Forensic DNA phenotyping

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Genome variation

99.8% identity

85% variation within individuals/local,
8% within continents,
7% within populations of the same continent


PAF!
BANG!
BLOiNG!
BLOiNG!

FORENSIC GENETICS

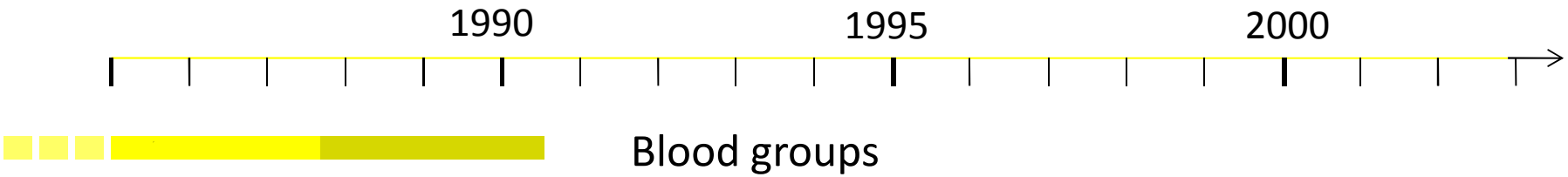
CASEWORK:

- Paternity testing
- Criminal casework
- Identification of human remains
- Criminal DNA databases
- Non human DNA typing

OTHERS:

- Toxicogenetics
- Forensic Molecular Pathology

DNA Typing in Forensic Analysis

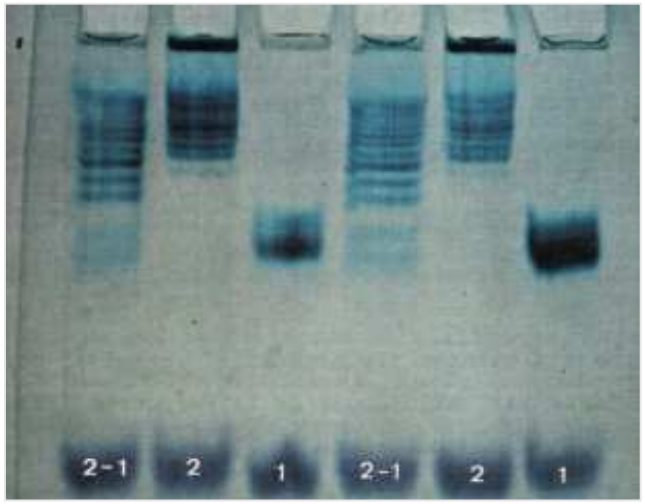


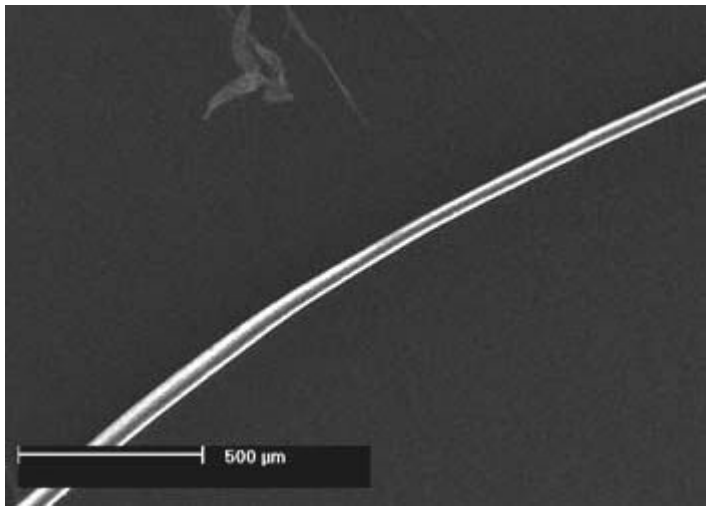
Blood groups

HLA

Serum proteins

Enzymes





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EMBL Outstation
European Bioinformatics Institute

OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University

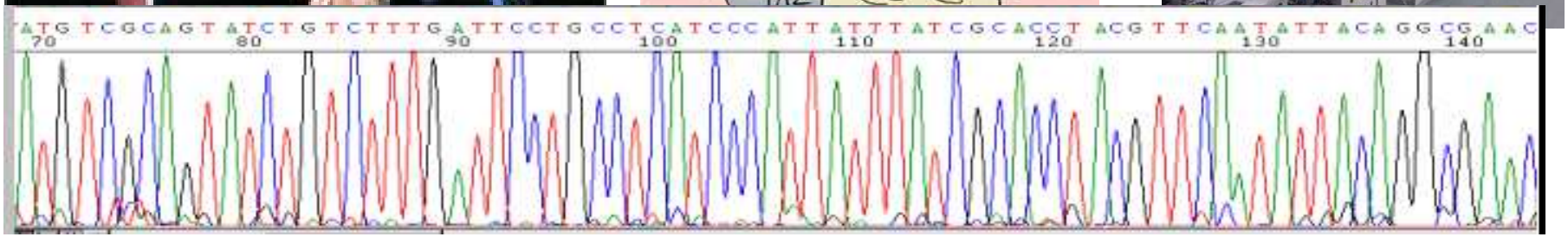
GENETests

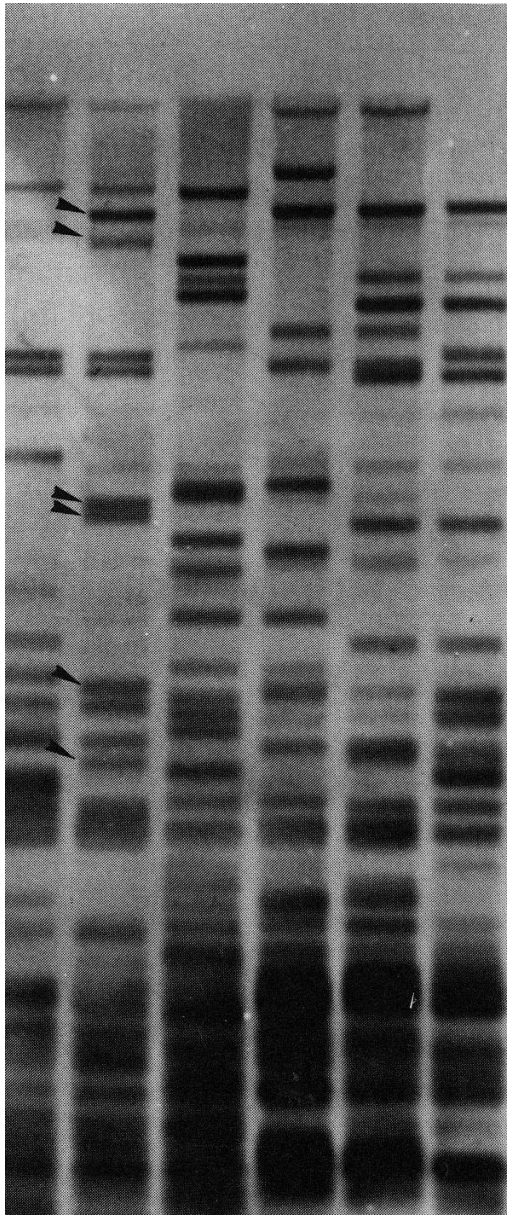
HGMD™
The Human Gene Mutation Database
Cardiff

SWISS-PROT

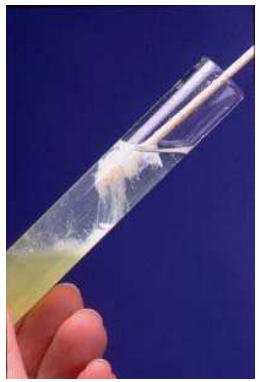
PDB™
PROTEIN DATA BANK

GeneCards™



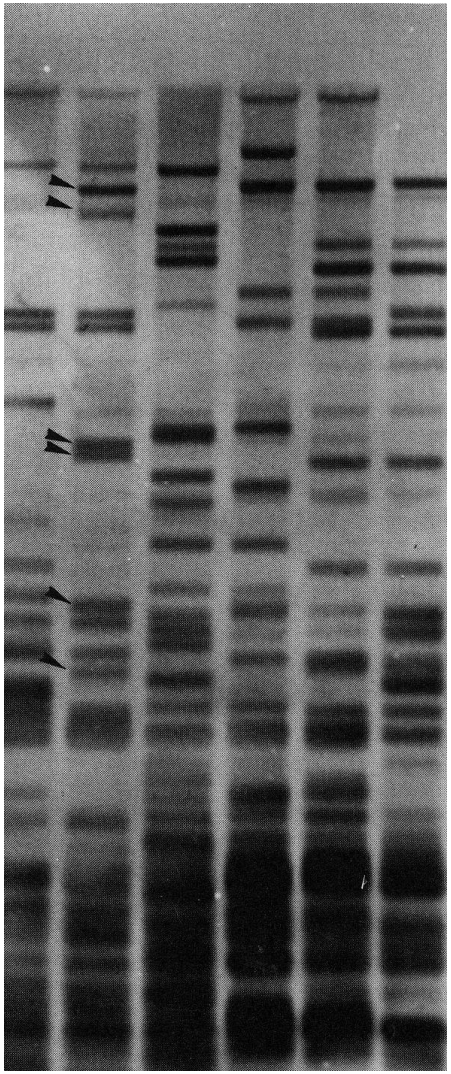


Alec Jeffreys
DNA fingerprint
1985

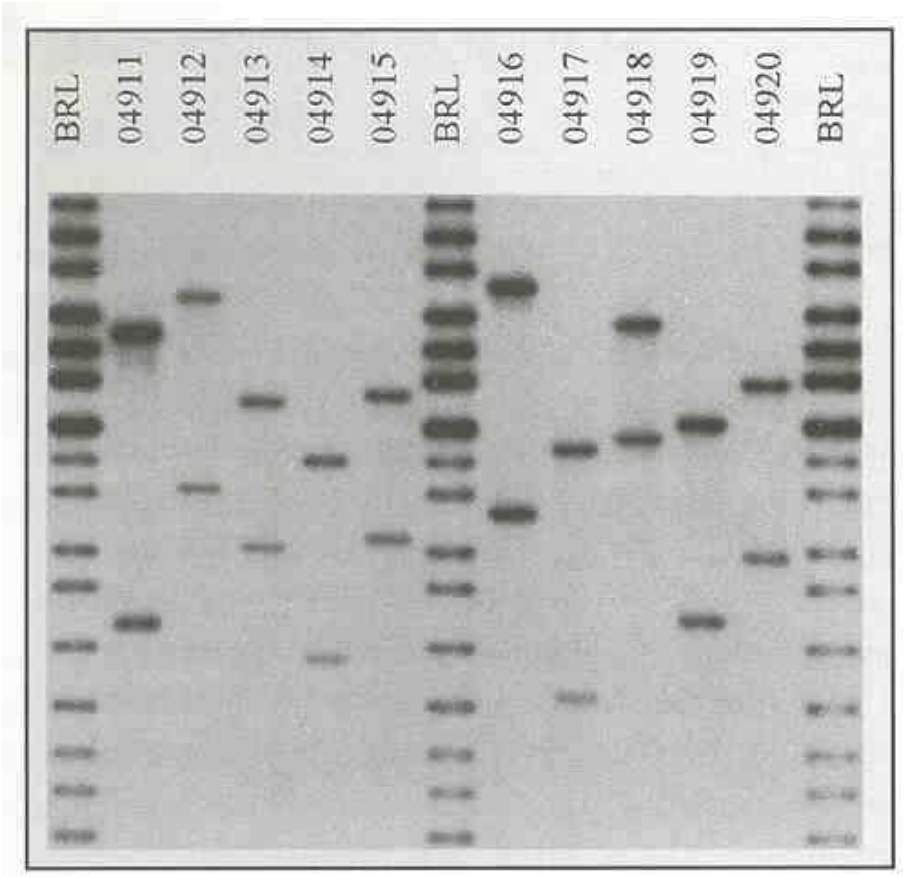


Jeffreys, A.J., Wilson, V., and Thein, S.L. Hypervariable minisatellite regions in human DNA. Nature 314 (1985) 67-73.

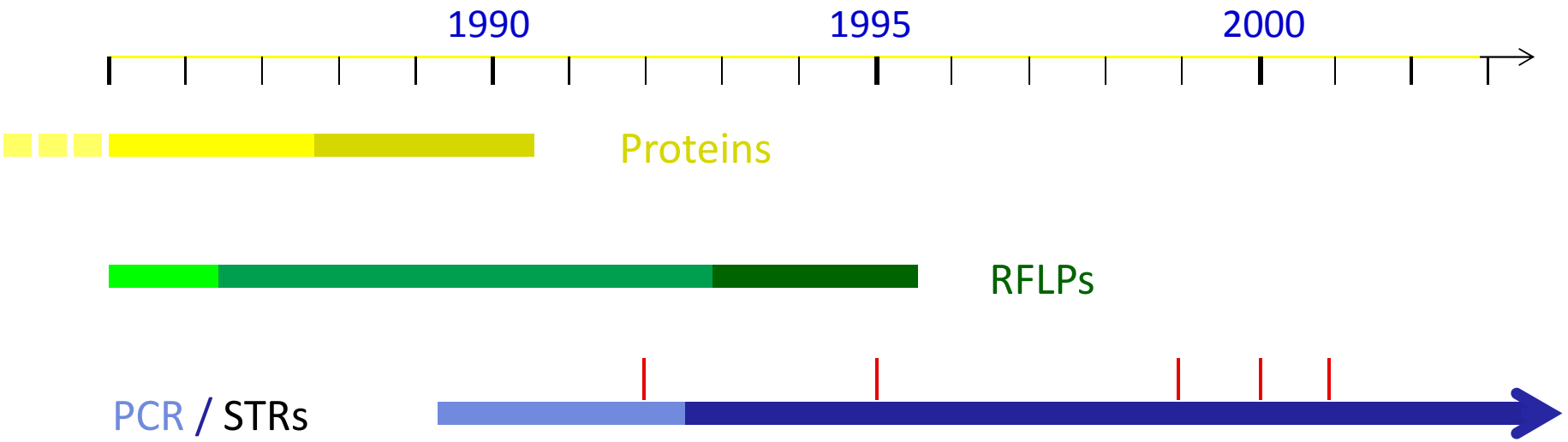
DETECTION OF MINISATELLITES USING MLPs

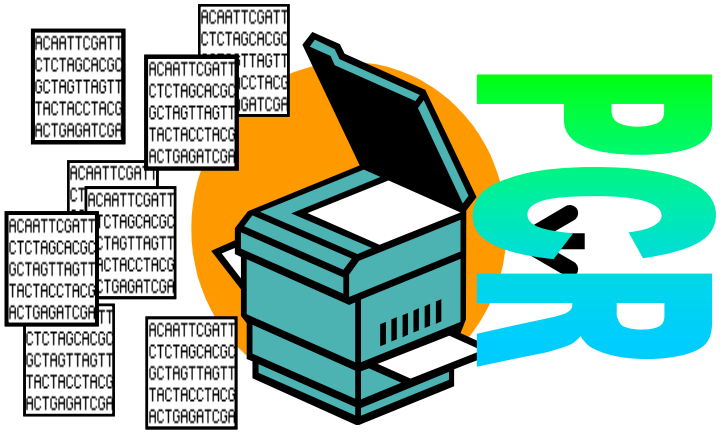


DETECTION OF MINISATELLITES USING SLPs

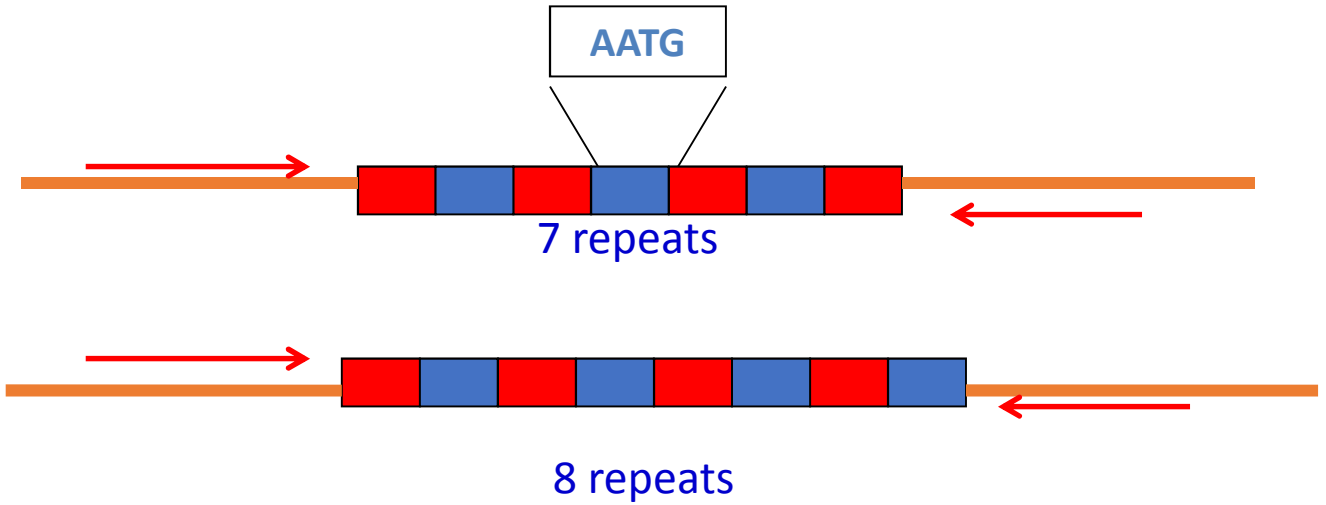


DNA Typing in Forensic Analysis





Short Tandem Repeats (STRs)



