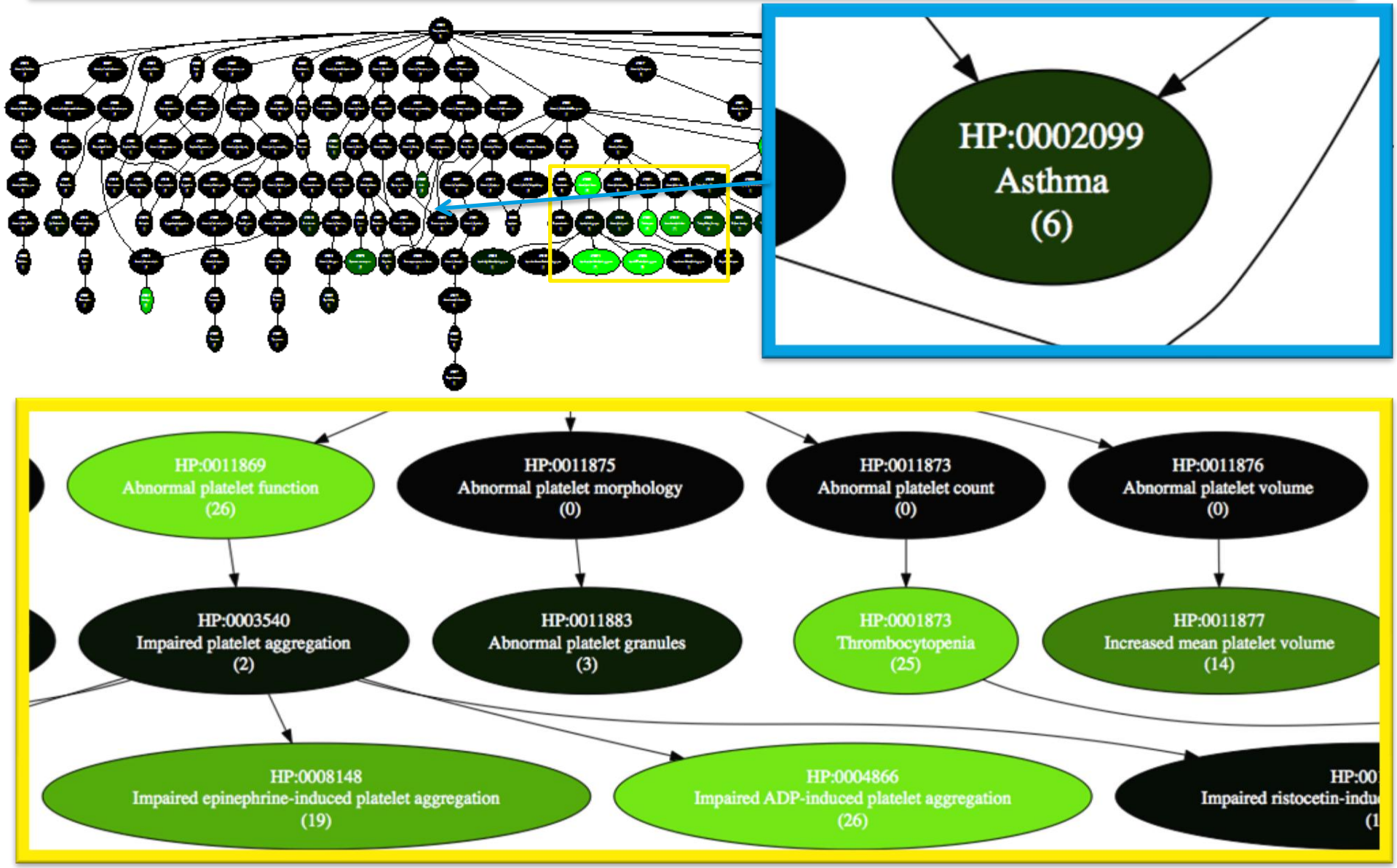
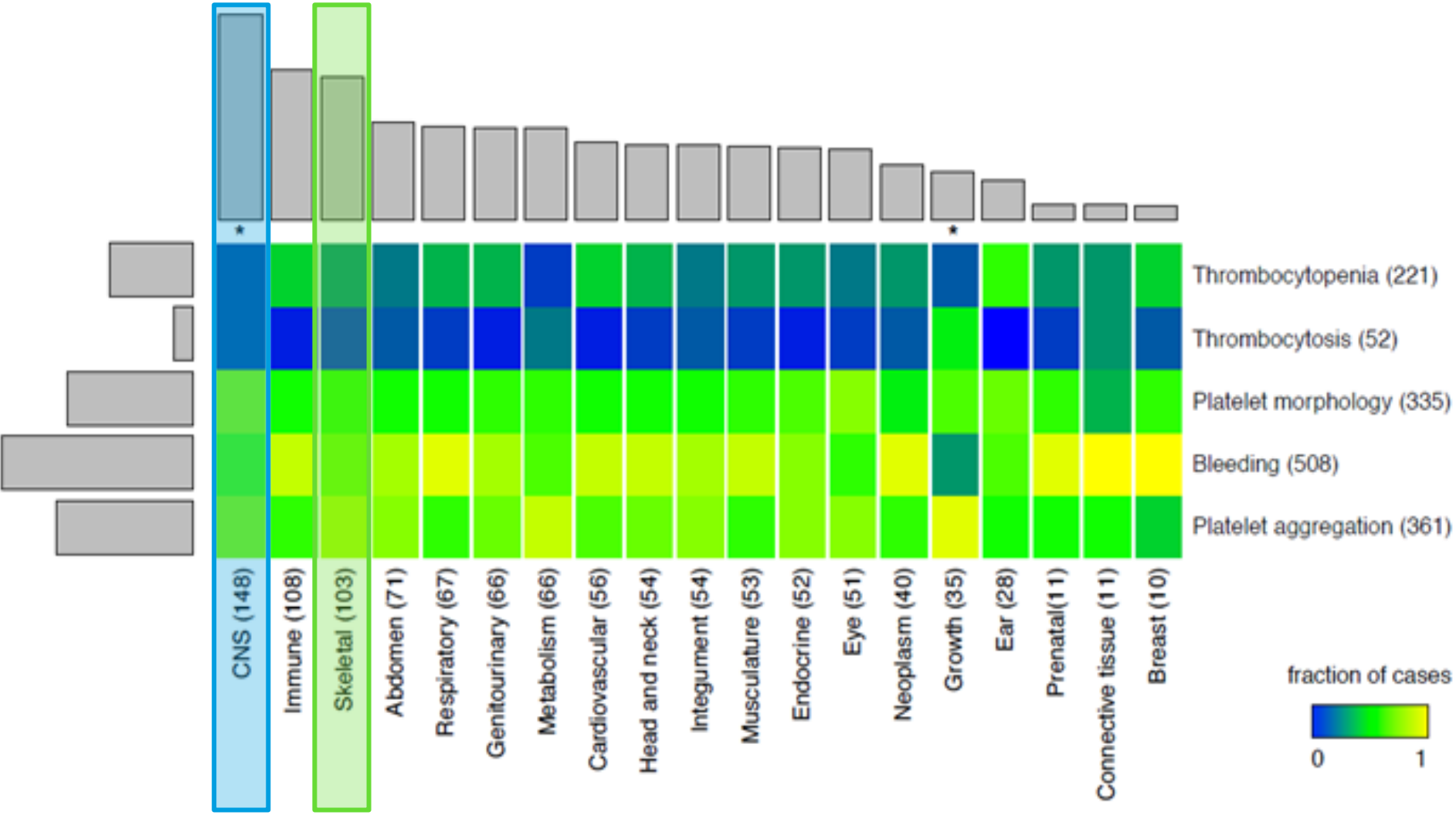