ADVANTAGES OF STRs OVER SLPs

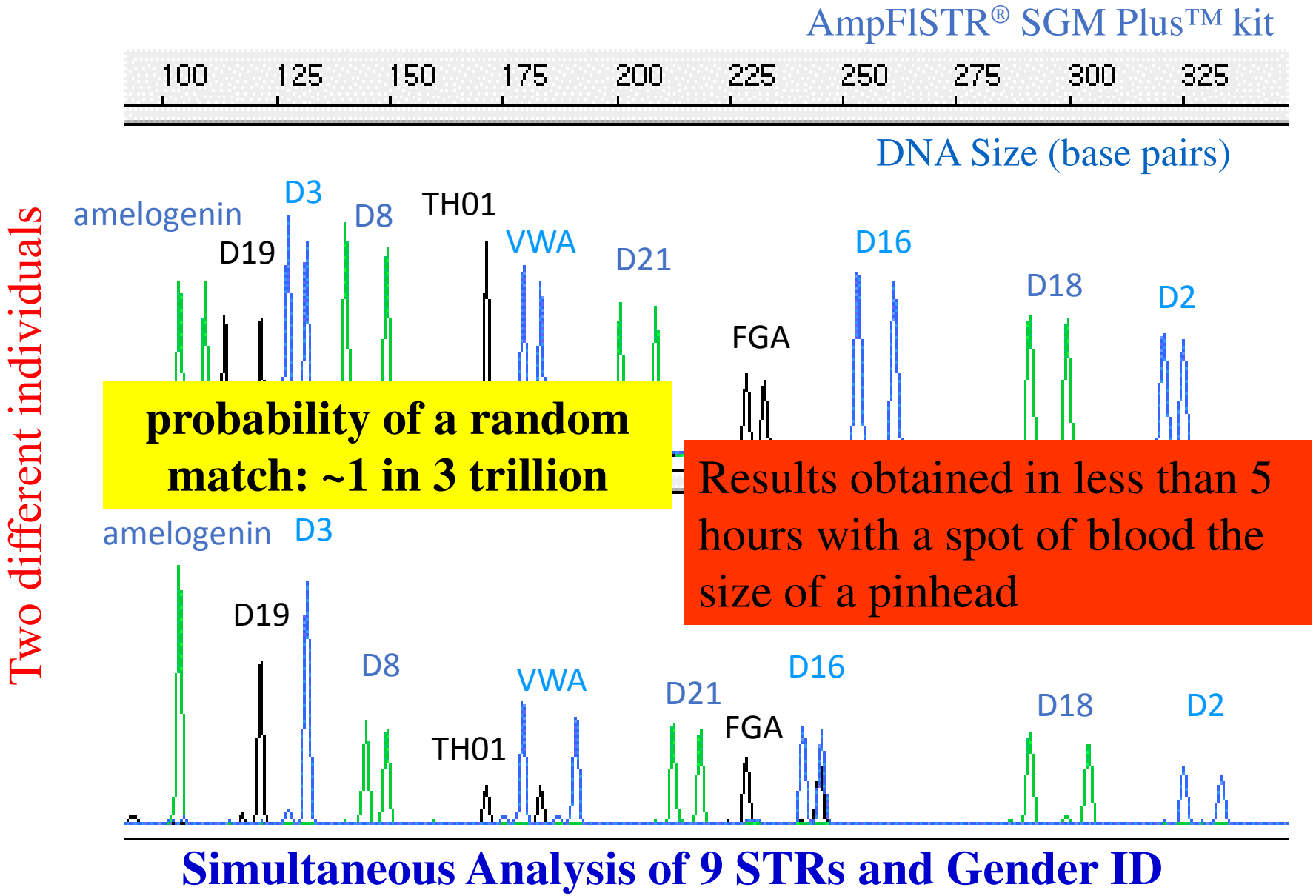
Amount of DNA required

Analysis of degraded samples

Time of analysis

Standardization and value of the evidence

Human Identity Testing with Multiplex STRs



Simultaneous Analysis of 9 STRs and Gender ID

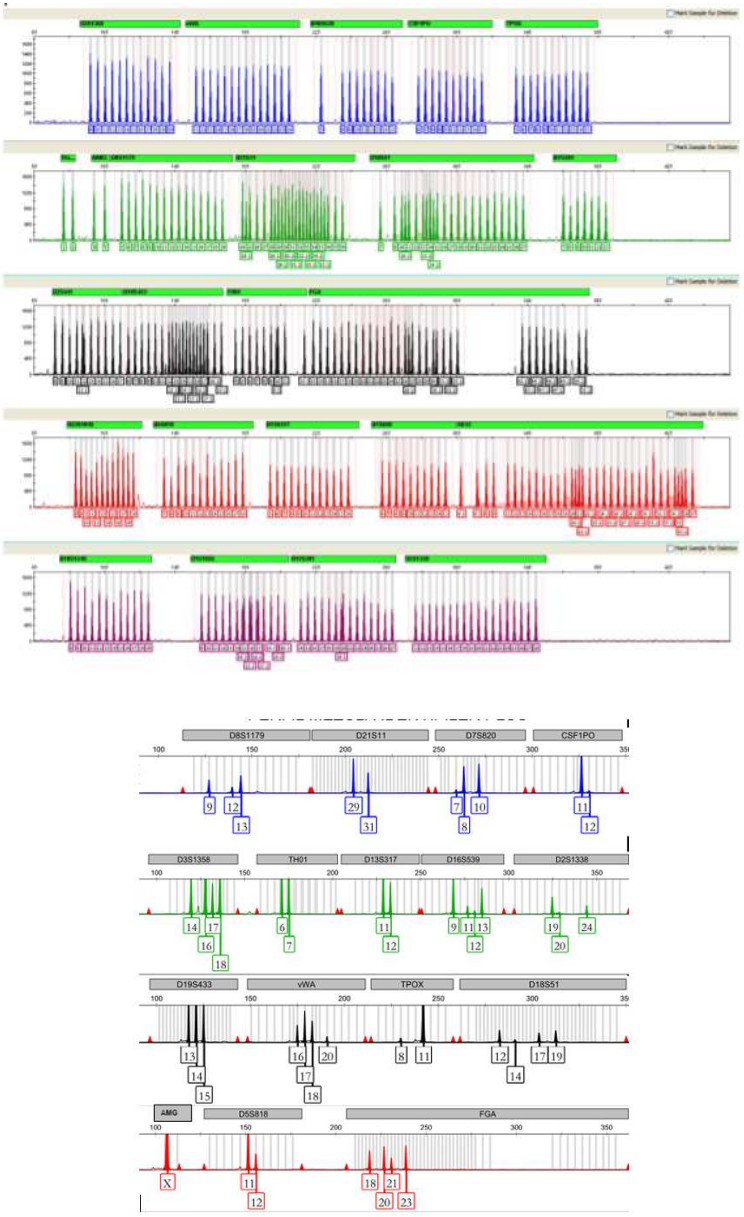
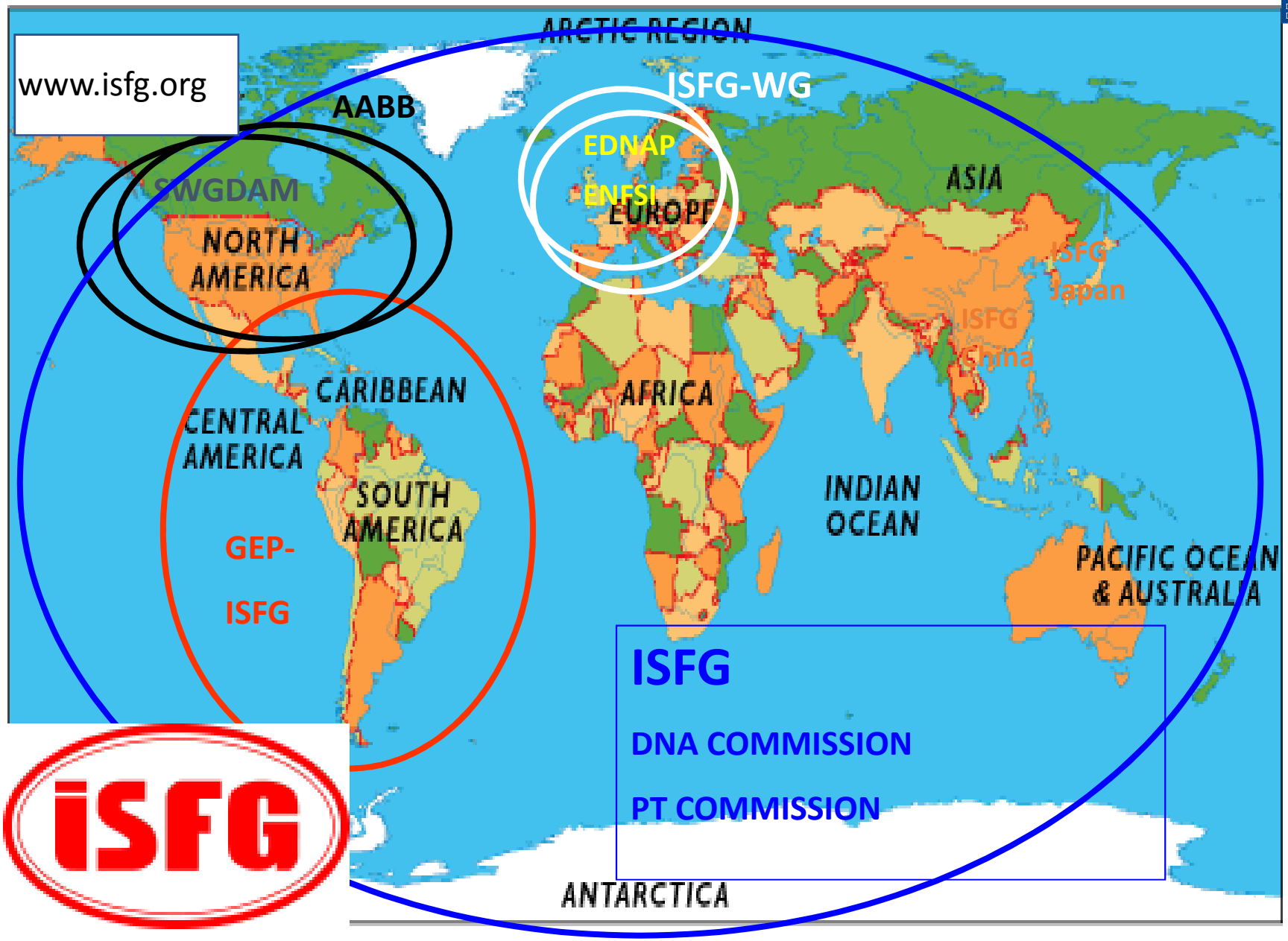


Imagen perfil mezcla de ADN de dos mujeres

En Europa aunque hay diferencias entre países en todos es obligatorio usar el denominado

GlobalFiler (AB)

STRs	ESS	CODIS
D3S1358	x	x
VWA	x	x
FGA	x	x
Amelogenina	(x)	
THO 1	x	x
TPOX		x
CSF1PO		x
D5S818		x
D13S317		x
D7S820		x
D2S1338		
D8S1179	x	x
D18S51	x	x
D21S11	x	x
D16S539		x
D19S433		
Penta D		
Penta E		
SE 33		
D22S1045	X	
D2S441	X	
D10S1248	X	
D12S391	X	
D1S1656	X	


www.isfg.org
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SWGDAM
NORTH AMERICA
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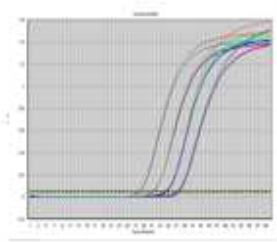
EDNAP
ENFSI
EUROPE
ASIA
SFG Japan
ISFG China
AFRICA
CARIBBEAN
CENTRAL AMERICA
SOUTH AMERICA
GEP-ISFG
INDIAN OCEAN
PACIFIC OCEAN & AUSTRALIA
ISFG
DNA COMMISSION
PT COMMISSION
ANTARCTICA
ISFG

The DNA analysis procedure in forensics



DNA Extraction (Chelex, Organic, Commercial columns, FTA® Paper) → **Quantification** (Optical Density, Quantiblot Fluorescence TaqMan) → **Multiplex STR Amplification** (Identifiler, Sefiler, SGM Plus, Powerplex16) → **Separation and allele size determination** → **Data Analysis**

Population genetics-Data → Statistical evaluation of the evidence → Communication

Revolution: technology and interpretation

Technology revolution:

Evolution of genetic markers

Evolution of equipment

Shorter response time

Revolution in interpretation:

Scientists are convinced that any opinion they give has a degree of uncertainty and that it is their duty and obligation to inform the judge of that **uncertainty**. In order to do that, a standard called **probability** exists.

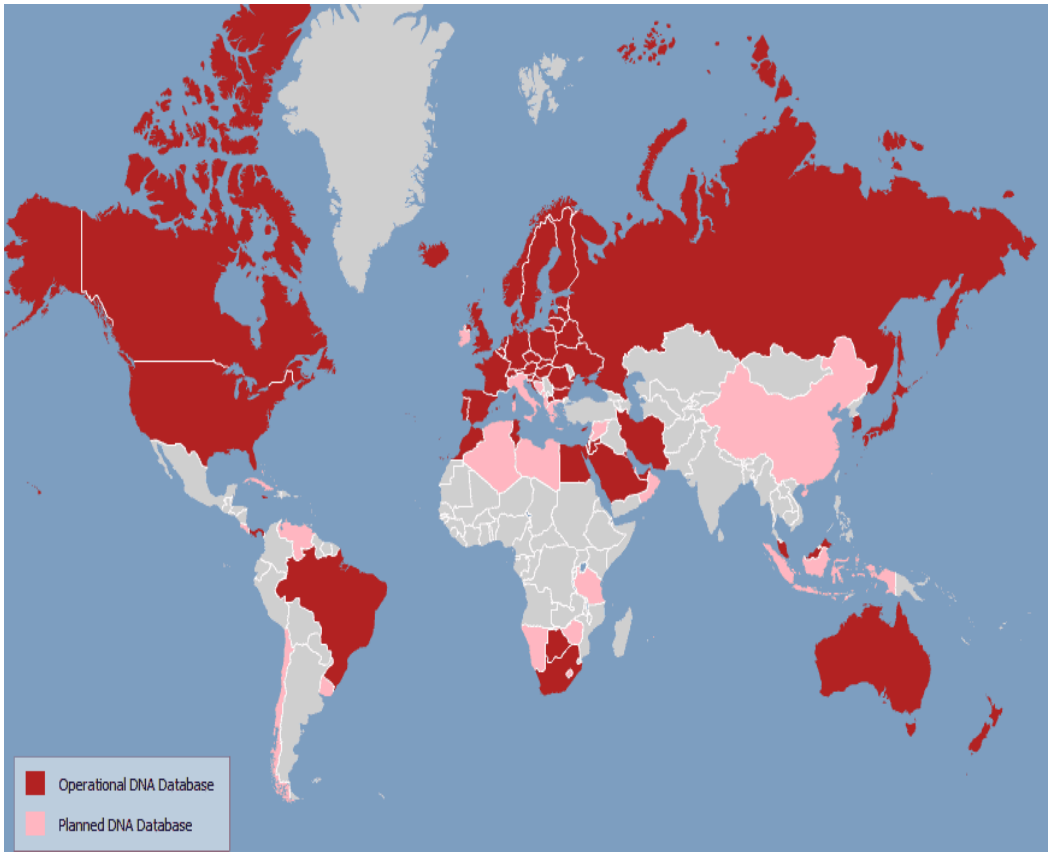
Statistics, interpretation and communication

The single most important advance in forensic science thinking is the realisation that the scientist should address the probability of the evidence

Still the area with most important challenges and need of standards

complex samples (partial genetic profiles, stochastic effects, DNA mixtures, low level DNA samples)

complex scenarios (massive identifications)



Kenya Government mandates DNA-linked national ID, without data protection law

Alice Munyua | February 8, 2019 | No responses yet

Last month, the Kenya Parliament passed a seriously concerning amendment to the country's national ID law, making Kenya home to the most privacy-invasive national ID system in the world. The rebranded, National Integrated Identity Management System (NIIMS) now requires all Kenyans, immigrants, and refugees to turn over their DNA, GPS coordinates of their residential address, retina scans, iris pattern, voice waves,

rst country in the world to collect
n all citizens and visitors:...
ment power to collect DNA samples is for national
waiti official.

Información sobre este sitio web

THEEPOCHTIMES.COM

Rwanda Plans to Collect DNA From 12 Million Citizens in World's First Nationwide Database

The New York Times

China Uses DNA to Track Its People, With the Help of American Expertise

The Chinese authorities turned to a Massachusetts company and a prominent Yale researcher as they built an enormous system of surveillance and control.

DNA Typing in Forensic Analysis

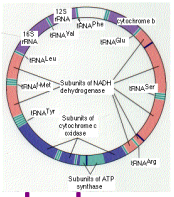
1985 1990 1995 2000 2005 2010

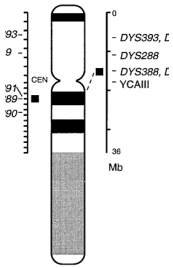
Blood Groups
Proteins

RFLPs

PCR / STRs

*mt*DNA sequencing



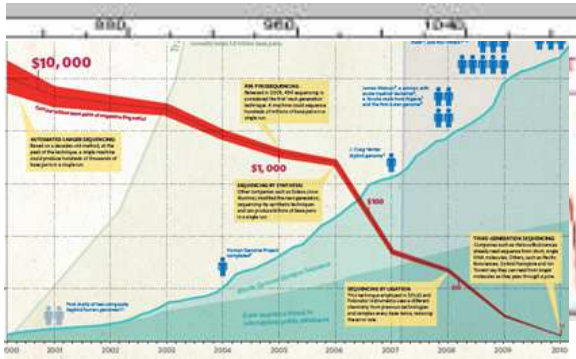


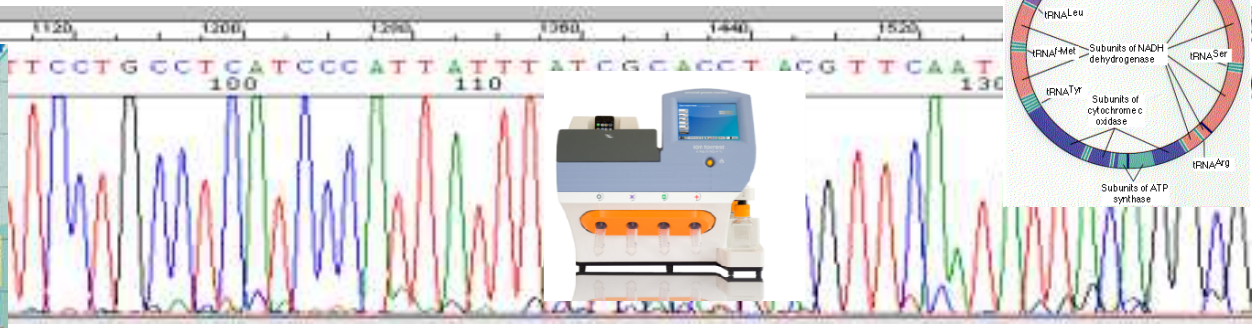
Sexual-chr markers

SNPs

mtDNA

There are thousands of copies of mtDNA in each cell compared to two copies of nucDNA, making mtDNA analysis a more sensitive assay, and thus, more successful on highly degraded specimens (e.g., old skeletal material and hair shafts)





Y STRs

Banaheia case
Kristiansand,
Norway

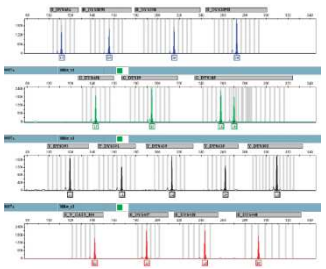
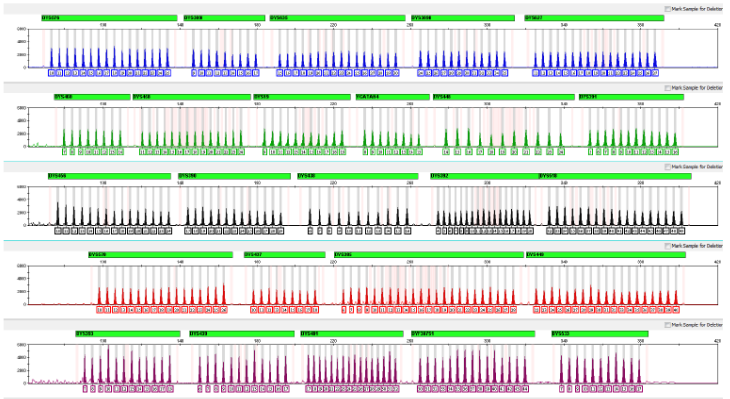


Figure 1 GeneMapper® *ID-X* Software v1.4 plot of the Yfiler® Plus Allelic Ladder



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EMPOP

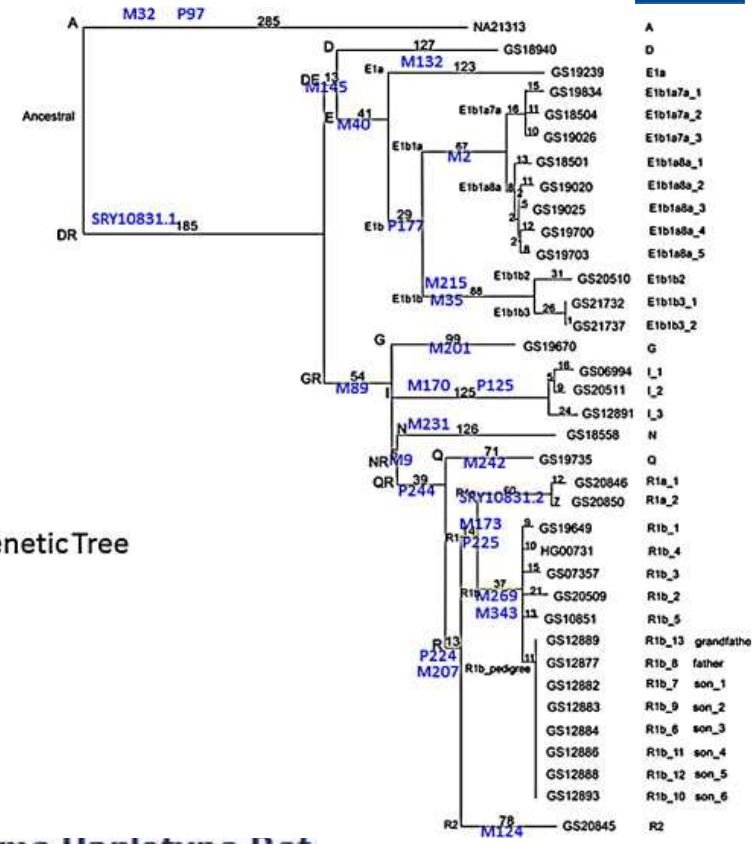
Mitochondrial DNA Control Region Database

Introduction

The high copy number per cell, the stability against degradation and the maternal mod
inheritance make the mitochondrial (mt) genome particularly suitable for palaeo-, medic
and forensic-genetic investigations. Its increased evolutionary rate led to sequence va
that has been generated by sequential accumulation of new mutations along radiating
maternal lineages during human dispersal into different parts of the world. Forensic mol
biology takes advantage of this variation for human identity testing by sequence analy
hypervariable segments within the mtDNA control region. MtDNA analysis is a powerful
exclude samples as originating from the same individual/matriline. If two samples canno
excluded the significance of the mtDNA match needs to be assessed by making referen
the frequency with which that particular mtDNA sequence (= mtDNA haplotype) has be
observed in a relevant population.

Concept

The EMPOP Database aims at the collection, quality control and the searchable prese
of mtDNA control region haplotypes from all over the world. The EMPOP project is a sci
collaboration between the Institute of Legal Medicine (GMI), Innsbruck Medical Univers
laboratories performing mtDNA research.



Phylogenetic Tree

y hrd
str database

Release 22:
52,655 Haplotypes
in **464** populations

About the "YHRD - Y Chromosome Haplotype Ref
Database"

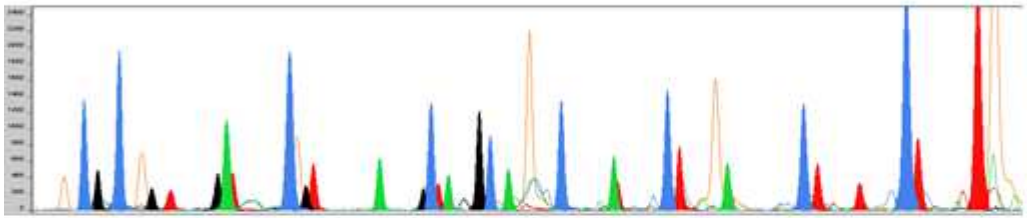
Please cite the database as follows: **Willuweit S, Roewer L, on behalf of the International Forensic Y Chromosome User Group (2007) Y chromosome haplotype reference database (YHRD): Update, Forensic Science International: Genetics 1(2) 83-87**(external link)

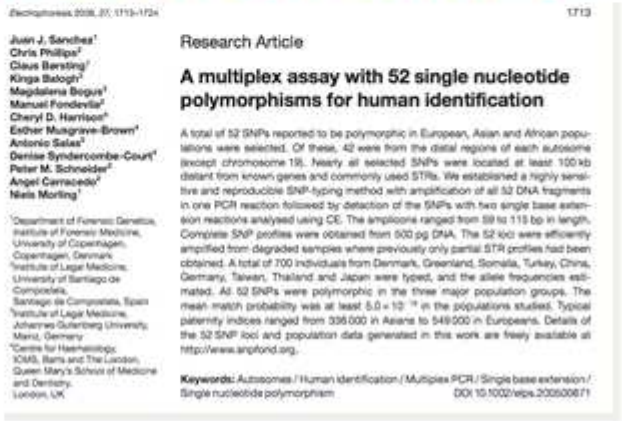
SNP: SINGLE NUCLEOTIDE POLYMORPHISM

ATCGGCGTACCTGATTCCGAATCCGTATCG
ATCGGCGTACCTGAATCCGAATCCGTATCG

The SNP for ID Consortium

The First Autosomal Multiplex





Research Article

A multiplex assay with 52 single nucleotide polymorphisms for human identification

SNPforID

small is beautiful

Degraded samples

Parental testing:
Distant relationships

DNA Phenotyping

SNP performance in critical samples

ISFG'05 Azores

SNPforID consortium

Saliva stains degraded for 147 days

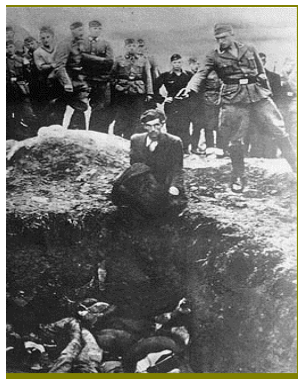
81% complete SNP profile /STRs were only 18% complete

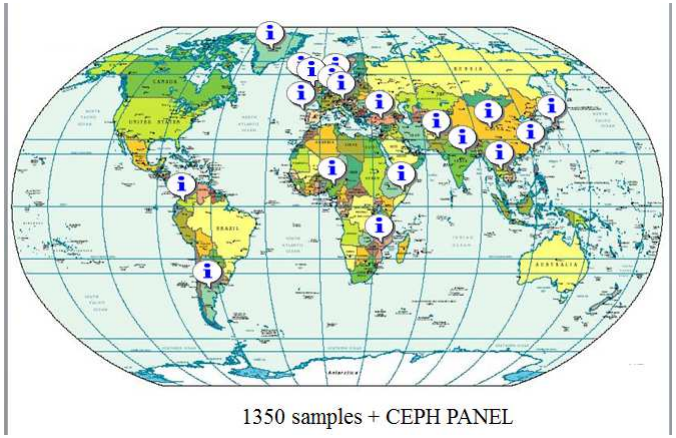
Blood degraded for 243 days

100% full SNP profiles /only 9% with STRs

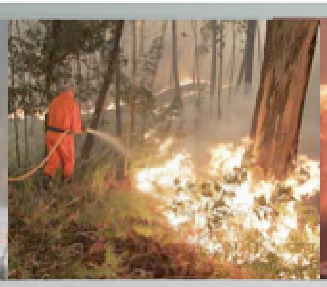
Low copy number from personal belongings

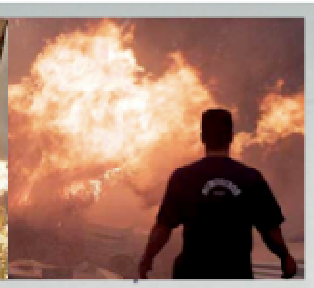
Full STR profile 24% / complete SNP profiles 92%





1350 samples + CEPH PANEL





Casework application challenging DNA analysis

- Charred human bones found by fire investigators followirg a severe forest fire 8-06
- An adult male had been reportec missing in the area 10 years previously
- A surviving daughter was sampled to allow comparison of any genotypes obtained
- Modified phenol-chloroform extraction of N_2 pulverized dust from white femur
- Identifiler - PP16 - mini NC01 & NC02 - Auto1 & Auto2 - PS-34plex - mtDNA

Contents lists available at ScienceDirect

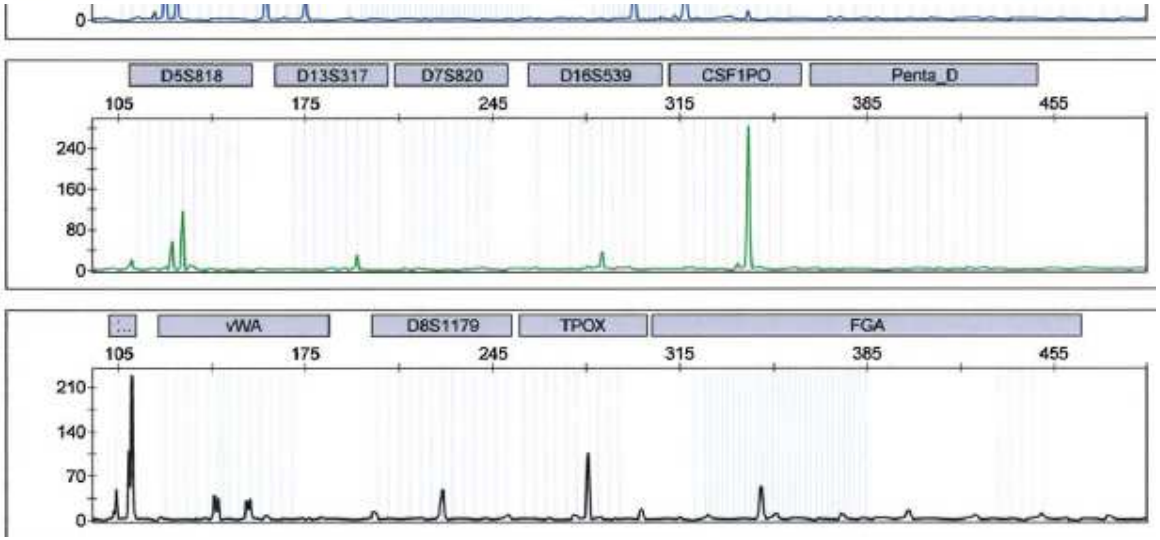
Forensic Science International: Genetics

journal homepage: www.elsevier.com/locate/fsig

A new SNP assay for identification of highly degraded human DNA

A. Freire-Aradas [a], M. Fondevila [a], A.-K. Kriegel [b], C. Phillips [a,*], P. Gill [c,d], L. Prieto [e], P.M. Schneider [b], Á. Carracedo [a], M.V. Lareu [a]

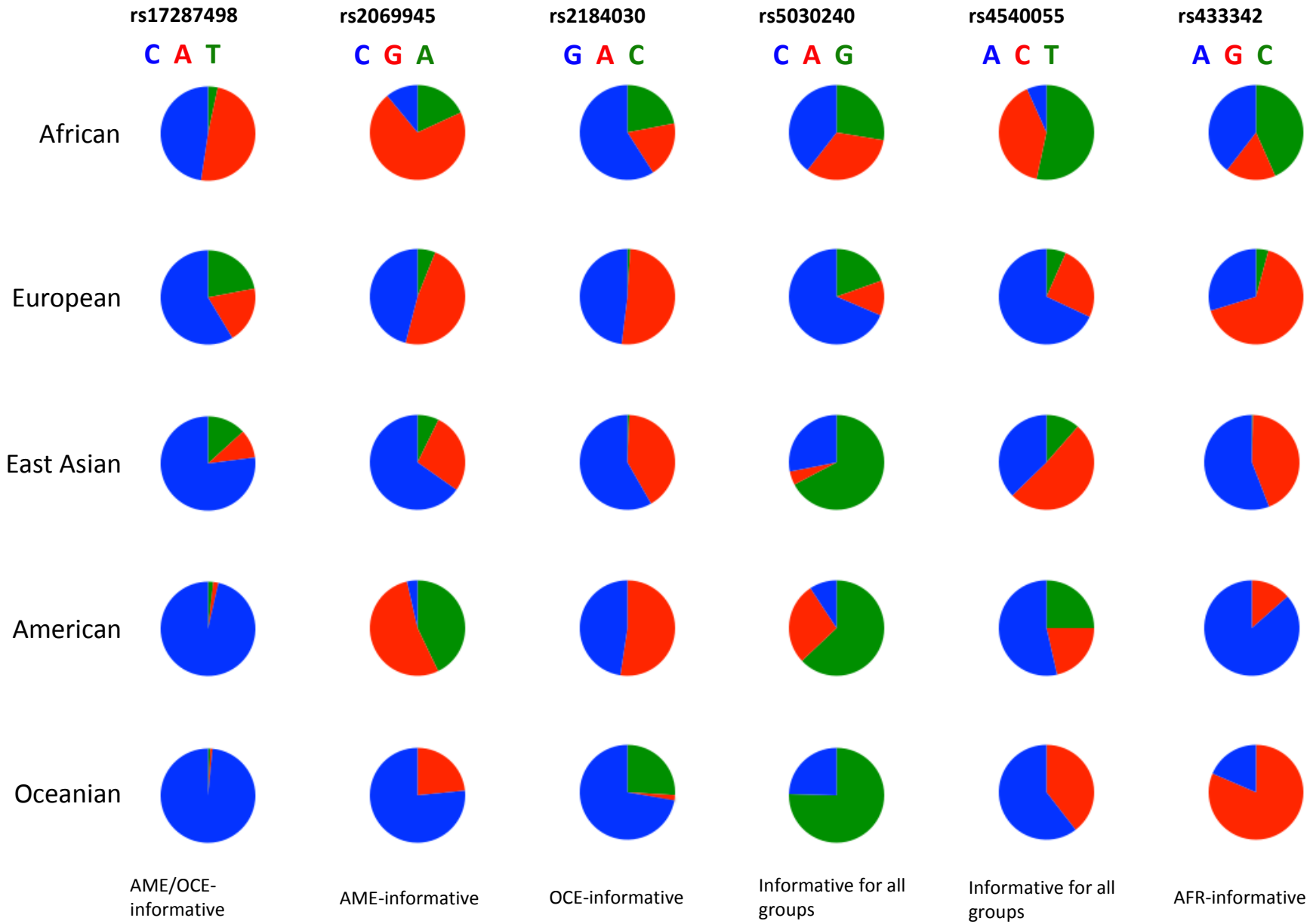
[a] Forensic Genetics Unit, Institute of Legal Medicine, University of Santiago de Compostela, Spain
[b] Institute of Legal Medicine, University Hospital, University of Cologne, Germany
[c] Institute of Legal Medicine, University of Oslo, Rikshospitalet, Norway
[d] Forensic Science Centre, University of Strathclyde, Glasgow, UK
[e] University Institute of Research Police Sciences (IUICP), DNA Laboratory, Comisaría General de Policía Científica, Madrid, Spain



Electrophoresis. 2009 Nov;30(21):3682-90.

A new multiplex for human identification using insertion/deletion polymorphisms.

Pereira R, Phillips C, Alves C, Amorim A, Carracedo A, Gusmão L.


rs17287498
C A T
rs2069945
C G A
rs2184030
G A C
rs5030240
C A G
rs4540055
A C T
rs433342
A G C
African
European
East Asian
American
Oceanian
AME/OCE-informative
AME-informative
OCE-informative
Informative for all groups
Informative for all groups
AFR-informative

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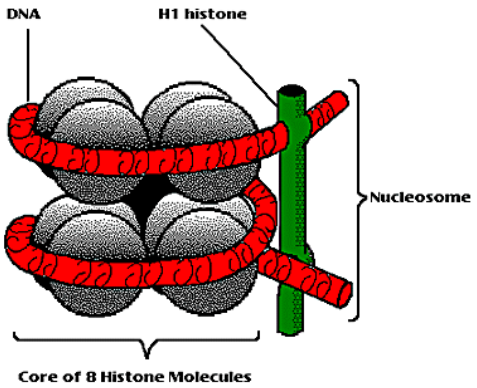
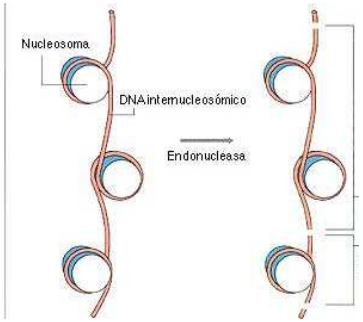
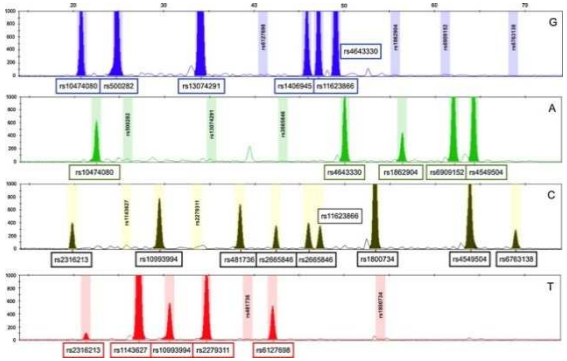
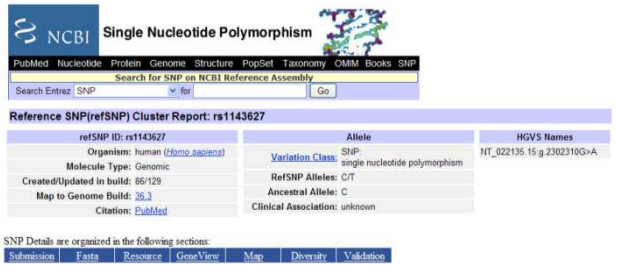






Nucleosome

Recon program



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Should not be frightened of difficult DNA

USC

DNA from Pre-Clovis Human Coprolites in Oregon, North America

M. Thomas P. Gilbert,[1]* Dennis L. Jenkins,[2]* Anders Götherstrom,[3] Nuria Naveran,[4] Juan J. Sanchez,[5] Michael Hofreiter,[6] Philip Francis Thomsen,[1] Jonas Binladen,[1] Thomas F. G. Higham,[7] Robert M. Yohe II,[8] Robert Parr,[9] Linda Scott Cummings,[9] Eske Willerslev[1]†

9 MAY 2008 VOL 320 SCIENCE

Science

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ScienceDirect

FSI GENETICS

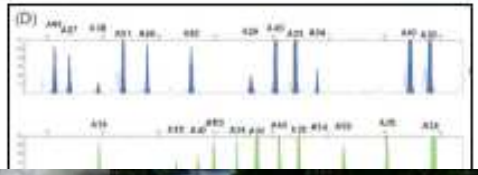
Case report: Identification of skeletal remains using short-amplicon marker analysis of severely degraded DNA extracted from a decomposed and charred femur

M. Fondevila[a], C. Phillips[a,b,*], N. Naveran[a], L. Fernandez[a], M. Cerezo[a], A. Salas[a,b], Á. Carracedo[a,b], M.V. Lareu[a,b]

14KYA 5-plex SNaPshot
2-SNP pyrosequencing mt codin

Double-degraded DNA 29-plex, 23-plex & 4-plex SNaPshot

used ancient DNA extraction system



ORIGINAL ARTICLE

Pigment phenotype and biogeographical ancestry from ancient skeletal remains: inferences from multiplexed autosomal SNPs

Caroline Bouakaze · Christine Keyser · Eric Crubézy · Daniel Montagnon · Bertrand Ludes

up to 5KYA 1+8+1-plex SNaPshot
AIMs and pigmentation SNPs

SNPs improves mini-STR sizes to combat degradative process

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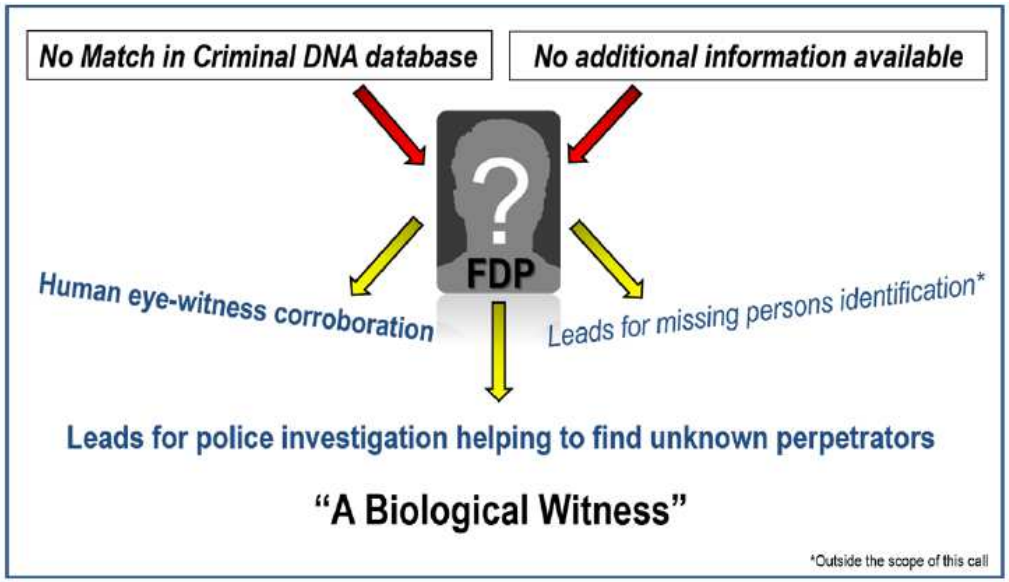
What is Forensic DNA Phenotyping

- Witness of a crime is usually asked about sex, appearance and age of the perpetrator
- DNA variants can be informative in terms of appearance phenotype and age prediction
- **FDP** refers to DNA prediction of externally visible traits of unknown sample donor from biological traces collected at the scene of a crime

FDP is an investigative tool



- Matching DNA profiles only works for known suspects
  - reference DNA profile match
  - DNA database profile match
- DNA mass screenings – when no match is found
- FDP allows for more precise selection of target group when searching for unknown suspects
- FDP may be useful in missing persons identification

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INNOCENCE PROJECT

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The Innocence Project, founded in 1992 by Peter Neufeld and Barry Scheck at Cardozo School of Law, exonerates the wrongly convicted through DNA testing and reforms the criminal justice system to prevent future injustice.

"Injustice anywhere is a threat to justice everywhere." Martin Luther King, Jr.

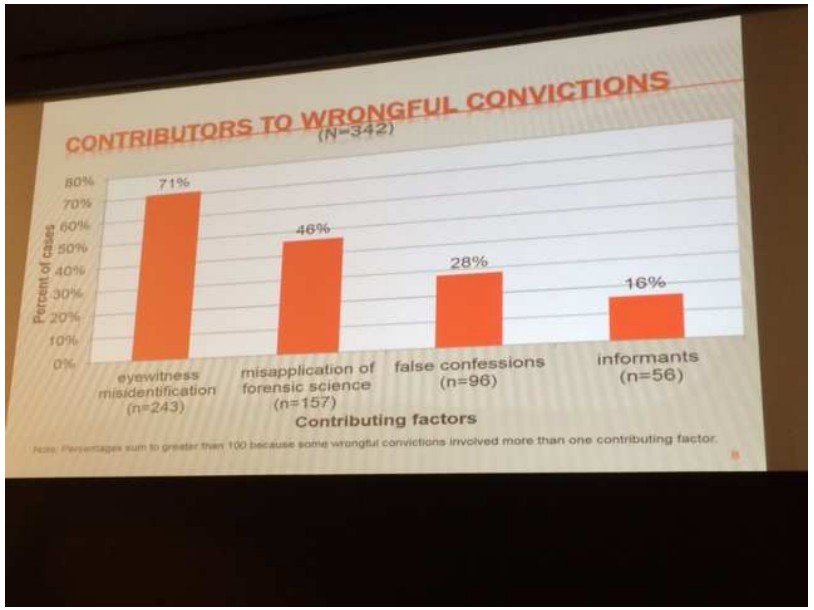
342

Number of DNA Exonerations

147

Number of Real Perpetrators found

71%



Forensic DNA Phenotyping

1. External visible characteristics
EVC: Pigmentation traits, body height, hair morphology, ear morphology, facial shape, and for some age-related appearance traits such as hair loss, pigmented age spots.

2. Bio- geographic ancestry i.e., the geographic region of origin of a person's biological ancestors

3. Estimation of age

Why mtDNA and Y chr are not ideal markers for forensic DNA phenotyping

Grandfather

Y-DNA R1b1

Grandmother

African

father

Y-DNA R1b1

Grandpather

African

Grandmother

mtDNA H1a

mother

mtDNA H1a

hijo

Y-DNA R1b1
mtDNA H1a

I'm European and white! Look at my DNA!!