HPO coding enabled us to capture the phenotypic complexity of BPD cases

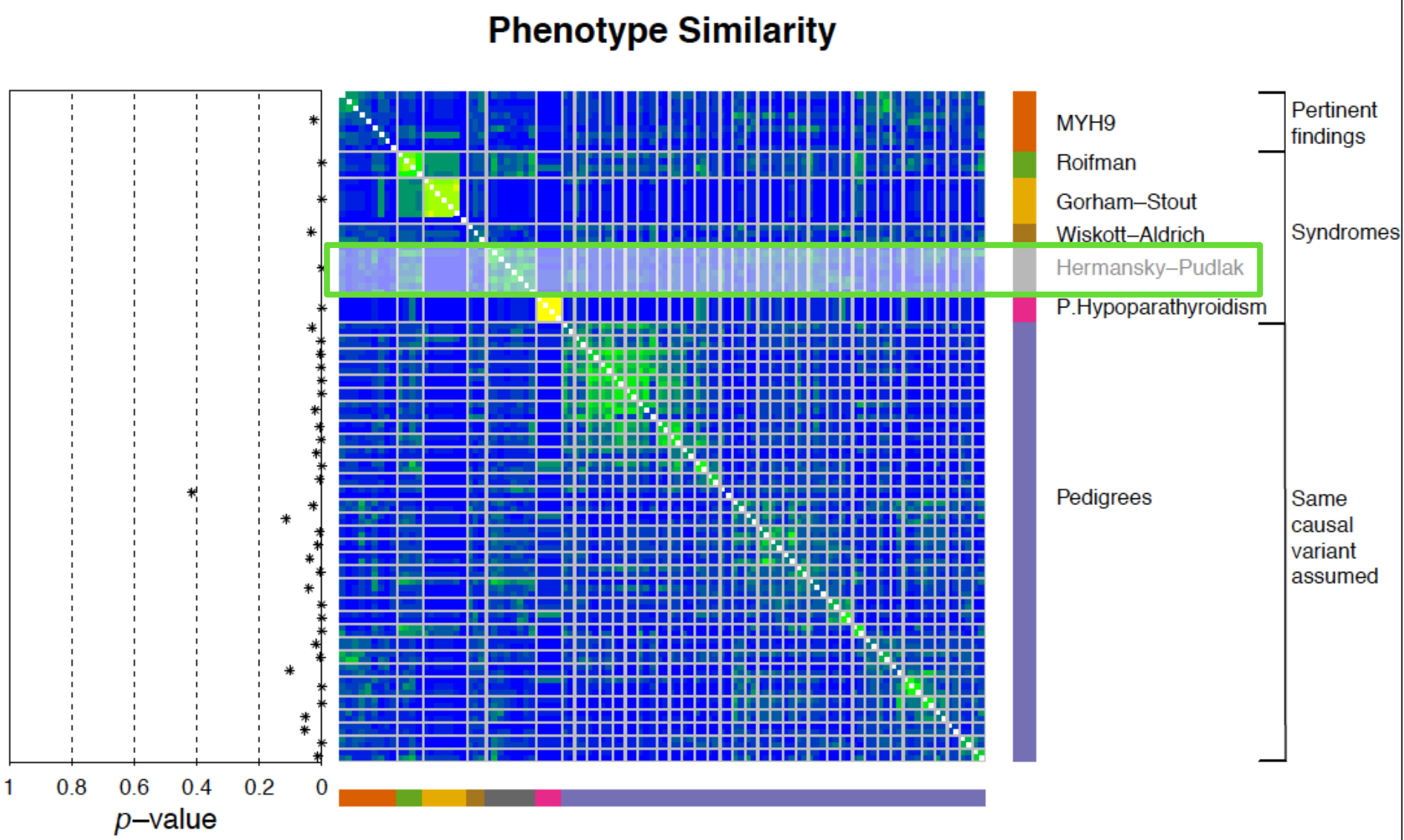
neurological, immunological and skeletal disorders are highly over-represented