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Genetics of Phenotypic Traits

- **Monogenic traits:** One gene explains all heritability
  - Mendelian inheritance (Mendelian traits)
  - E.g. Lactose intolerance (Chr2, *MCM6-LCT*)
- **Polygenic traits:** Many genes, all with small effects
  - Complex pattern of inheritance
  - Most appearance traits, e.g. body height (700 SNP: 16% variance Nat Genet 2014)
- **The middle class:** One or few major gene(s) + many additional genes with minor effects
  - Semi-Mendelian inheritance
  - E.g. blue / brown eye color (major effect: Chr15, *HERC2*)
  - E.g. male pattern baldness (major effect: ChrX, *AR*)

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How To Find Genes / Predictive Markers

- **Linkage Analysis:** use of related individuals / family samples
  - suitable to identify rare alleles with relatively large phenotypic effects (Mendelian traits)
  - Candidate region or genome-wide approach
- **Association Testing:** use of unrelated individuals / population samples
  - Suitable to identify common alleles with medium to small phenotypic effects (polygenic / complex traits)
  - Candidate gene or genome-wide association study (GWAS)
  - Large sample size to *safely* identify small effect genes / SNPs
  - Association threshold for SNP array GWAS: $P<5x10^{-8}$
  - Replication in independent samples needed to trust results

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Human Genetic Association Study Design

Blue eyes
Baldness

Brown eyes
No hair loss

International HapMap Project

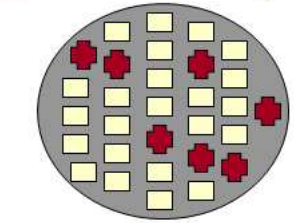
SNPs are the ideal markers

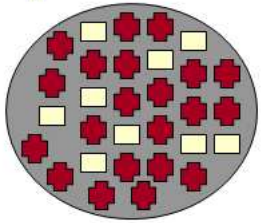
Allele 1

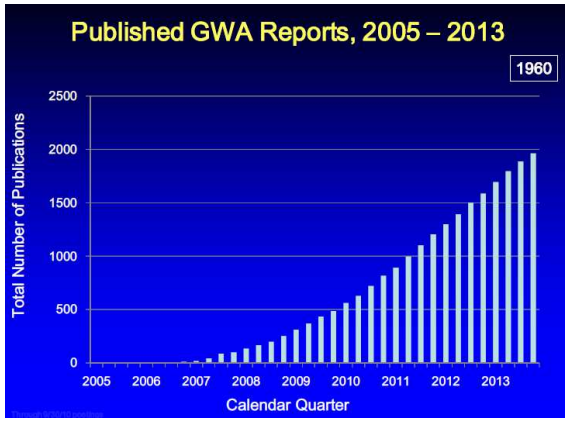
Allele 2

Marker A:
Allele 1
Allele 2

Marker A is associated with Phenotype







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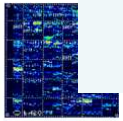
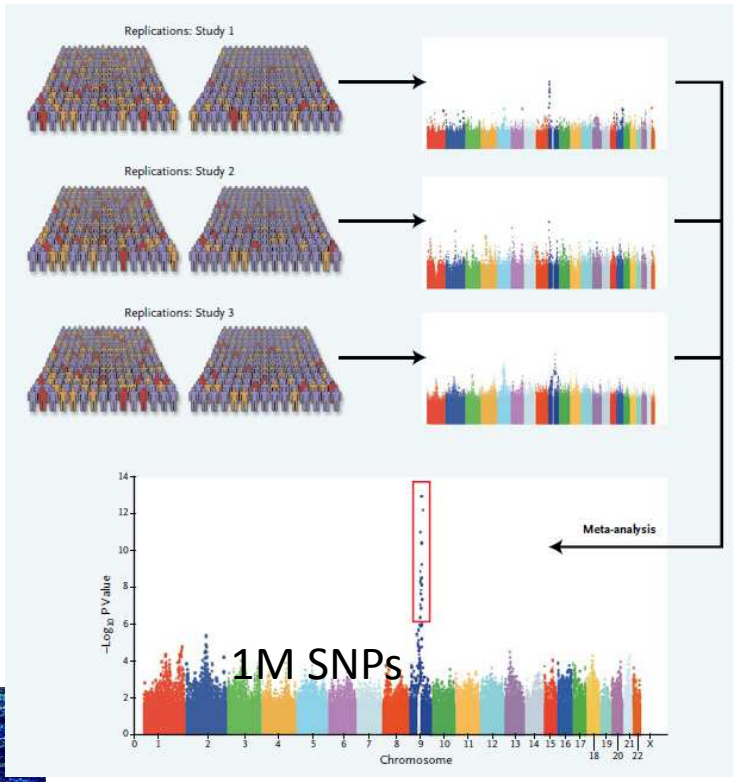
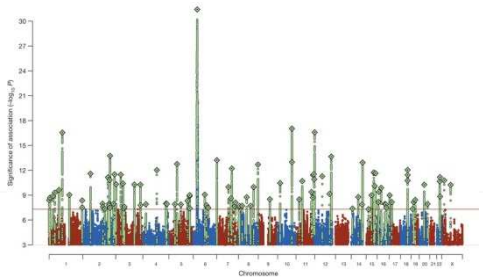




Discovery of pigmentation markers

- Animal models and albism affected people indicate **candidate genes in humans**
- ***MC1R*** – the red hair color and fair skin gene
- ***TYR***, ***OCA2***, ***TYRP1***, ***SLC45A2*** – albinism genes, candidates for natural eye, hair and skin color variati
- >10 Successful **GWA studies**:

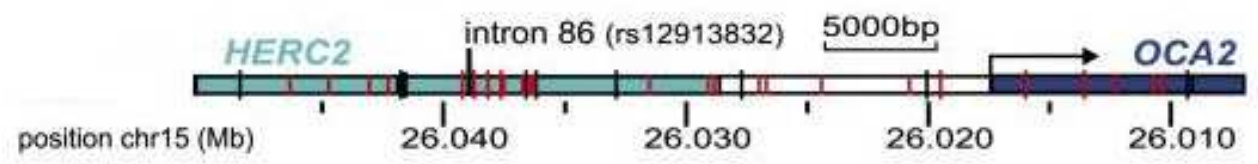


- Confirmation of already known loci associated with pigmentation (*TYR*, *MC1R*, *OCA2*, *TYRP1*, *ASIP*, *SLC45A2*, *SLC24A5*)
- Novel pigmentation and non-pigmentation genes
  - Eye colour: *HERC2*, *SLC24A4*, *IRF4*, *LYST*, *DSCR9*
  - Hair colour: *KITLG*, *IRF4*, *EXOC2*, *TPCN2*, *HERC2*
  - Skin colour and type: *IRF4*, LOC401937

HERC2 – powerful eye colour regulator

- **rs12913832 in *HERC2*** – key predictor in all eye colour prediction models

- This polymorphism regulates expression of *OCA2* – the important pigmentation gene



HERC2 **rs12913832** modulates human pigmentation by attenuating chromatin-loop formation between a long-range enhancer and the OCA2 promoter.
Visser M, Kayser M, Palstra RJ.
Genome Res. 2012 Mar;22(3):446-55.

From the SNP to the causal gene – Functional studies

- **Associated SNP is the causal DNA variant**
  - mutation in a codon leads to aminoacid change that changes the protein to influences the trait
- **Most SNPs found associated via SNP arrays not causal**
  - because of e.g. SNP chip design biased towards no-gene regions
  - May have regulatory function i.e. a mutation changes a binding site of a transcription factor which regulates the expression of a gene that directly influences the trait
  - Maybe indirectly associated because of linked inheritance with causal or regulatory SNPs that are not represented on the SNP chip used

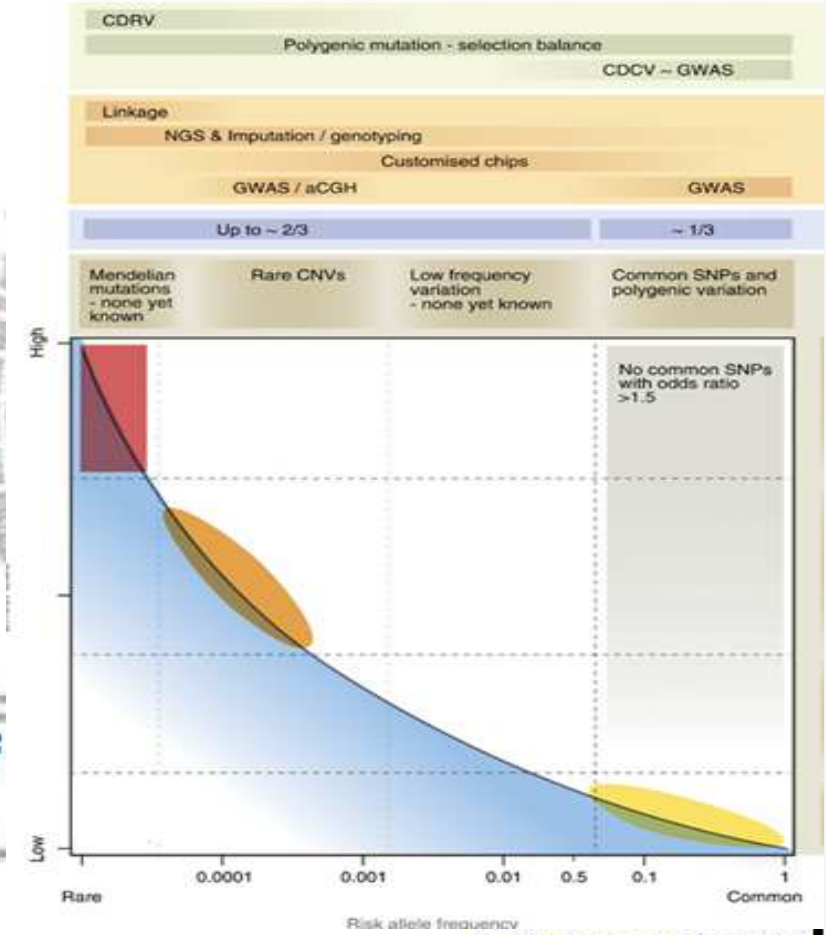
Power of GWAS depends on:

- Trait heritability (environmental impact)
- Genotyping tools / marker types used (SNP arrays versus sequencing)
- Sample size
- Allele effect size
- Effect allele frequency
- Genetic model used

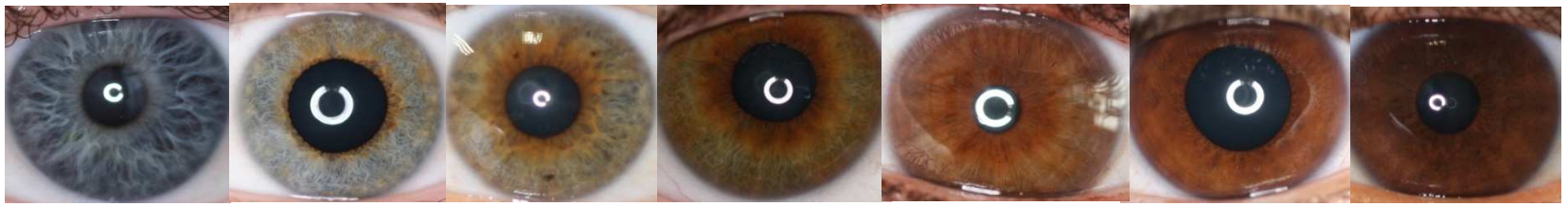
- **Reliable association results: $p<5x10^{-8}$ and replicated in independent samples**
- **At best with causal / regulatory effect experimentally proven**

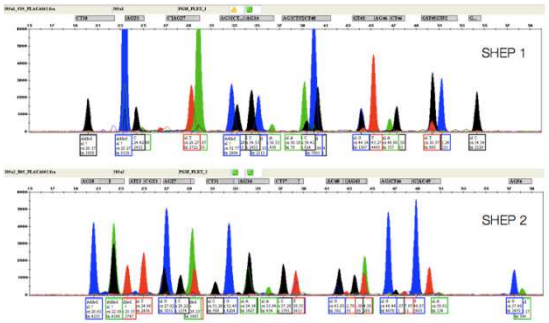
What's not found by SNP array GWAS?

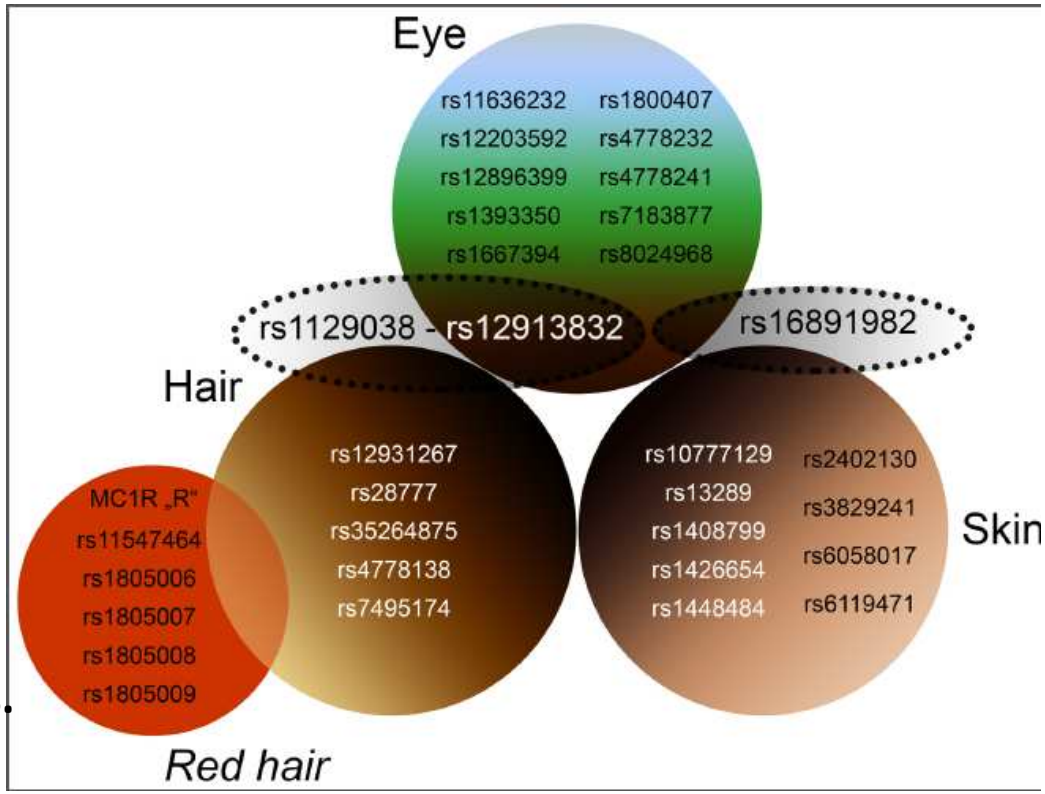
- DNA variants with very small effects
- Rare DNA variants
- Recessive DNA variants
- Allelic heterogeneity
- Genetic interaction effects
- Compound heterozygote effects
- **= Missing heritability of complex traits**



Kettunen et al. 2012







[Forensic Sci Int Genet.](#) 2015 Sep;18:33-48. **Forensic DNA Phenotyping: Predicting human appearance from crime scene material for investigative purposes.** [Kayser M](#)

The Genetics of Skin, Hair, and Eye Color Variation and Its Relevance to Forensic Pigmentation Predictive Tests

O. Maroñas[1], J. Söchtig[1], Y. Ruiz[2], C. Phillips[1]*, Á. Carracedo[1,3,4], M. V. Lareu[1]

FORENSIC SCIENCE REVIEW
www.forensicsciencereview.com

2015

HIrisPlex-S Eye, Hair and Skin Colour DNA Phenotyping Webtool

12px ▼

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Welcome to the Department of Genetic Identification of Erasmus MC

With the advancement of DNA phenotyping as a tool in Forensic and Anthropological usage, we now provide an easy to use interactive website to predict eye, hair and skin colour from DNA using the IrisPlex, HIrisPlex and HIrisPlex-S systems.

This work is in collaboration with the Walsh laboratory of Indiana-University-Purdue-University-Indianapolis (IUPUI), USA.

The HIrisPlex-S System

	Gene	SNP	Allele	No. of Alleles
1	*MC1R*	rs312262906	A	0 1 2 NA
2	*MC1R*	rs11547464	A	0 1 2 NA
3	*MC1R*	rs885479	T	0 1 2 NA
4	*MC1R*	rs1805008	T	0 1 2 NA
5	*MC1R*	rs1805005	T	0 1 2 NA
6	*MC1R*	rs1805006	A	0 1 2 NA
7	*MC1R*	rs1805007	T	0 1 2 NA
8	*TUBB3*	rs1805009	C	0 1 2 NA
9	*MC1R*	rs201326893	A	0 1 2 NA
10	*MC1R*	rs2228479	A	0 1 2 NA
11	*MC1R*	rs1110400	C	0 1 2 NA
12	*SLC45A2*	rs28777	C	0 1 2 NA
13	*SLC45A2*	rs16891982	C	0 1 2 NA
14	*KITLG*	rs12821256	G	0 1 2 NA
15	*LOC105374875*	rs4959270	A	0 1 2 NA
16	*IRF4*	rs12203592	T	0 1 2 NA
17	*TYR*	rs1042602	T	0 1 2 NA
18	*OCA2*	rs1800407	A	0 1 2 NA
19	*SLC24A4*	rs2402130	G	0 1 2 NA
20	*HERC2*	rs12913832	T	0 1 2 NA
21	*PIGU*	rs2378249	C	0 1 2 NA
22	*LOC105370627*	rs12896399	T	0 1 2 NA
23	*TYR*	rs1393350	T	0 1 2 NA
24	*TYRP1*	rs683	G	0 1 2 NA
25	*ANKRD11*	rs3114908	T	0 1 2 NA
26	*OCA2*	rs1800414	C	0 1 2 NA
27	*BNC2*	rs10756819	G	0 1 2 NA
28	*HERC2*	rs2238289	C	0 1 2 NA
29	*SLC24A4*	rs17128291	C	0 1 2 NA
30	*HERC2*	rs6497292	C	0 1 2 NA
31	*HERC2*	rs1129038	G	0 1 2 NA
32	*HERC2*	rs1667394	C	0 1 2 NA
33	*TYR*	rs1126809	A	0 1 2 NA
34	*OCA2*	rs1470608	A	0 1 2 NA
35	*SLC24A5*	rs1426654	G	0 1 2 NA
36	*ASIP*	rs6119471	C	0 1 2 NA
37	*OCA2*	rs1545397	T	0 1 2 NA
38	*RALY*	rs6059655	T	0 1 2 NA
39	*OCA2*	rs12441727	A	0 1 2 NA
40	*MC1R*	rs3212355	A	0 1 2 NA
41	*DEF8*	rs8051733	C	0 1 2 NA

Display Predicted Phenotype | Download Predicted Phenotype

https://hirisplex.erasmusmc.nl/

Human height – small additive effects

- 70-90% of variance of human height may be due to genetic component
- 35 GWA studies and meta-analyses on height until 2016
- Additive effects of multiple loci with small effect (OR ~ 1.1) explain variance of human height
- **Lango-Allen** et al. (2010): 10% of height variance explained by 180 loci in the human genome (prediction of extremely tall stature with AUC=0.75
- **Wood** et al. (2014) – 9500 SNPs explains 29% of height variance

Update on the predictability of tall stature from DNA markers in Europeans

Fan Liu[a,b,*], Kaiyin Zhong[b], Xiaoxi Jing[a], André G. Uitterlinden[c,d], A. Emile J. Hendriks[e], Stenvert L.S. Drop[f], Manfred Kayser[b,*]

DOI: https://doi.org/10.1016/j.fsigen.2019.05.006

Article Info

Abstract | **Full Text** | Images | References | Supplemental Materials

Highlights

- Current forensic DNA phenotyping focuses on pigmentation traits.
- Update on DNA predictability of tall stature in Europeans is presented.
- 689 SNPs provided AUC of 0.79, while a subset of 412 SNPs achieved 0.76.
- New models improved prediction accuracy compared to previous ones.

Facial morphology

- Genes involved in cleft lip and other craniofacial pathologies – candidate loci for natural variation (e.g. **Boehringer** et al. 2011)
- **Liu** et al. (2012) – GWAS identified *PRDM16, PAX3, TP63, C5orf50* and *COL17A1*
- Small effect size of the identified DNA variants
- **Claes** et al. (2014a, b) – complex mathematical approach for predictive modeling involving ancestry, sex and genes

    - 24 SNPs improve by 1% accuracy of face morphology prediction

Male pattern baldness

- Very high estimated heritability 85-95%
- **Brockschmidt** et al. (2011) – *AR-EDA2R,* 20p11.22
- **Li** et al. (2012) – *AR-EDA2R, PAX1, HDAC4, HDAC9, TARDBP,* 17q21.31, *AUTS2, SETBP1*
- *AR-EDA2R* – confirmed in Europeans in several studies
- MPB risk is predictable at an accuracy level of 0.74 when 14 SNPs were included in the model (Liu et al, 2016)
- EUROFORGEN-NoE project on baldness up to 0.80

Liu et al. Eur J Hum Genet. 2016 Jun;24(6):895-902..
Prediction of male-pattern baldness from genotypes.

Hair morphology

- Heritability 85-95% as estimated from twins study
- Very variable among Europeans (straight-curly-wavy)
- One GWA study and several candidate studies
- **Medland** et al. (2009) – strongest association with *TCHH* on 1q21.3
- Merely 6% of variance of hair morphology explained
- **Eriksson** et al. (2010) - other candidate genes: *WNT10A* (chr 2), *FRAS1* (chr 4), *LCE3E* (chr 1), *OFCC1* (chr 6)

Forensic Science International: Genetics

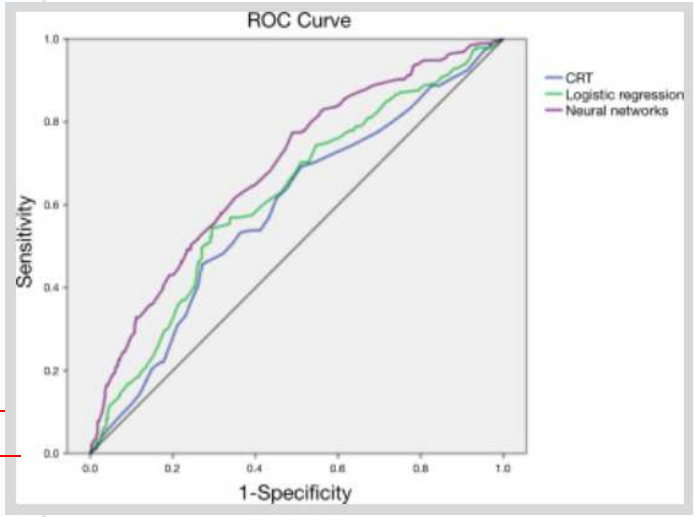
Volume 19, November 2015, Pages 280–288

Research paper

Evaluation of the predictive capacity of DNA variants associated with straight hair in Europeans

Ewelina Pośpiech[a], Joanna Karłowska-Pik[b], Magdalena Marcińska[c], Sarah Abidi[d], Jeppe Dyrberg Andersen[e], Margreet van den Berge[f], Ángel Carracedo[g, h], Mayra Eduardoff[g], Ana Freire-Aradas[g], Niels Morling[e], Titia Sijen[f], Małgorzata Skowron[i], Jens Söchtig[g], Denise Syndercombe-Court[d], Natalie Weiler[f], Peter M. Schneider[k], David Ballard[d], Claus Børsting[e], Walther Parson[i, l], Chris Phillips[g], Wojciech Branicki[a]

- A replication study was made of SNPs most closely associated with hair morphology variation in Europeans (assigning straight, wavy and curly hair phenotypes).
- Analysis of 670 samples from seven European populations revealed the strongest association for rs11803731 in *TCHH*, rs7349332 in *WNT10A* and rs1268789 in *FRAS1*.
- Applying three different mathematical models to assess the predictive capacity of the SNPs indicated neural networks gives the best performing model to predict straight hair with high sensitivity and better specificity than logistic regression and CRT methods.
- The combined TTGGGG SNP genotype (rs11803731-rs7349332-rs1268789) was identified as the best predictor, giving greater than 80% probability of straight hair.
- The reported study is the first assessment of the forensic suitability of hair morphology as an externally visible characteristic. The results provide the basis for extended analyses of SNPs associated with this trait.



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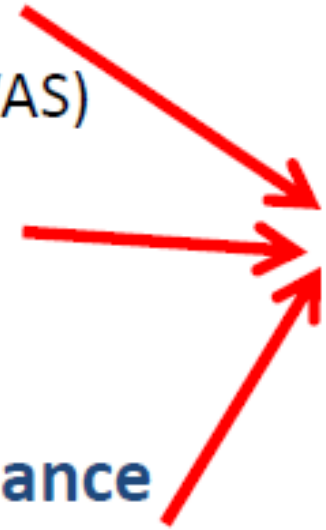
Association is NOT Prediction

- Prediction accuracy is determined by:
  - (Sample-size)
  - Allele effect size
  - Effect allele frequency
  - Genetic model
- Prediction considers the joint effect of multiple SNPs
- SNPs with high association but strong linkage disequilibrium provide no independent / additional prediction value

Three Steps in Prediction Studies

- **1. Identify DNA predictors**
  - E.g. Association studies (GWAS)
- **2. Build prediction models**
  - Linear / logistic regressions
  - Other models
- **3. Evaluate model performance**
  - Categorical traits: Sensitivity, specificity, area under the receiver operating characteristic curves
  - Continuous traits: Explained variance (R^2), mean squared error (MSE)



Prediction modeling in forensics

- Regression methods, Bayesian statistics, classification trees
- Prediction model building
  - samples with known phenotype – training set (usually 70-80%)
  - selecting the most accurate model
- Prediction model testing
  - Independent samples with known phenotype – testing set (usually 20-30%)
- Parameters defining performance of the model
  - sensitivity, specificity, PPV, NPV, AUC

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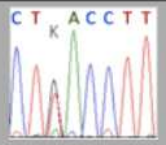


The Snipper 2.5

app suite

Need help?

Input search string

Search Snipper

Main Home

Binary AIM classification of individuals

You are entering our portal on SNP-Indel classification, hosting the *Snipper App suite* version 2.5. It is the companion site to several papers.

- **Faster algorithms**. NEW
- Improved **Multinomial Logistic Regression** (MLR) implementation. NEW
- Revised **density plots** and **3D views** no longer dependent on Java. NEW
- A new **tool to predict age** is available. NEW

Green colour in links means fixed training sets. On the other hand, red means custom training sets. Available tasks are:

- **Classification as Europe-East Asia-Africa-America-Oceania (34 SNPs, 46 Indels, or both sets)**
- **Classification as individual having black-intermediate-white skin**
- **Classification as individual having fair-dark or red-blond-brown-black hair**
- **Classification as individual having blue-greenhazel-brown eyes**
- **Classification with a custom Excel file of populations**
- **Classification of multiple profiles with a custom Excel file of populations**
- **Tune up your training/testing set**
- **Classification with the 32 STR training set or a custom Excel file of frequencies**
- **Thorough analysis of population data of a custom Excel file**
- **Profile generator for fixed or custom training sets**
- **Plot some or all the populations of a custom Excel file**

Age prediction in forensics

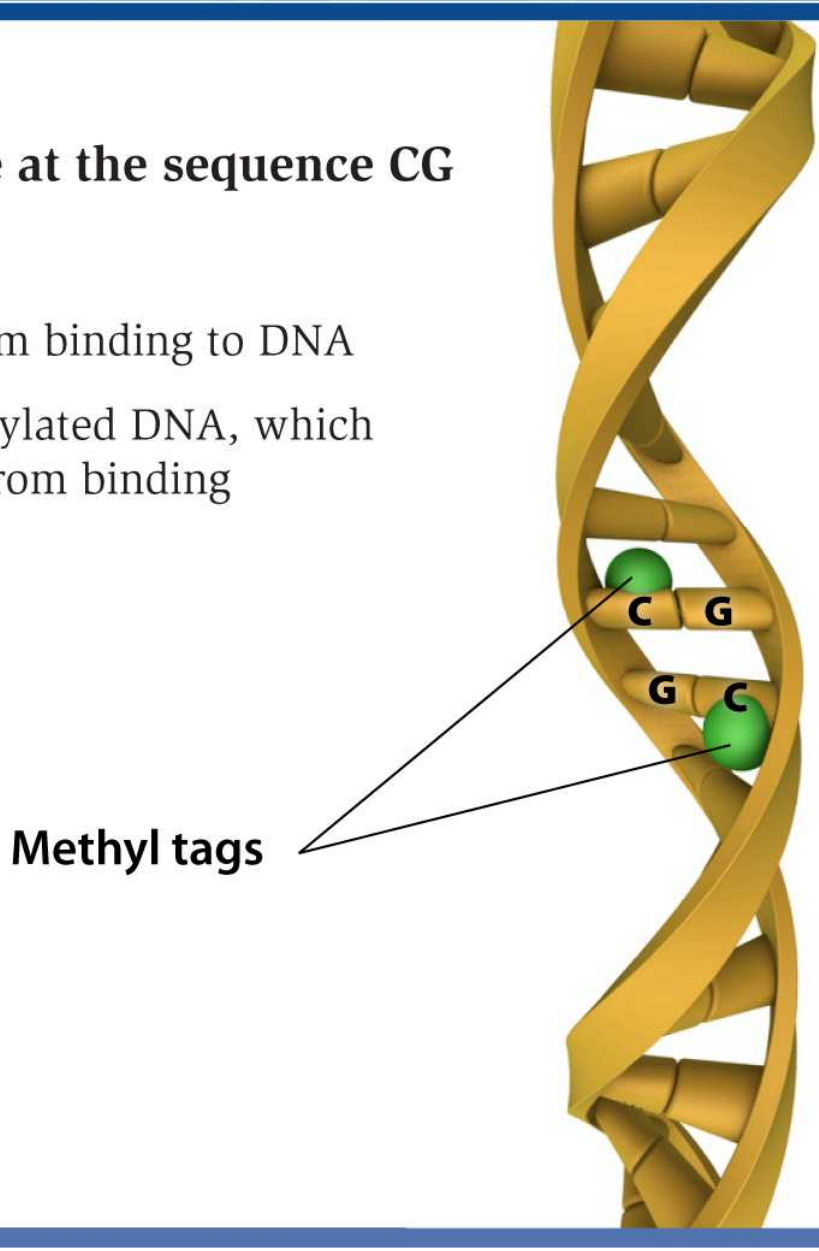
- Age estimation may significantly improve precision of a portray of an unknown individual
- Various methods considered in forensic science
  - shortening of telomeres
  - accumulation of 4977 bp deletion in mitochondrial DNA
- Decrease in the number of sjTREC molecules caused by thymus involution occurring in the course of human life
- **Zubakov** et al. (2010) – accurate prediction of age groups based on sjTREC quantification
- DNA methylation of markers linearly correlated with age

Methyl tags usually turn genes off

Methyl tags are added to a cytosine at the sequence CG

They silence genes by:

- Blocking transcription machinery from binding to DNA
- Recruiting proteins that bind to methylated DNA, which then block transcription machinery from binding



Development of a methylation marker set for forensic age estimation using analysis of public methylation data and the Agena Bioscience EpiTYPER system

A. Freire-Aradas, C. Phillips, A. Mosquera-Miguel, L. Girón-Santamaría, A. Gómez-Tato, M. Casares de Cal, J. Álvarez-Dios, J. Ansede-Bermejo, M. Torres-Español, P.M. Schneider, E. Pośpiech, W. Branicki, Á. Carracedo, M.V. Lareu

FSI Genetics 24: 65-74 (2016)

- Illumina HumanMethylation 450 BeadChip data from populations all over the world.
- 177 CpG sites with informative methylation patterns analyzed with EpiTYPER technology
- *Most informative ELOVL2, ASPA, PDE4C, FHL2, CCDC102B*

, C1orf132 and chr16:85395429

- Training set of 725 European individuals (18-104 y) and a test set of 52 monozygotic twin pairs
- Multivariate quantile regression age predictor placed in *Snipper*

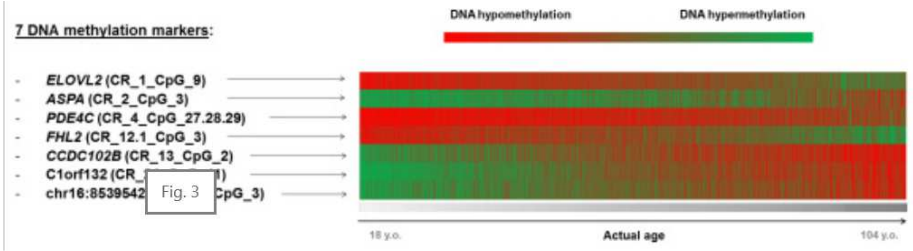
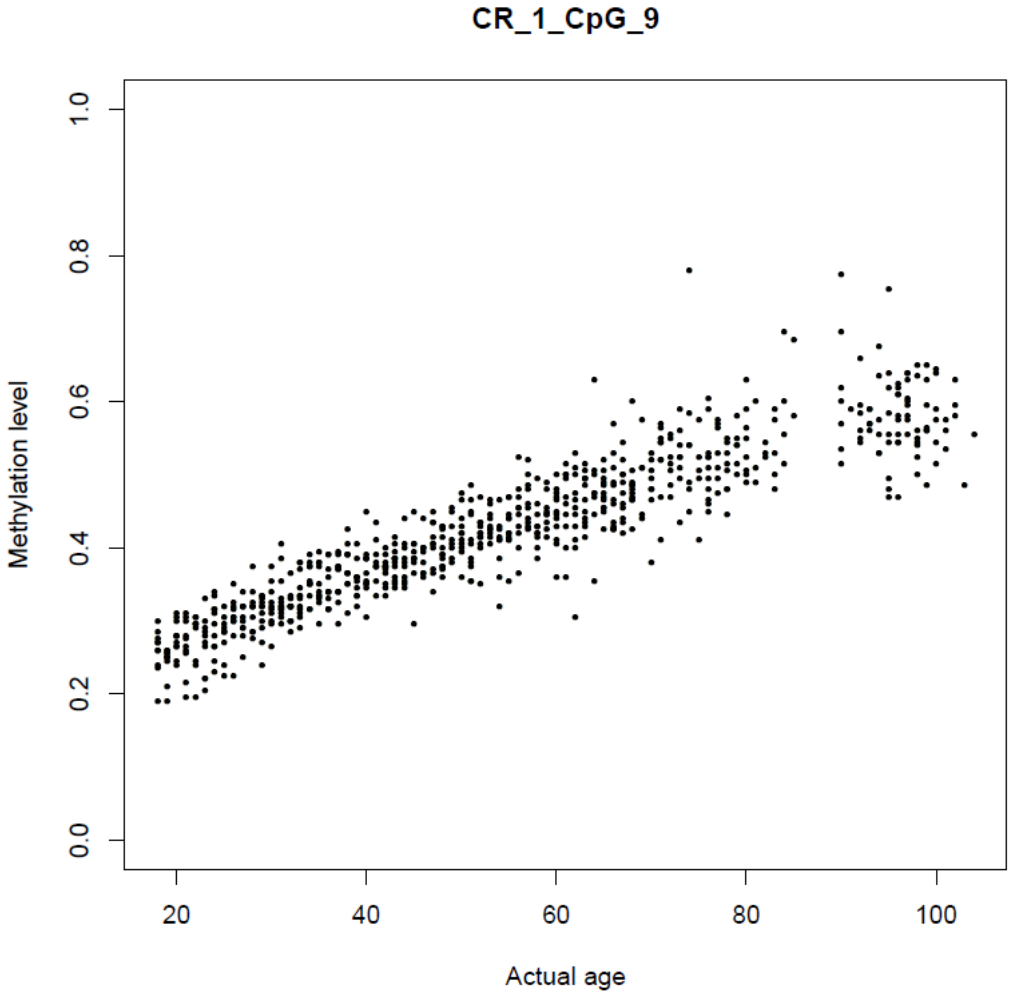


Fig. 3



- Median absolute age prediction error of ±3.07 years
- Percentage of prediction error relative to the age of 6.3%

Freire-Arada et al., FSIGEN 2016

Development of methylation marker sets for forensic age estimation using analysis of public methylation data and the Agena Bioscience EpiTYPER system. Freire-Aradas et al. FSIGEN (2016)

Predicted age with the panel: 64.48
Real age: 63.50

Age prediction with DNA methylation

Input the methylation values for the seven CpG's shown on the table below. Blanks will be ignored:

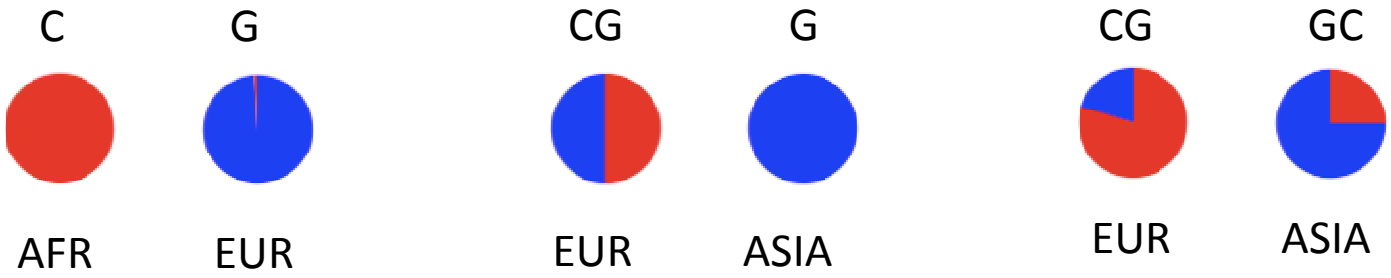
Gene	Internal code	CpGID	GRCh38 chromosome position
ELOVL2	CR_1_CpG_9	cg21572722	chr6:11044661
ASPA	CR_2_CpG_3	cg02228185	chr17:3476273
PDE4C	CR_4_CpG_27.28.29	none	chr19:18233127/31/33
FHL2	CR_12_1_CpG_3	cg06639320	chr2:105399282
CCDC102B	CR_13_CpG_2	cg19283806	chr18:58722183
C1orf132	CR_21_CpG_11	none	chr1:207823715
no associated	CR_23_CpG_3	cg07082267	chr16:85395429

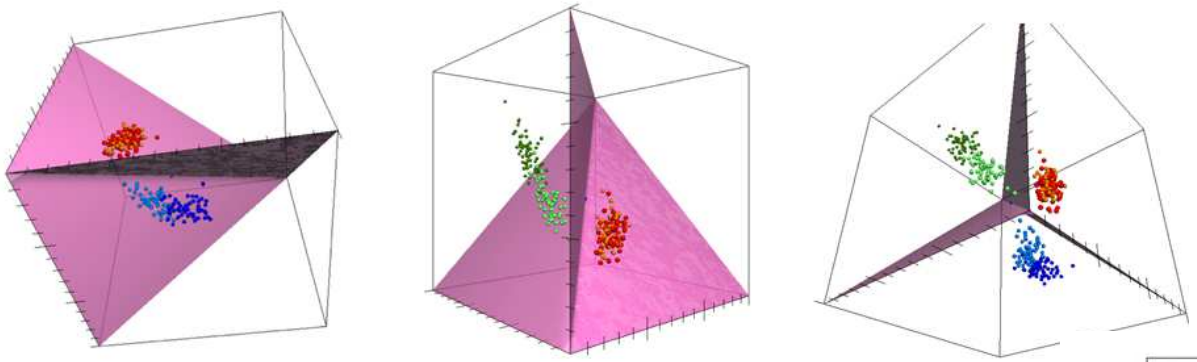
Name	CR_1_CpG_9	CR_2_CpG_3	CR_4_CpG_27.28.29	CR_12_1_CpG_3	CR_13_CpG_2	CR_21_CpG_11	CR_23_CpG_3
Values	0.37	0.535	0.21	0.485	0.18	0.455	0.415

Clear values Calculate

Age prediction interval is [51.64, 69.91] (0.1 and 0.9 quantiles, respectively) and the predicted age is 60.08 (in years).

Ancestry informative makers: AIMS



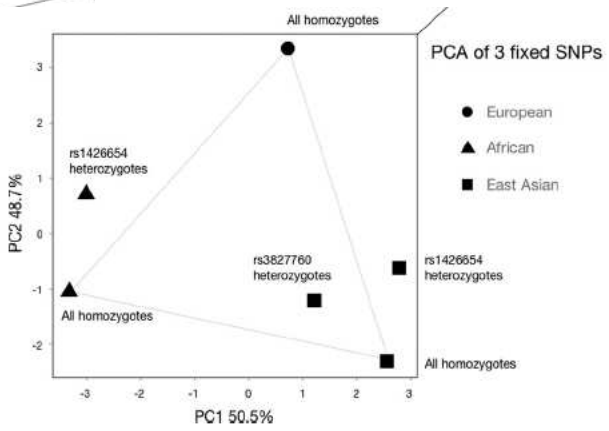


USC 34plex panel
Phillips et al., FSIGEN 2010

Chinese - Taiwanese

Mozambican - Somali

Danish - Galician



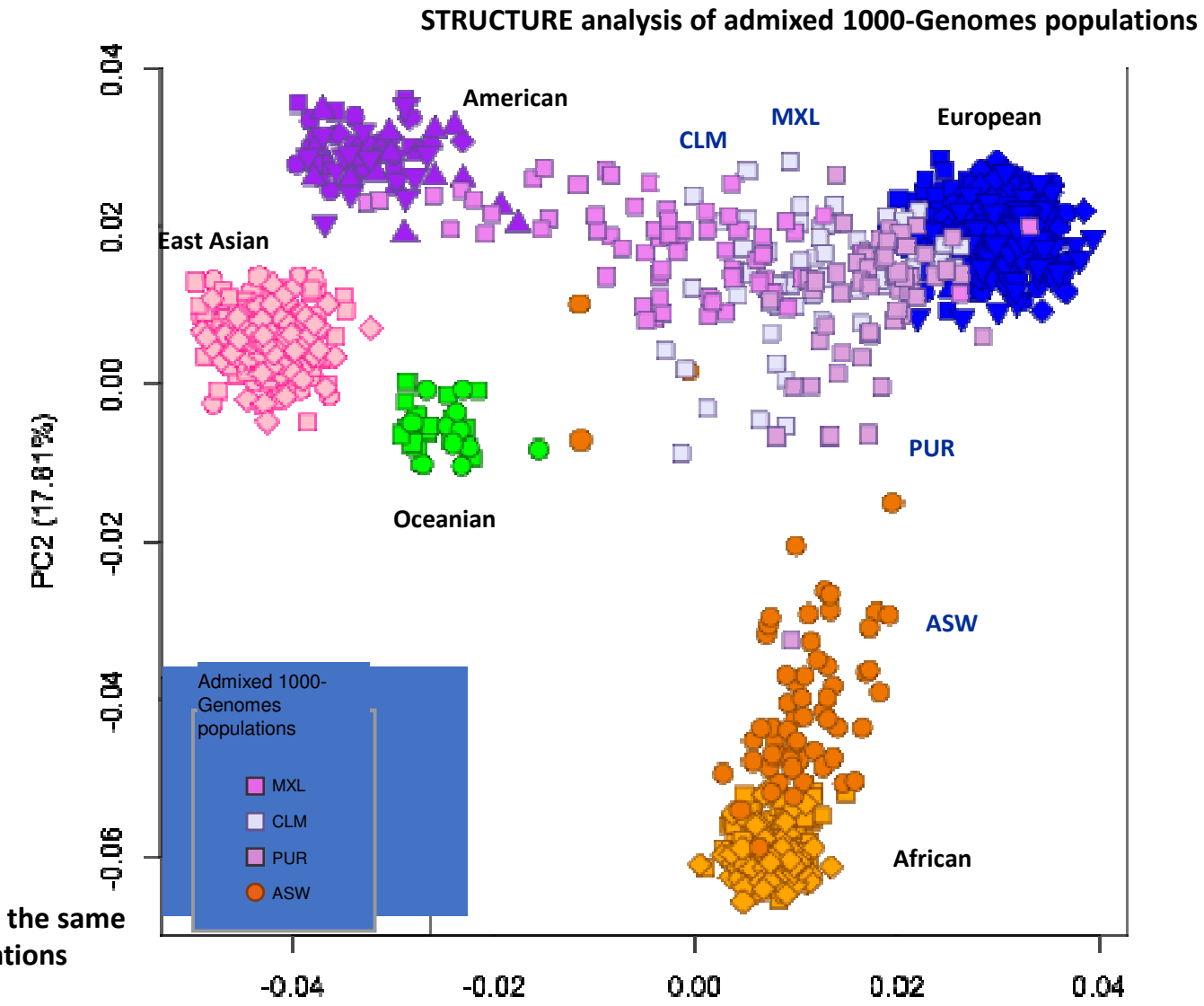
C. Phillips. Forensic genetic analysis of bio-geographical ancestry . FSI Genetics 18 (2015) 49-65

CDX
KHV
E ASN

GWD
MSL
ESN
ACB
AFR

PEL
AME

GIH
PJL
BEB
STU
ITU
S ASN



PCA of the same populations

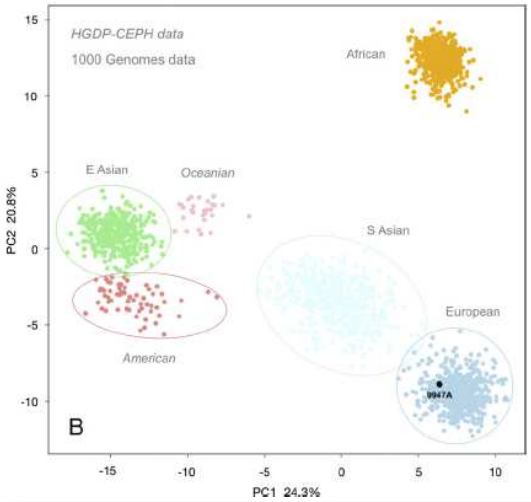
Forensic Science International: Genetics

Volume 23, July 2016, Pages 178–189

Research paper

Inter-laboratory evaluation of the EUROFORGEN Global ancestry-informative SNP panel by massively parallel sequencing using the Ion PGM™

M. Eduardoff[a, 1], T.E. Gross[b, 1], C. Santos[c], M. de la Puente[c], D. Ballard[d], C. Strobl[a], C. Børsting[e], N. Morling[e], L. Fusco[e], C. Hussing[e], B. Egyed[f], L. Souto[g], J. Uacyisrael[h], D. Syndercombe Court[d], Á. Carracedo[c, i], M.V. Lareu[c], P.M Schneider[b], W. Parson[a, j], C. Phillips[c], , The EUROFORGEN-NoE