Westbury *et al. 2014 (submitted)*

Computer based HPO-driven clustering of BPD cases across centres

it is hoped that this will maintain power of gene discovery

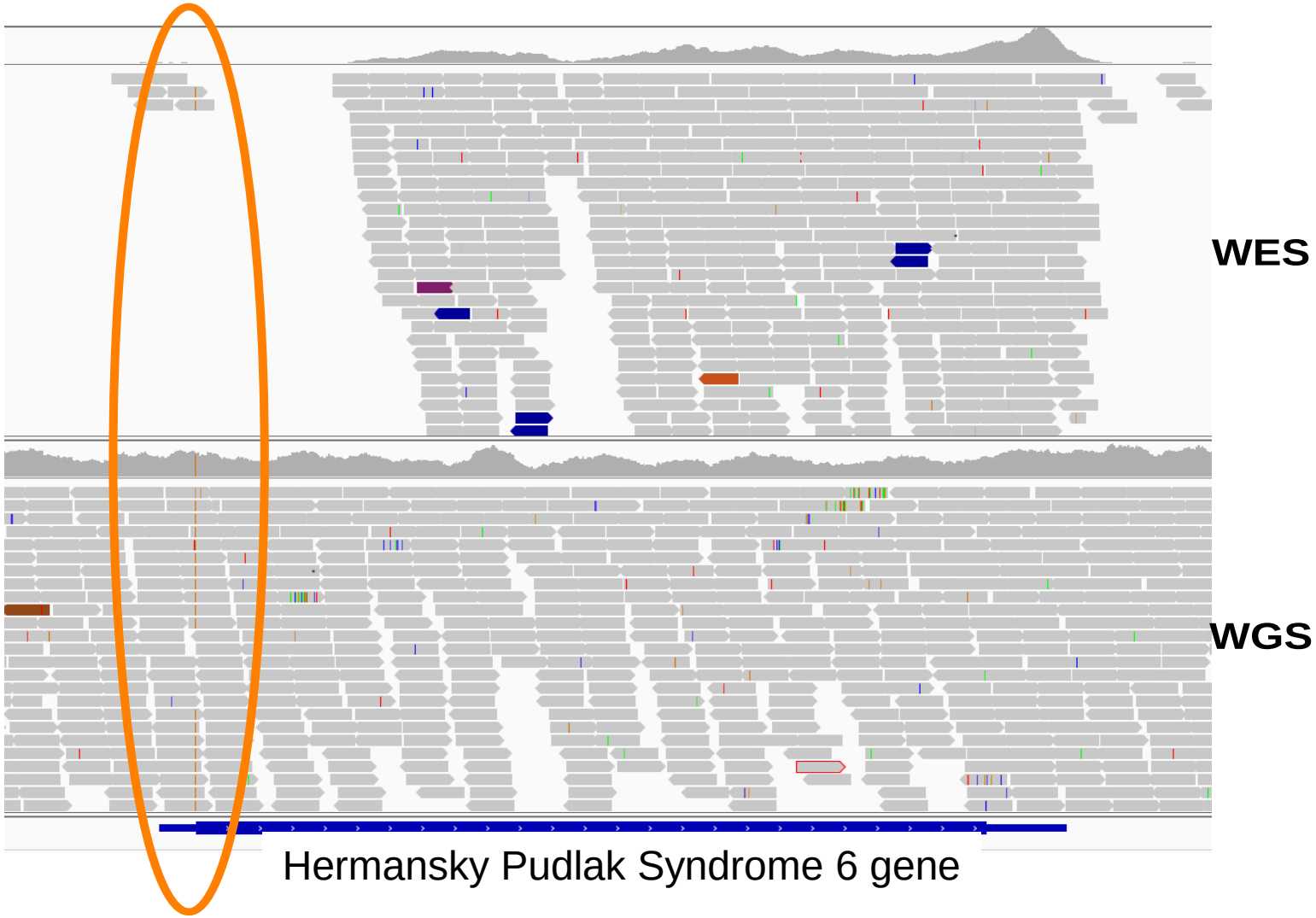


Westbury *et al. 2014 (submitted)*

WES vs WGS

HPS case identified by HPO clustering tested negative by WES but positive by WGS

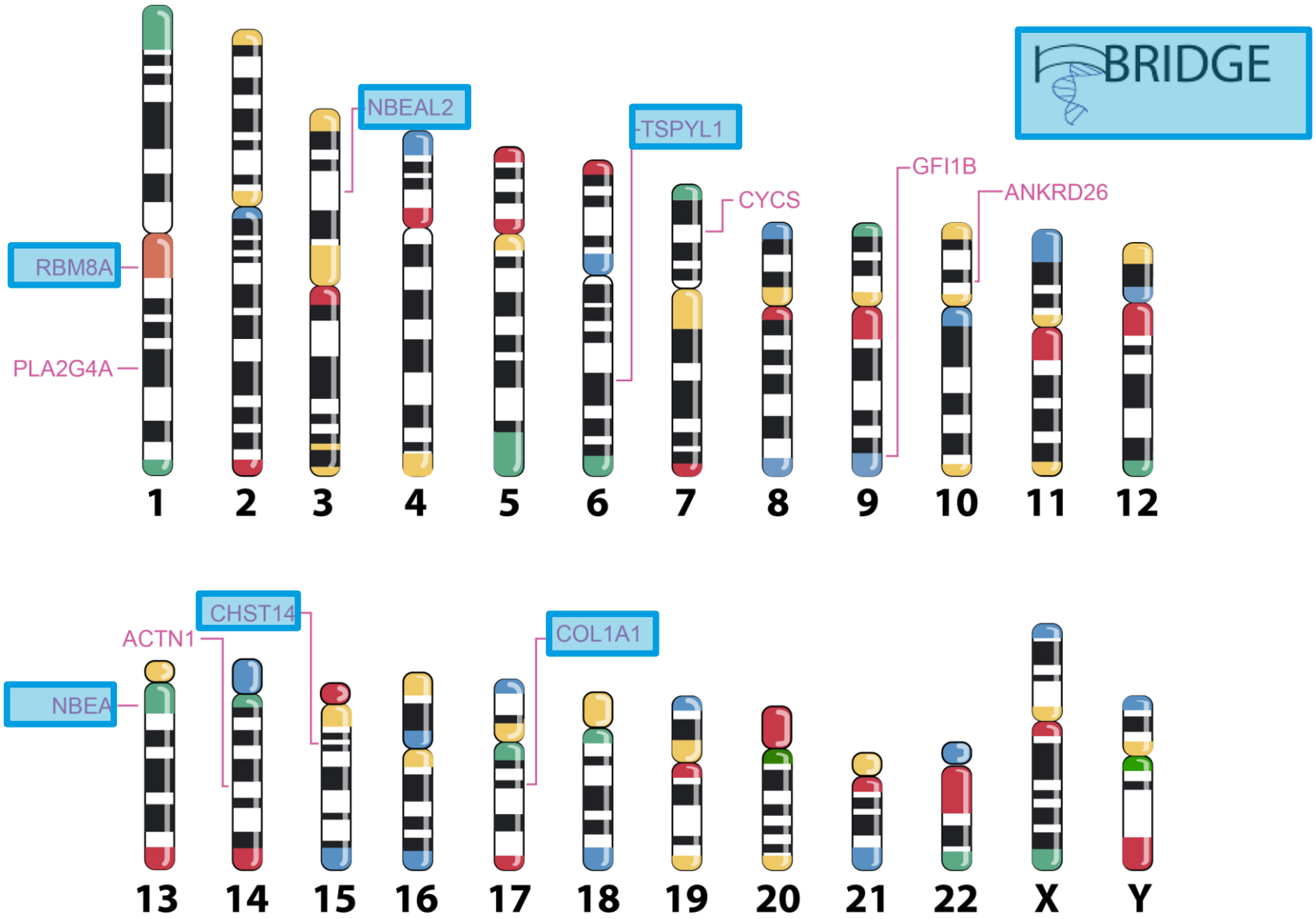
Coverage – how often is a nucleotide seen



Hermansky Pudlak Syndrome 6 gene

Inherited bleeding and platelet disorders (BPD)

modern genomics added 11 genes since 2010



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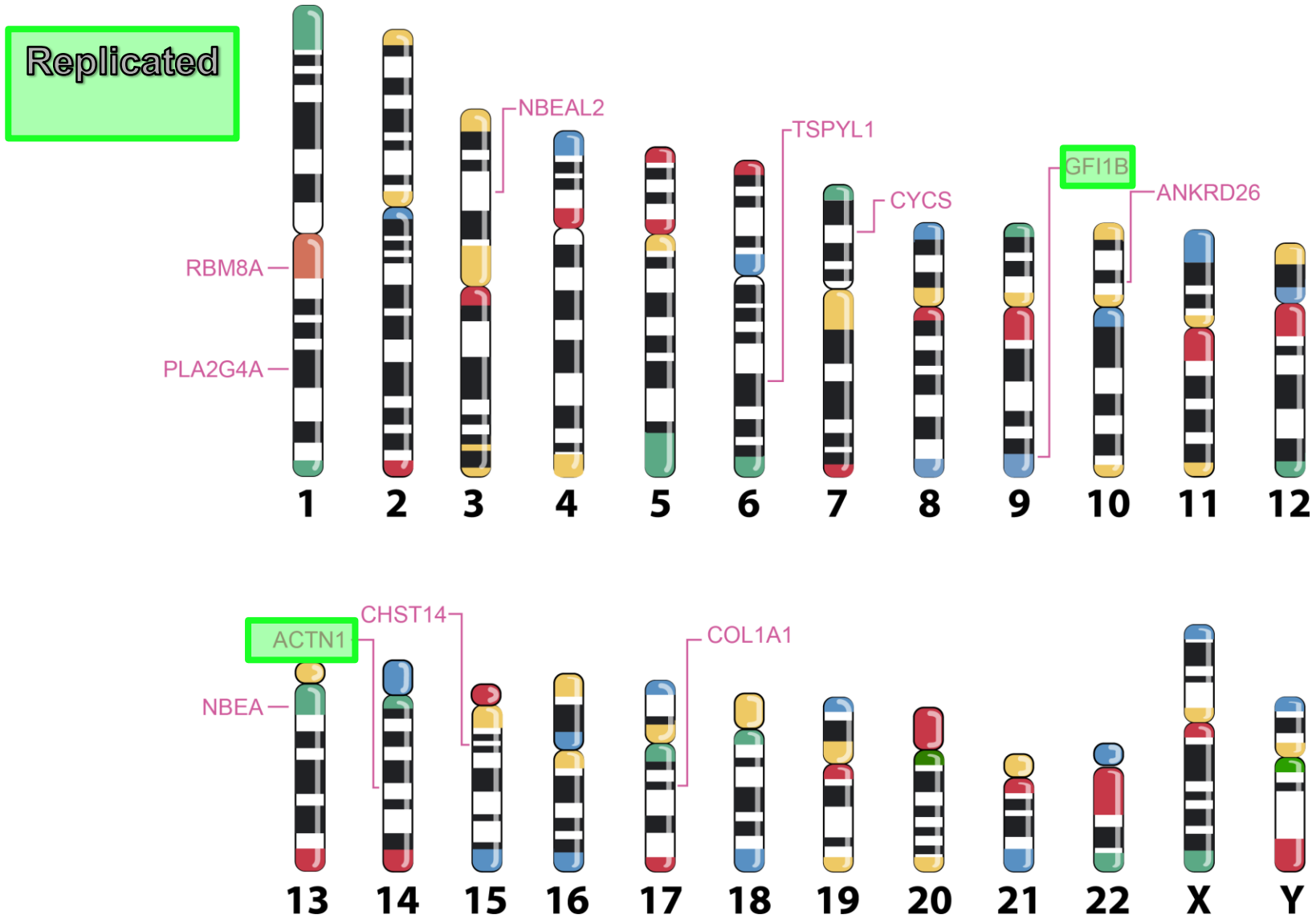