Evaluation of the Global AIM-SNP panel with Ion PGM™

Global AIMs markers

↓

97.6% assay conversion rate

↓

Inter-laboratory validation (**5** collaborators)

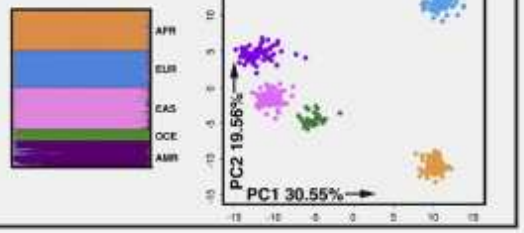
↓

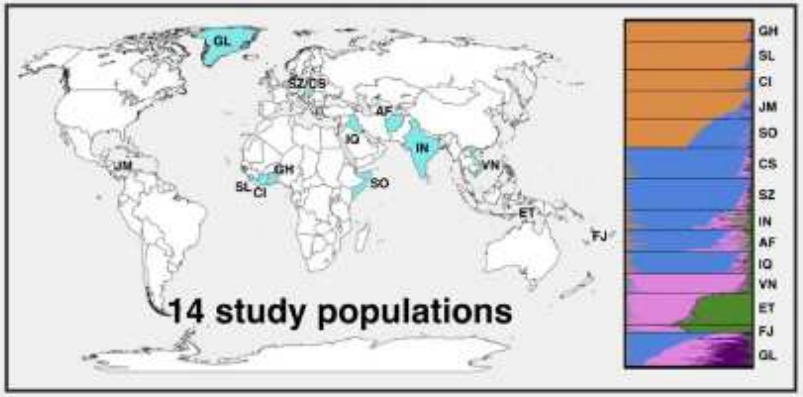
inter-laboratory database | concordance **> 99.8%**

full concordance down to **100pg of DNA**

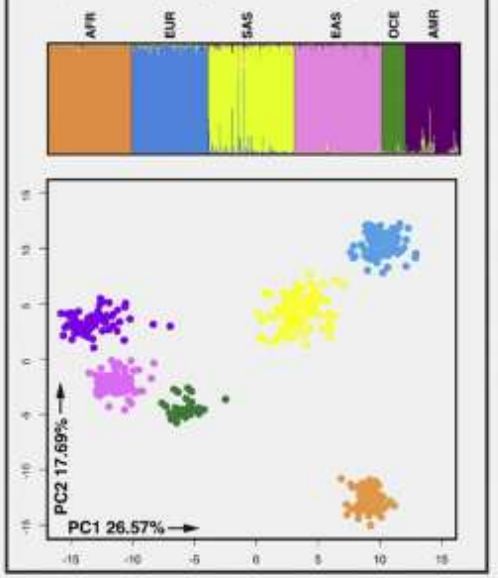
mixtures detected up to **1:9** ratio

Designed for **5 population groups**





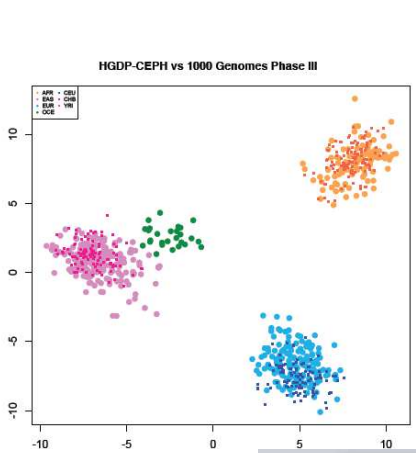
Possibility to differentiate up to **6 population groups**

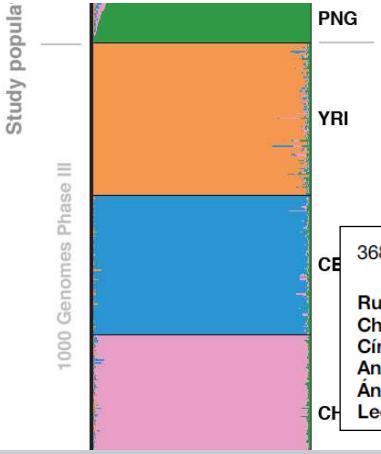


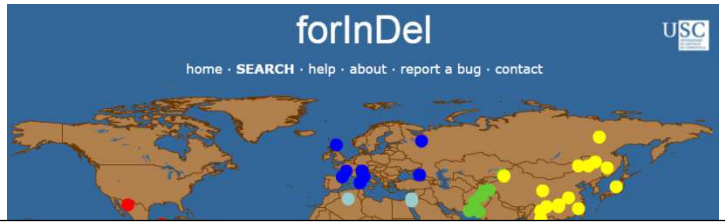
Forensic Sci Int Genet. 2016 Jan;20:71-80. doi: 10.1016/j.fsigen.2015.10.003. Epub 2015 Oct 20.

Pacifiplex: an ancestry-informative SNP panel centred on Australia and the Pacific region.

Santos C[1], Phillips C[2], Fondevila M[2], Daniel R[3], van Oorschot RA[3], Burchard EG[4], Schanfield MS[5], Souto L[6], Uacyisrael J[7], Via M[8], Carracedo Á[9], Lareu MV[2].







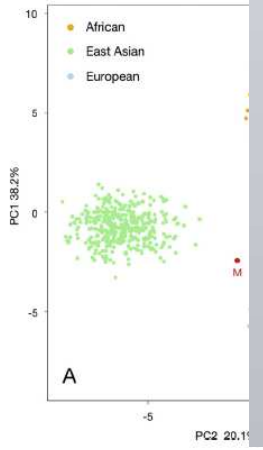
3682

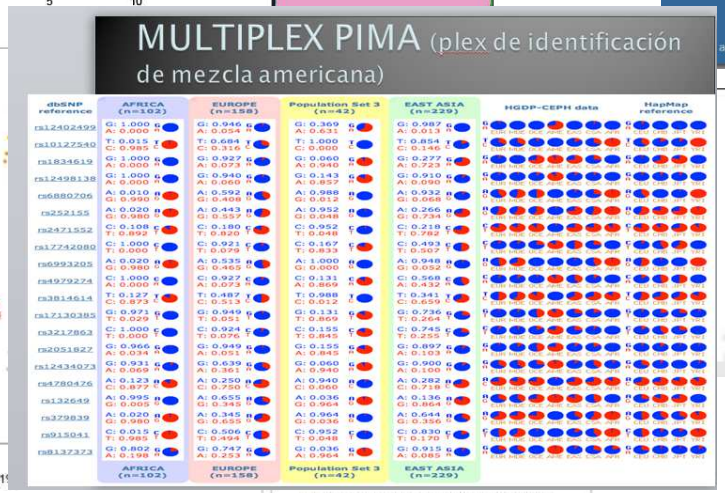
Electrophoresis 2009, *30*, 3682–3690

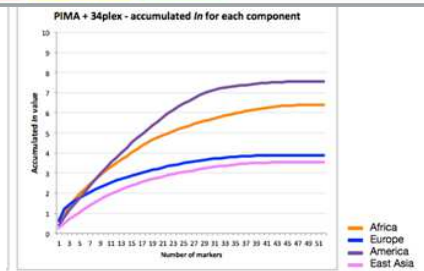
Rui Pereira[1,2]
Christopher Phillips[2]
Cíntia Alves[1]
António Amorim[1,3]
Ángel Carracedo[2,4]
Leonor Gusmão[1]

Research Article

A new multiplex for human identification using insertion/deletion polymorphisms



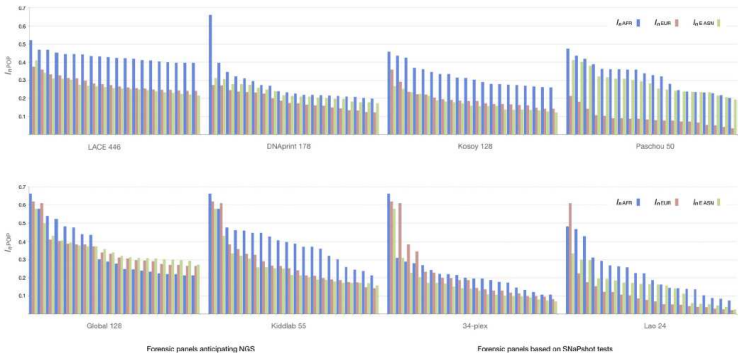




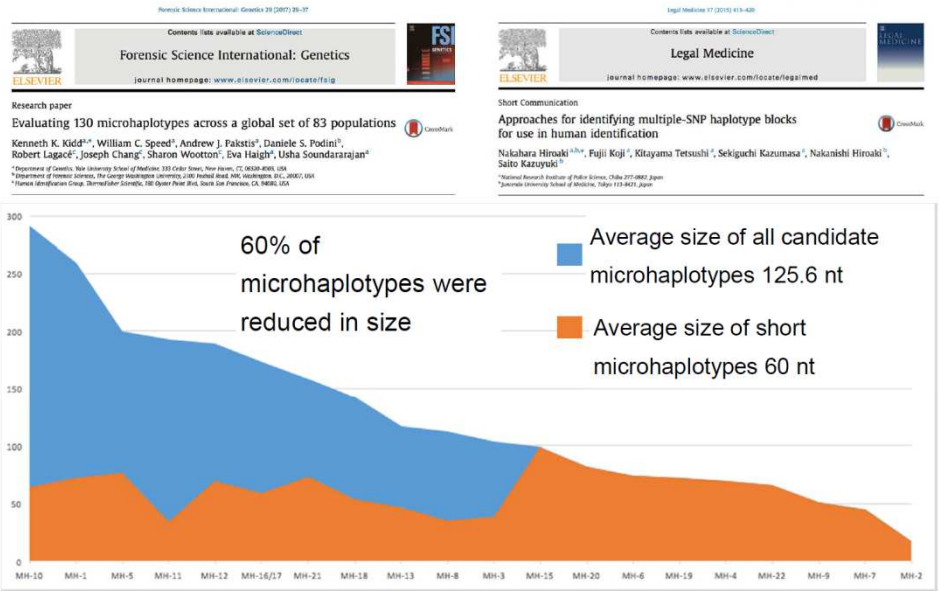
PIMA plex
L. Porras et al. 2013

Eurasiaplex: A forensic SNP assay for differentiating European and South Asian ancestries

C. Phillips [a,*], A. Freire Aradas [a,1], A.K. Kriegel [b,1], M. Fondevila [a], O. Bulbul [c], C. Santos [a], F. Serrulla Rech [d], M.D. Perez Carceles [e], A. Carracedo [a], P.M. Schneider [a], M.V. Lareu [a]

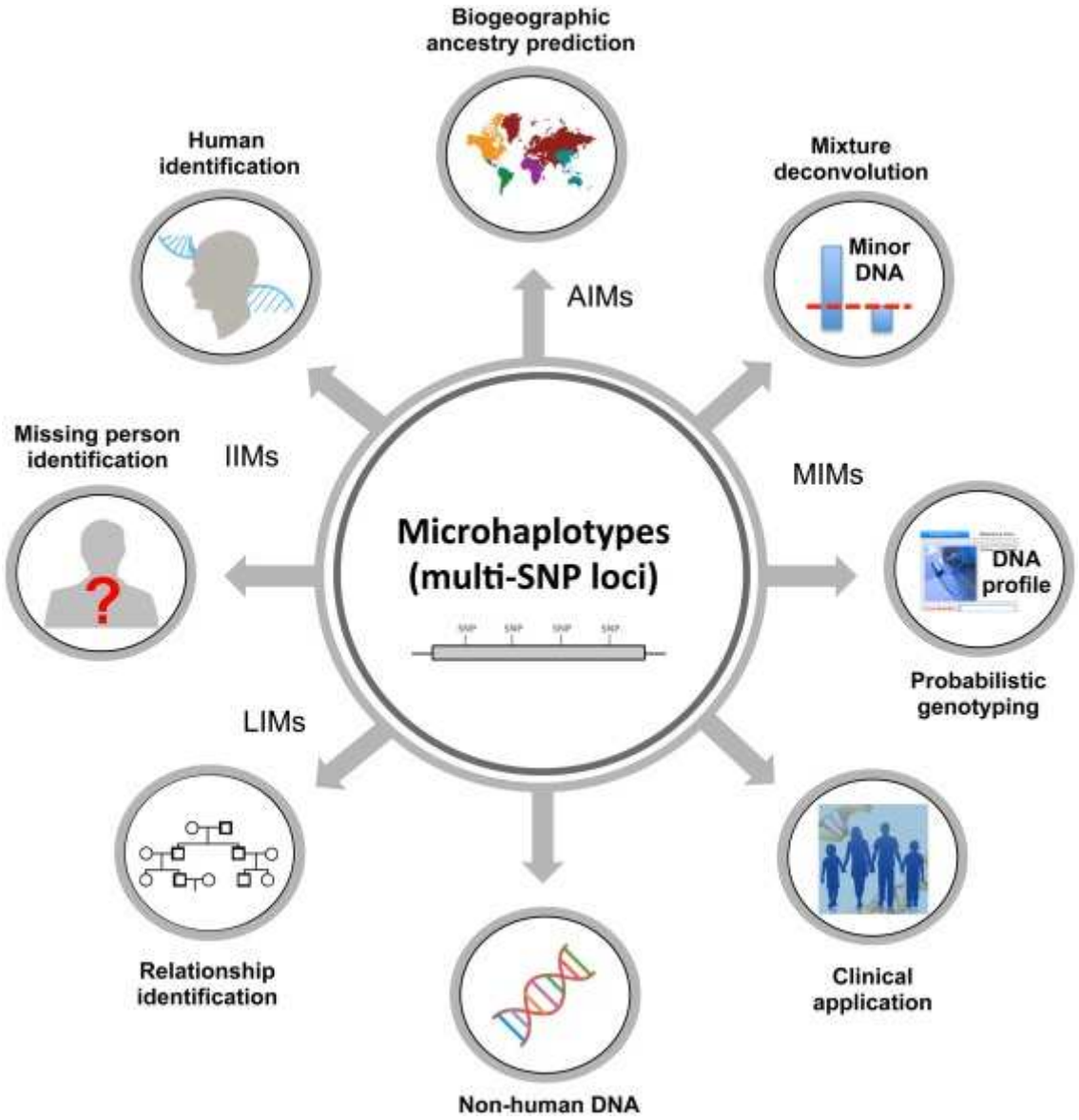


Phillips et a. Ancestry markers for Asia-Pacific region

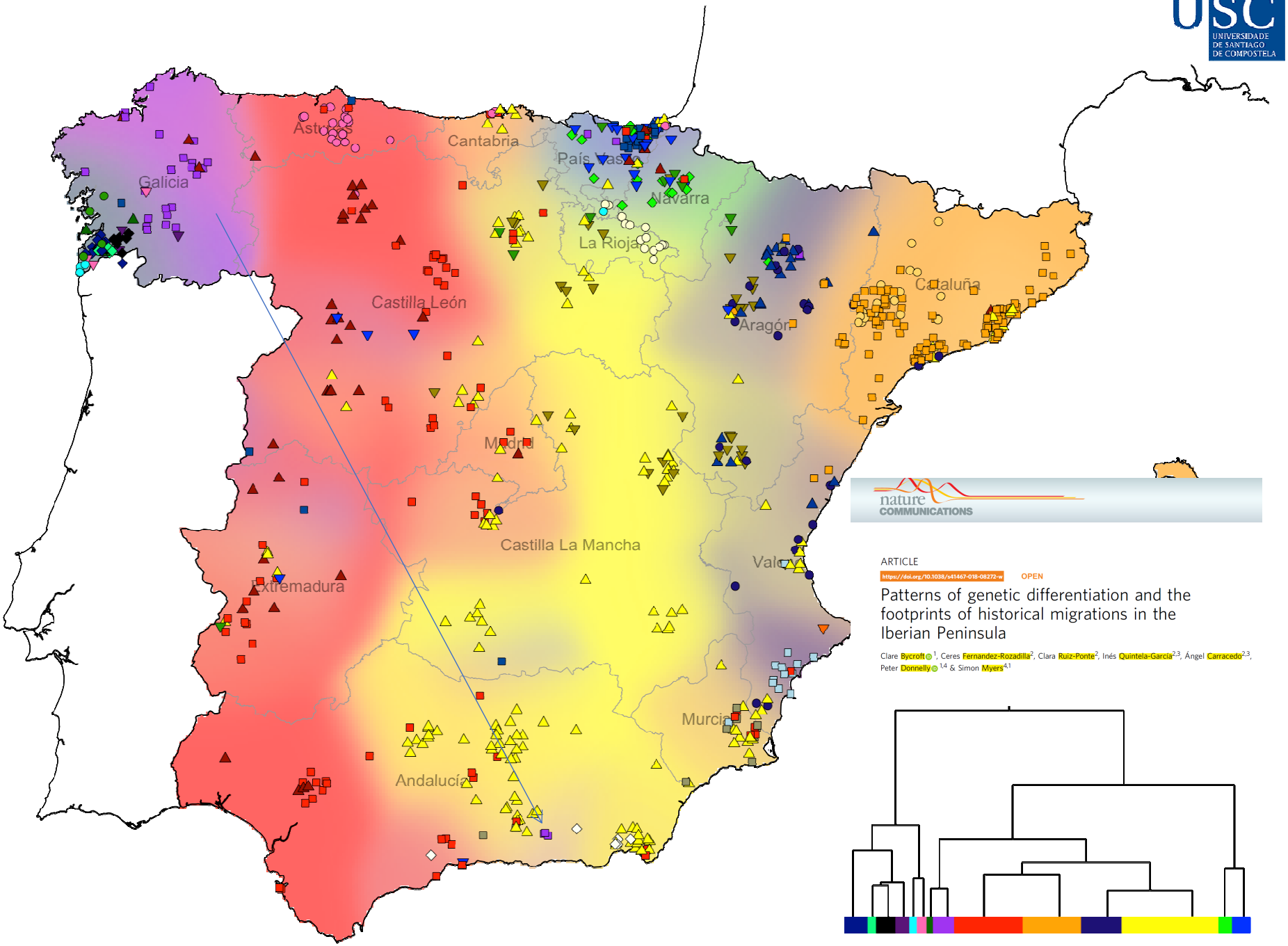


MAPlex
Middle East Asia Pacific

	34plex (CE)	gAIMs (MPS)	MAPplex (MPS)
Population specific SNPs	13	12	
Skewed frequency SNPs	14	93	122 > 84
Fixed difference SNPs	4	17	
Tri allelic SNPs	3	6	30
South Asian informative AIMs (Eurasiaplex+)			24
Short amplicon microhaplotype markers (x22)			80



Microhaplotypes in forensic genetics
Fabio Oldoni, Kenneth K. Kidd, Daniele Podini
FSI: Genetics January 2019



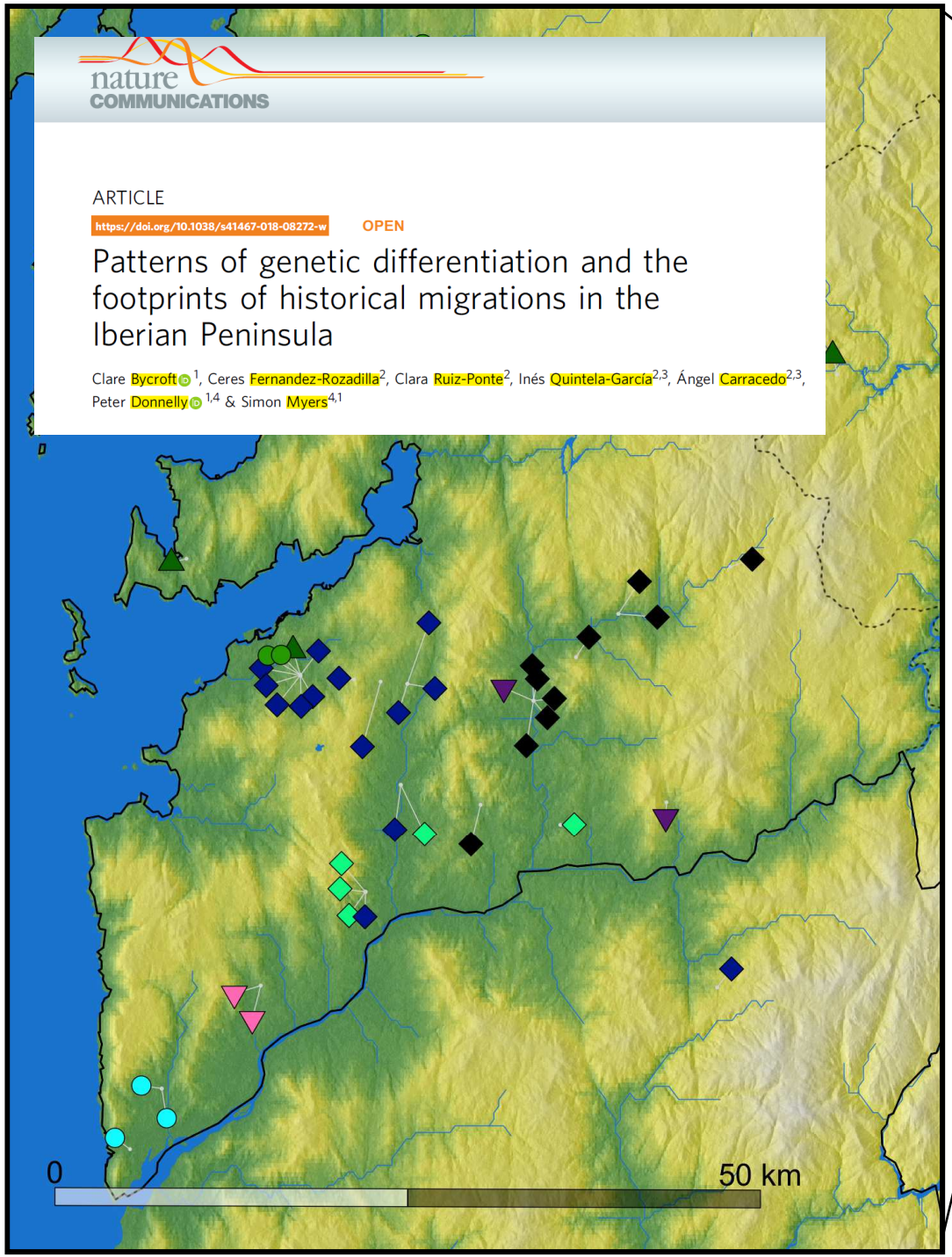
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-018-08272-w OPEN