NIHR BioResource
Rare Diseases

Conclusions

Genomics
england

1. Pilot projects have been essential to develop systems to achieve national scalability in 2015 for the 100,000 genomes

2. WGS provides excellent coverage of the virtual WES space and the regulome

3. Rare and common SNPs in regulatory elements are causative of rare conditions

Cambridge BRC

NHS
Blood and Transplant

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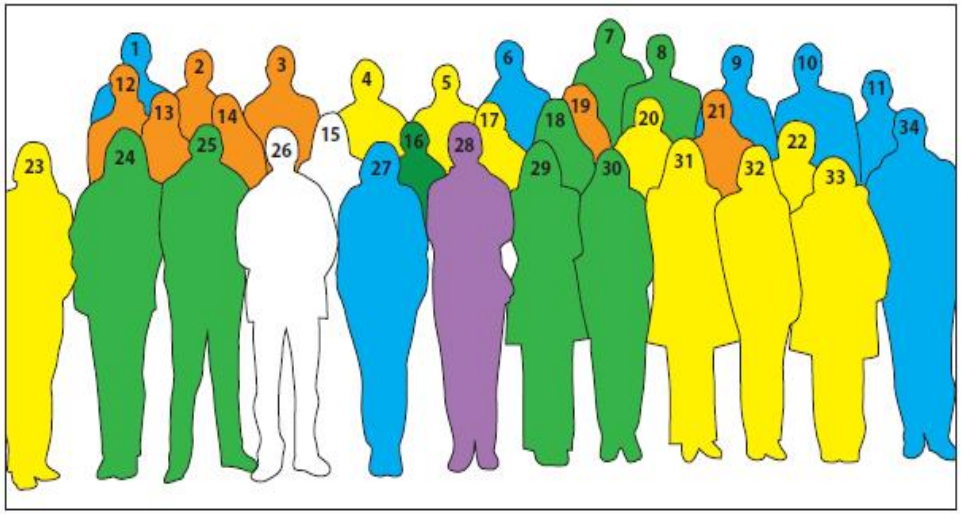
BLUE GROUP: Clinical Bioinformatics & Statistical Genetics
ORANGE GROUP: Platelet Biology & Genomics
GREEN: Epigenomics of Blood Cells (BluePrint)
YELLOW: BioResources (Cambridge BioResource, NIHR BioResource, INTERVAL)
WHITE: Visitors



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CHOC Children's Children's Hospital of Orange County
LUMC Leids Universitair Medisch Centrum
Charité
CRPP
The Children's Hospital of Philadelphia Research Institute
Royal Free London NHS Foundation Trust
CHU Hôpitaux de Bordeaux
CATGO CAmbridge Translational GenOmics Laboratory
University of Bristol
Imperial College London
MHH Medizinische Hochschule Hannover

Funding

NHS National Institute for Health Research
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British Heart Foundation
NHS Blood and Transplant
MRC Medical Research Council
NIHR BioResource Rare Diseases