Patterns of genetic differentiation and the footprints of historical migrations in the Iberian Peninsula

Clare Bycroft[1], Ceres Fernandez-Rozadilla[2], Clara Ruiz-Ponte[2], Inés Quintela-García[2,3], Ángel Carracedo[2,3], Peter Donnelly[1,4] & Simon Myers[4,1]


nature COMMUNICATIONS
ARTICLE
https://doi.org/10.1038/s41467-018-08272-w OPEN
Patterns of genetic differentiation and the footprints of historical migrations in the Iberian Peninsula
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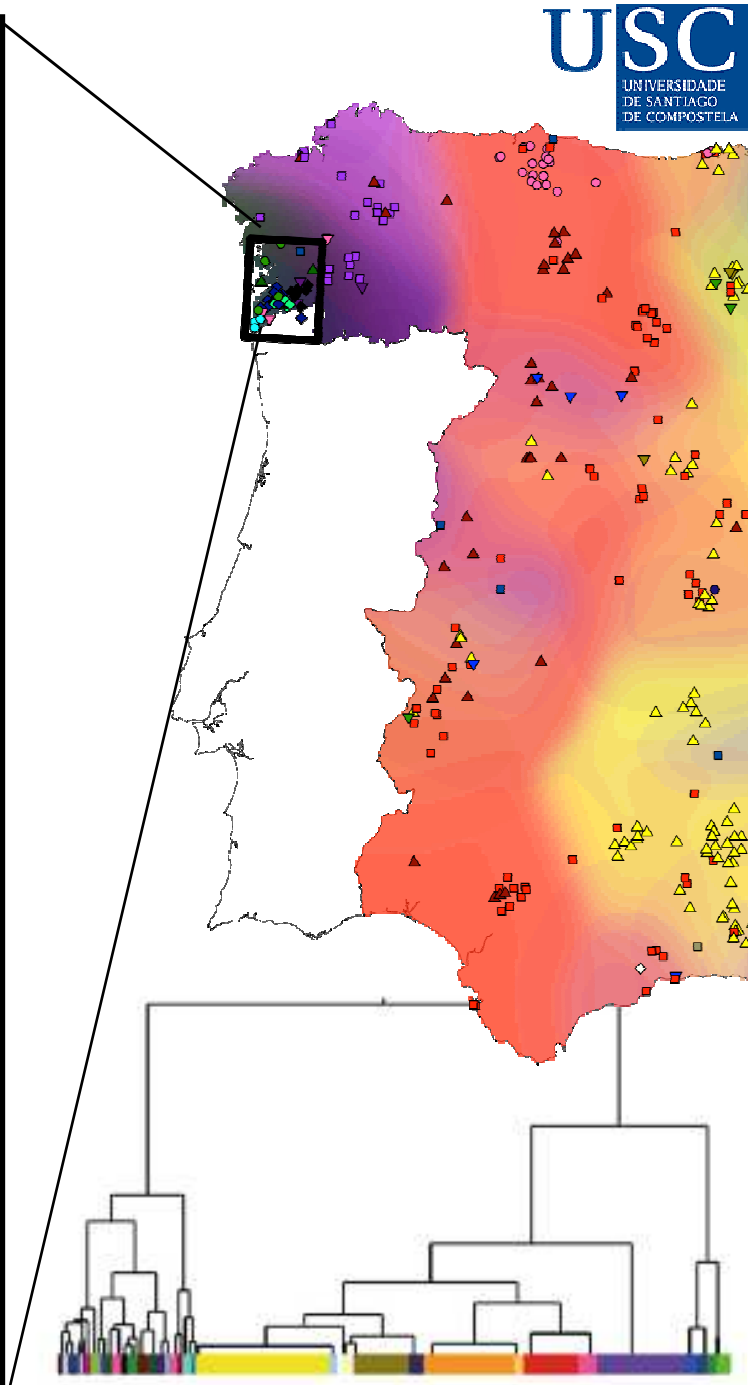
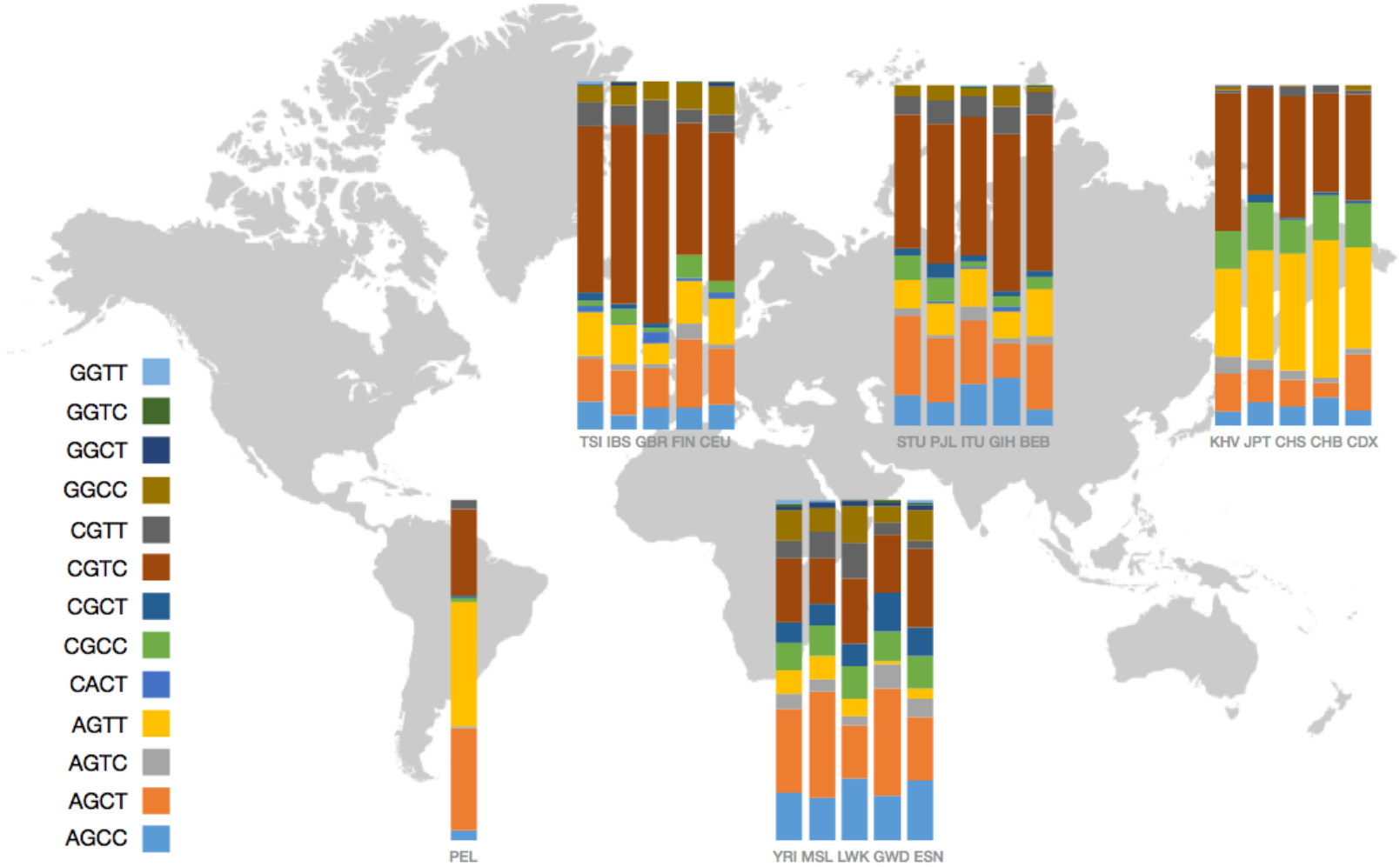
0
50 km


USC
UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Some microhaplotypes are very informative

MH-21 73nt 4 SNPs **rs6517970-rs202132081-rs8131148-rs6517971**



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 740580.

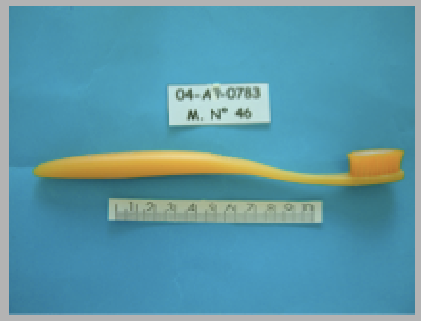
11 M bombing attack

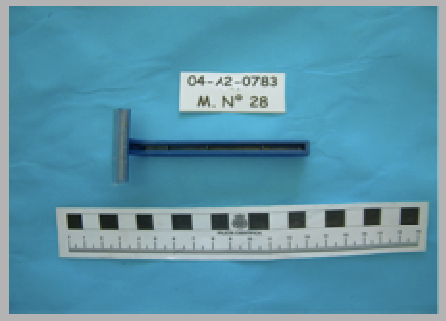
Madrid, 2004

Terrorist attack on four commuter trains

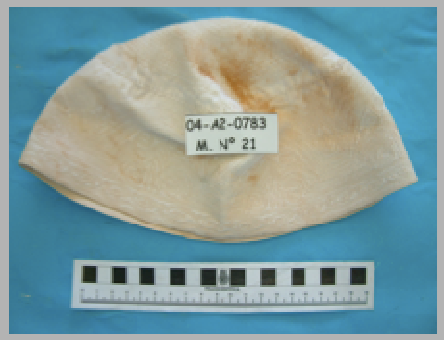
10 explosive devices were detonated simultaneously

191 people were killed and more than 1700 were injured





11-M was a 'closed' ancestry analysis



personal items from bomb assembly site in Leganés with DNA profiles that didn't match with the terrorists

un-detonated explosives in a holdall found at El Pozo station

Calculation results

Executing the query with 3 default populations and the 34 SNPs of the individual to classify :
GTCCCCCTAGAACTCCAACTGGGGTTCCAACCAACCAAGGCCAACCTTACAAGGTTCGAAGGTTACAC

The **-log(LIKELIHOOD)** (lower is best) and **PERCENTILE** (percent of population samples with lower likelihoods than individual submitted).

Gal-Dani	41.109466	2.50%
Moz-Som	66.935324	0.00%
Chi-Taiw	65.629561	0.00%

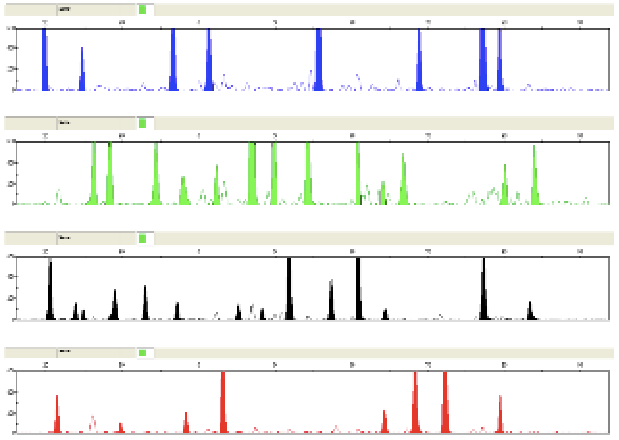
This person was European

training set:	-log likelihood	percentile	exp	¨times more likely to be:	verbal predicate
Gal-Dani	41.109466	2.50%	1.40083E-18	EUR not AFR	
Moz-Som	66.935324	0.00%	8.5184E-30	1.64448E+11	*164 billion times more likely to be European than African*
Gal-Dani	41.109466	2.50%	1.40083E-18	EUR not ASN	
Chi-Taiw	65.629561	0.00%	3.14372E-29	44559668806	*44 billion times more likely to be European than Asian*
Moz-Som	66.935324	0.00%	8.5184E-30	AFR not ASN	
Chi-Taiw	65.629561	0.00%	3.14372E-29	0.270965709	

GT	GG	GG	TT	CC	AA	CC	AA	CC	AA	GG	CC	AA	CC	TT	AC	TT	GG	TT	AA	CG	TT	GG	AC	AC

Phillips C, Prieto L, Fondevila M, Salas A, Gómez-Tato A, Alvarez-Dios J, Alonso A, Blanco-Verea A, Brión M, Montesino M, Carracedo A, Lareu MV
***Ancestry analysis in the 11-M Madrid bomb attack investigation*. PLoS One. 2009 Aug 11;4(8):e6583.**

34plex



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SNIPPER

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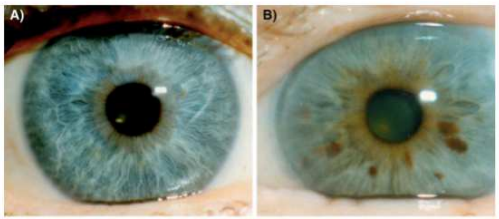
GT	CC	CC	CT	AG	AA	CT	CC	AA	CT	GG	GG	TT	CC	AA	CC	AA	CC	AA	GG	CC	AA	CC	TT	AC	TT	GG	TT	AA	CG	TT	GG	AC	AC

... and had blue eyes: rs12913832 = GG

GG

Blue



AG

Green
(Unknown)

BEY1

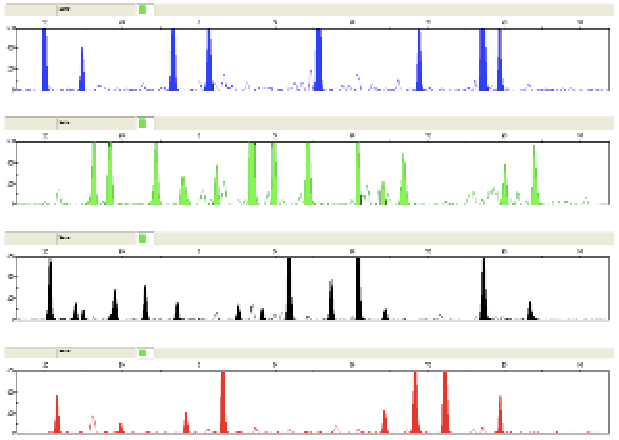
Green
Hazel

AG

AG / (AA)
Brown

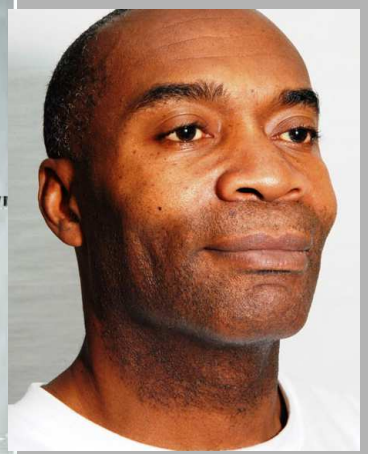
BEY2

34plex



Operation Minstead

A elderly victm of an attack in May helped police with the e-fit



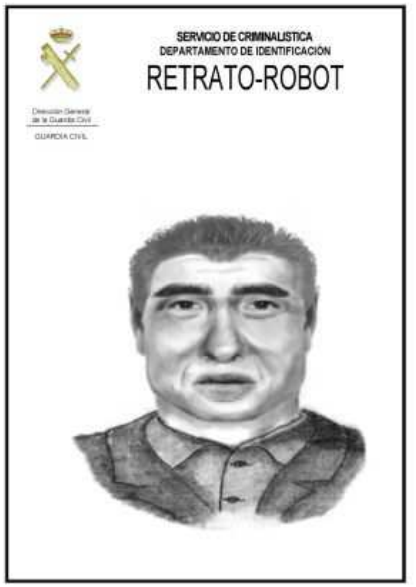
- 18 year investigation of a series of aggressive rapes of elderly victims in London

- USC testing ancestry independently plus skin pigmentation SNPs to reduce suspect pool

- 82% AFR, 12% AME 6% EUR and suggest this shows Windward Island origins Y=EUR, mt=AFR

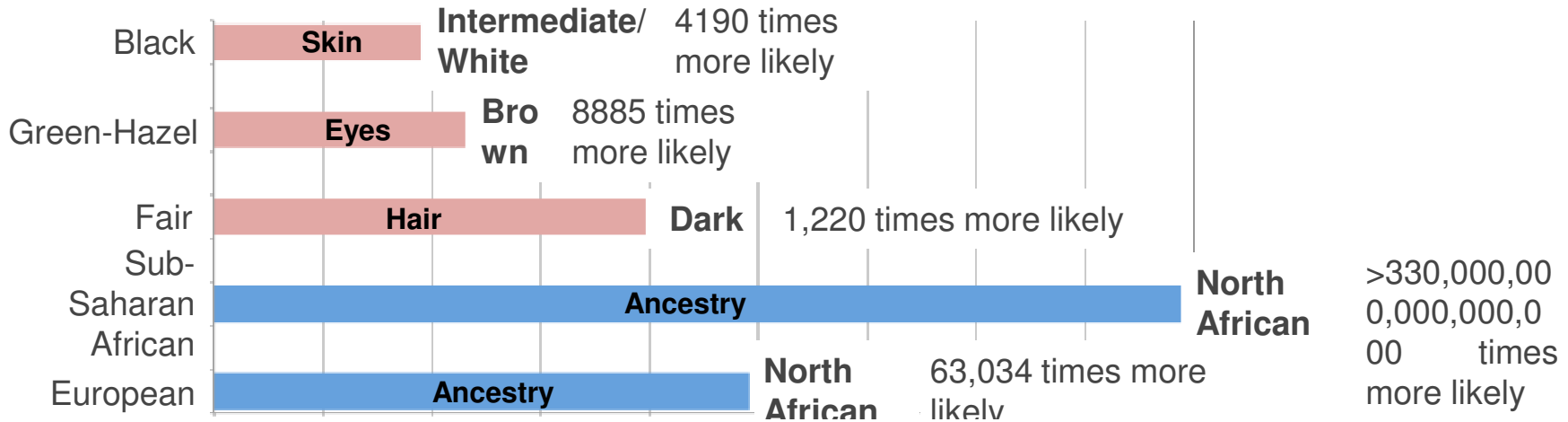
The murder of Eva Blanco Puig - a cold case investigation

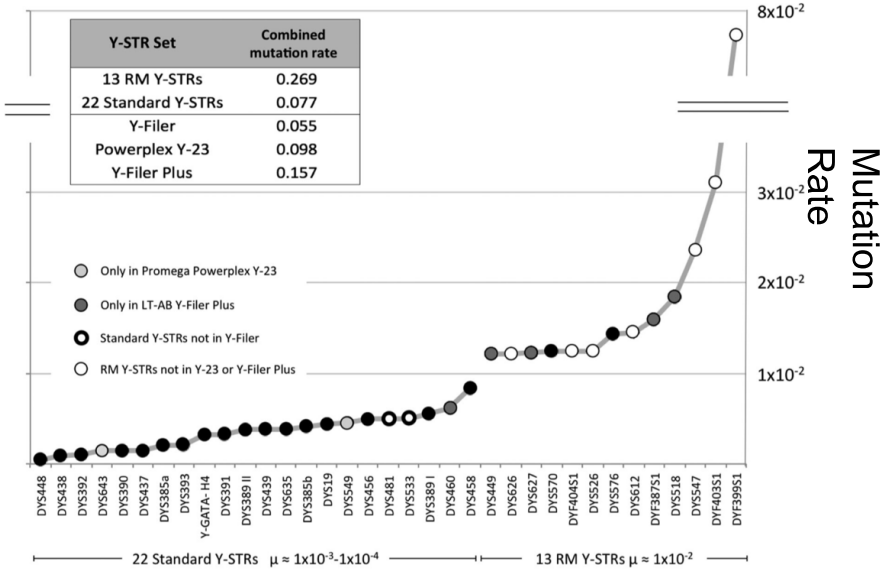
- Eva Blanco was raped and murdered in April, 1997
- Heavy rain obscured tyre marks and footprints at scene
- Small semen stain on underwear
- Police requested a mass screen of 2000 males from Algete
- Judge deemed it too expensive and likely to be ineffectual



USC asked to analyse ancestry and pigmentation

- 75 / 80 ancestry-informative SNPs successfully genotyped
- 18 / 19 pigmentation-predictive ‘SHEP’ SNPs successfully genotyped





- Successful application to screen 300 Moroccans living in a larger area around Algete

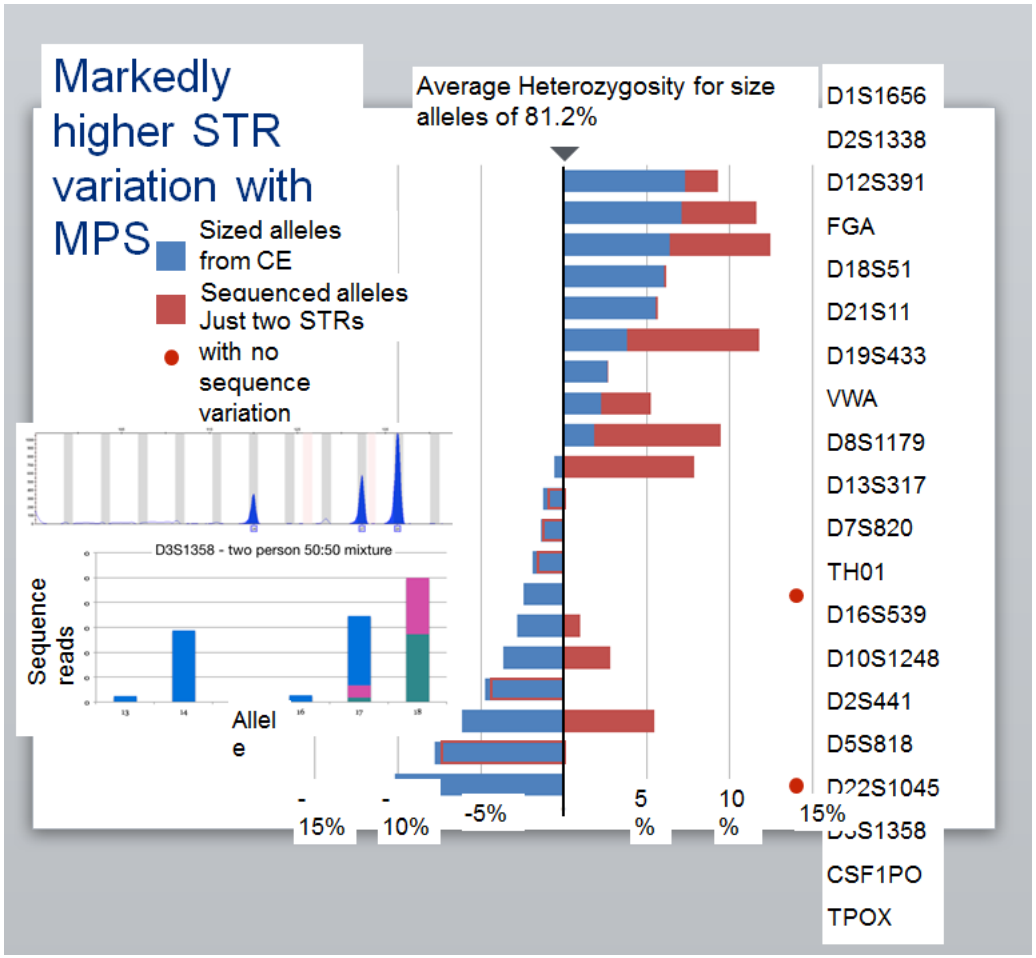
- One sample gave a full Y-STR match - led to identification of a brother who had left Spain in 1999 and lived in France

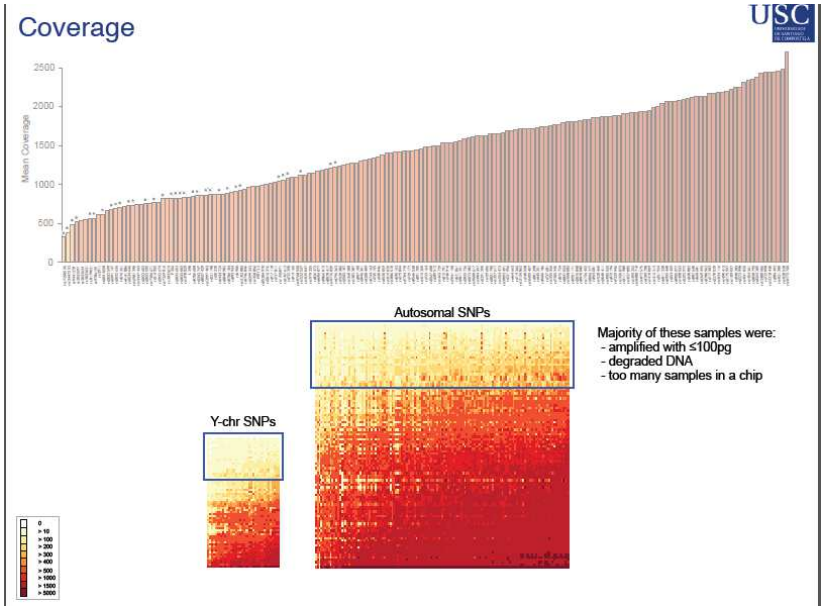
Legal and ethical issues

- Former terms “coding” and “non-coding” referring to DNA sequences lost their meaning
- The issue of amendment of the law allowing for FDP (Netherlands, UK, France)
- Externally visible traits of an individual are publically available
- FDP is useful at the stage of investigation
- Data processed to predict EVC are not stored in forensic databases

Pais	Rasgos físicos	Edad	Ancestralidad	Bases de datos
Austria	No claro- No se hace	No claro-No se hace	No claro. Si se hace con ADNmt y cromosoma Y	No permitido(ADN codificante)
Francia	Caso judicial que lo permitió en 2015 -	No se hace. Abierta la posibilidad	Si se hace	No permitido(ADN codificante)
Alemania	No permitido explícitamente por el código penal	No permitido explícitamente por el código penal	No permitido explícitamente por el código penal	No permitido(ADN codificante)
Polonia	No regulado, permitido y se hace	No regulado, permitido y se hace	No regulado, permitido y se hace	No permitido(ADN codificante)
Suecia	No regulado, no prohibido y se subcontrata	No regulado, no prohibido y no se ha hecho	No regulado, no prohibido y se hace para casos de identificación	Poco claro. No se hace
Holanda	Permitido explícitamente por la ley	No regulado pero no prohibido- Se ha solicitado	Permitido explícitamente por la ley	No para rasgos físicos y edad, posible para ancestralidad
Reino Unido	No regulado: considerado permitido	No regulado: considerado permitido	No regulado: considerado permitido	No regulado: considerado permitido

NGS





New ISFG Nomenclature!!!

STRs + SNPs validation Santiago Ion Torrent

Next-Generation Sequencing Technologies

Library preparation

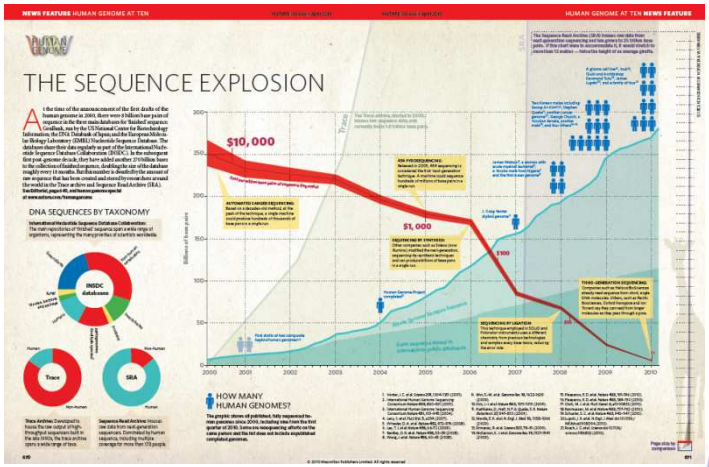
Sequencing

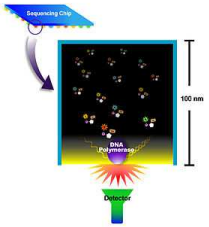
Analysis

NGS platforms

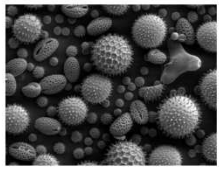
NGS versus Capillary Electrophoresis

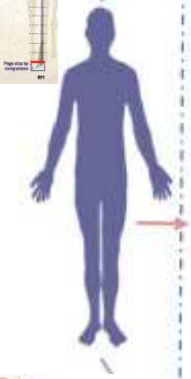
	Advantages	Disadvantages
CE	• Established technology • Accepted in court • Relatively easy workflow	• Limited multiplex capability • Complex mixture analysis • Genotyping based on length only
NGS	• Genotyping based on length and sequence • Greater multiplex capability • High dynamic range • Potential improvement to mixture interpretation • Smaller amplicons (degraded DNA)	• High cost per sample • Large amount of data • Pooling of samples needed to reduce cost per sample • No guidelines available yet • More complex workflow • Time to result

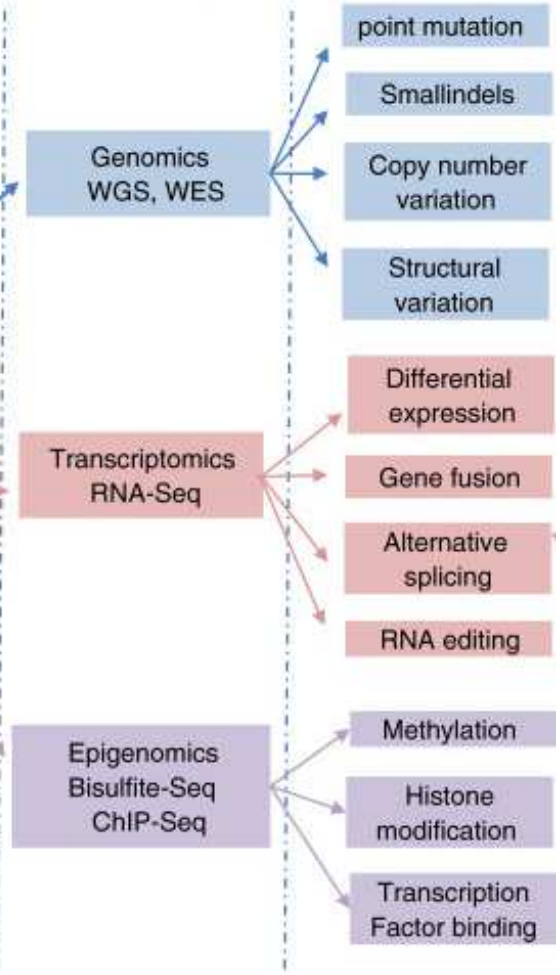




Non human DNA typing







The workflow of integrating omics data in forensic research and applications

A.C. ’t Hoen et al. Reproducible mRNA and small RNA sequencing across different aboratories. Nature Biotechnology (2013)

Ten times more bacterial DNA than human DNA in the human body

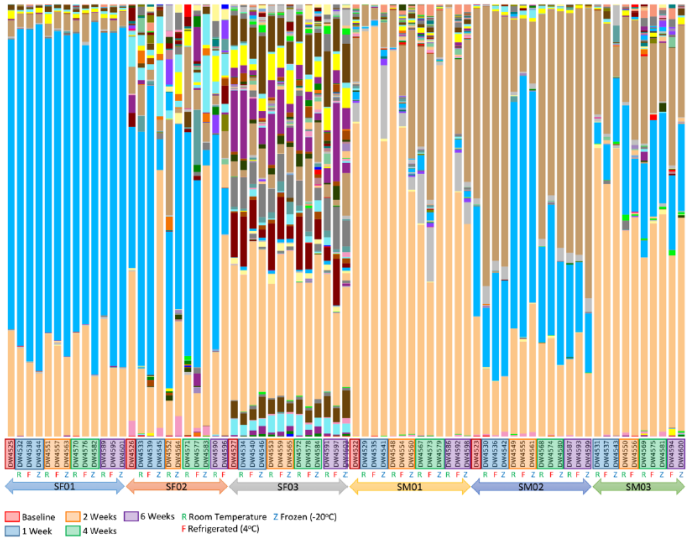
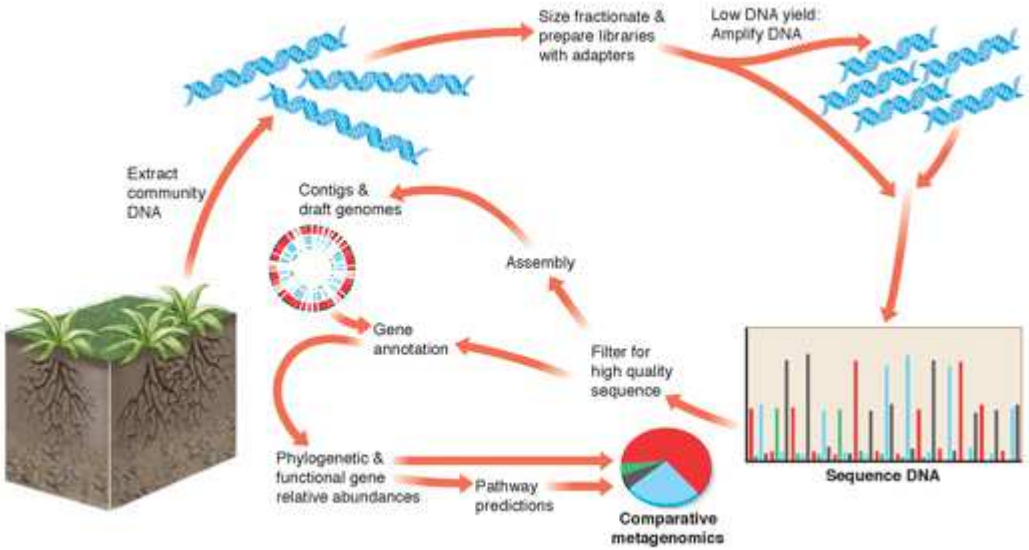


Figure 1: Taxonomic distribution at the genus level across storage time and temperature conditions. Sorted by individuals. Samples were normalized to 900 reads per sample.

Effects of storage time and temperature on pubic hair bacterial communities. Williams &Gibson FSIGEN (in press)

- Short term storage of pubic hair at various temperatures does not significantly affect the recover bacterial microbiome.
- The greatest sources of variation in the pubic hair microbiome are attributed to the individual and gender.



Soil metagenomics

Intraindividual variations
Validation
Statistical challenges

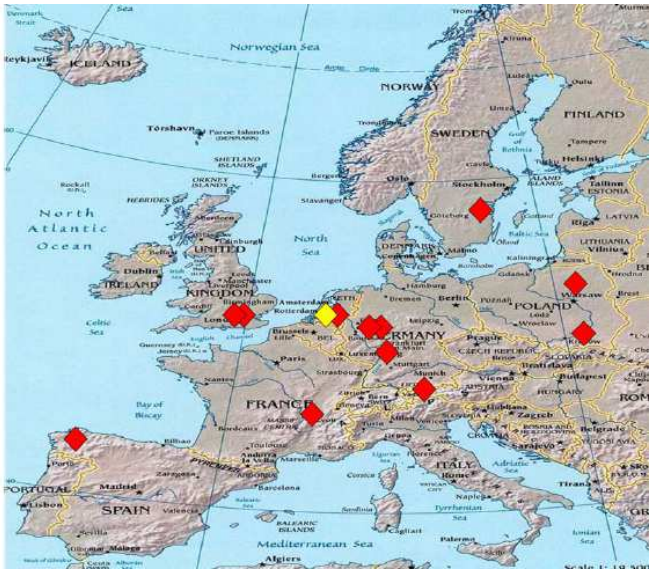
We are good with some physical traits, geogrpahic origin and age but still far from photofit portrait

Low frequency- Intermediate penetrance variants

Gene-gene interactions, GxE interactions

Methylation-MicroRNA-… other approaches

Ethical/Legal problems for EVCs in some countries



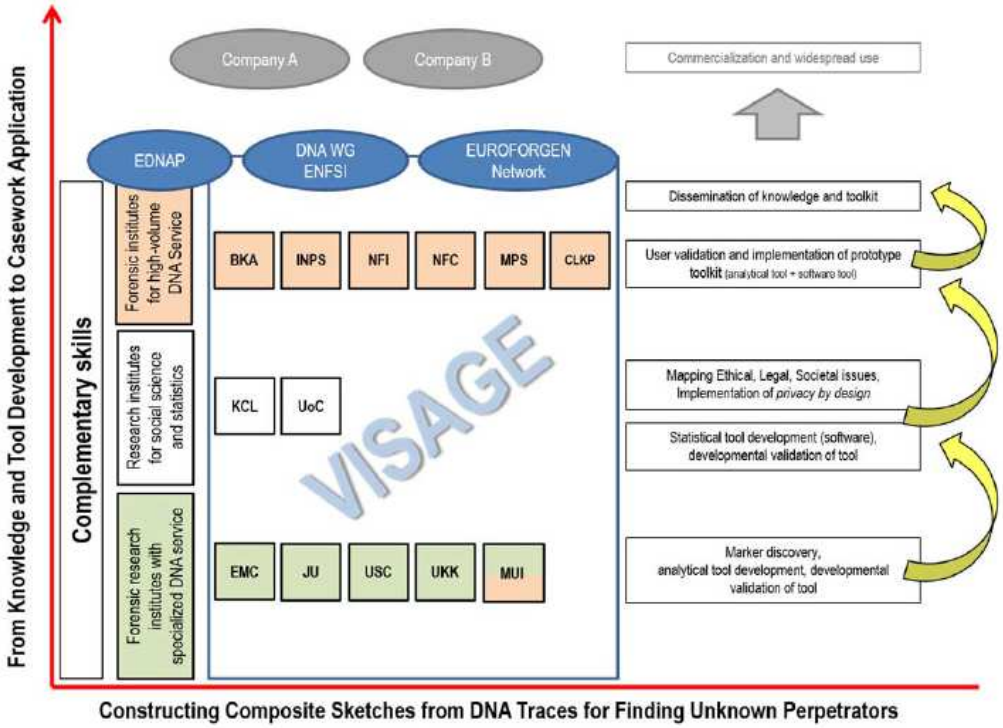


Figure 6. VISAGE expertise along the value chain (drawn in a simplified way).

H2020 EU research and innovation programme-grant agreement No 740580.

Obtaining good results is not always possible

Forensic tests are infallible

Results are obtained immediately

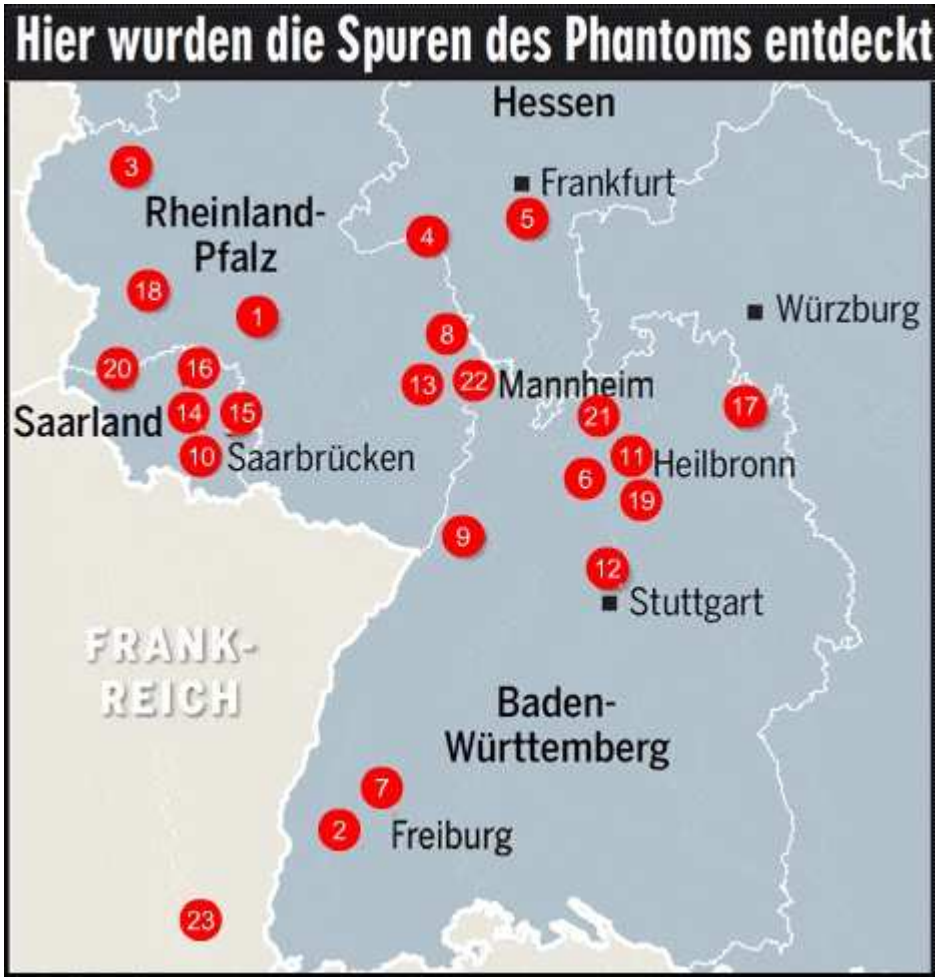
THE CSI EFFECT

Creates false expectations

Creates a distorted perception of the forensic test in judges, prosecutors and jurors

The hunt for the "phantom" – a critical reappraisal of DNA database reality

- In 2007, a female police officer was shot in her car, her male colleague was severely wounded
- A female DNA profile was identified in the car
- The profile generated multiple hits in the DNA databases of Germany and Austria
- The profile resurfaced 39 times in subsequent analyses of other cases (from burglaries to homicides)


Hier wurden die Spuren des Phantoms entdeckt
Hessen
Frankfurt
Rheinland-
Pfalz
Würzburg
Mannheim
Saarland
Saarbrücken
Heilbronn
Stuttgart
FRANK-
REICH
Baden-
Württemberg
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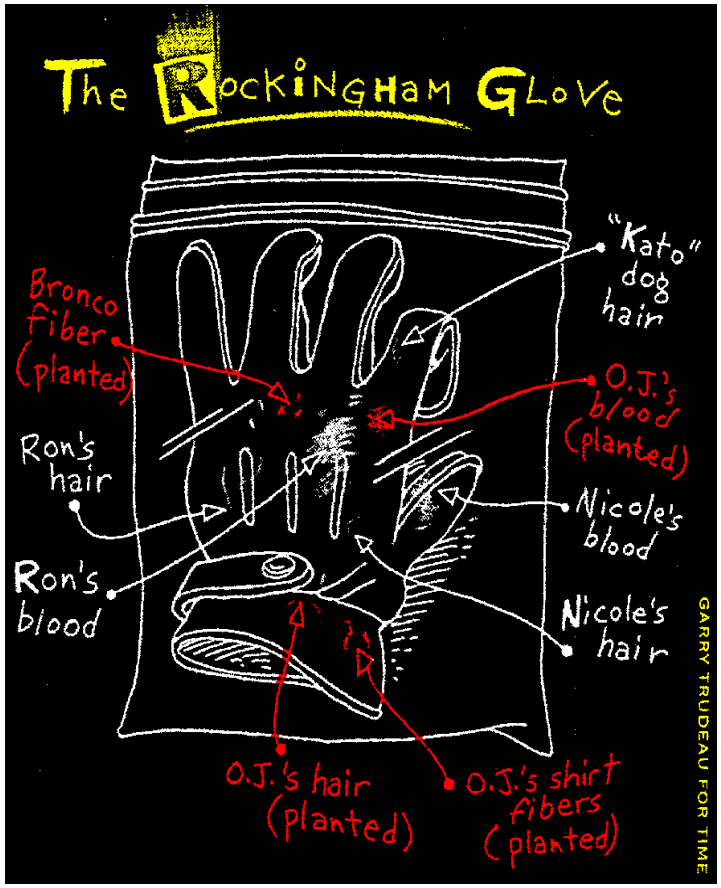
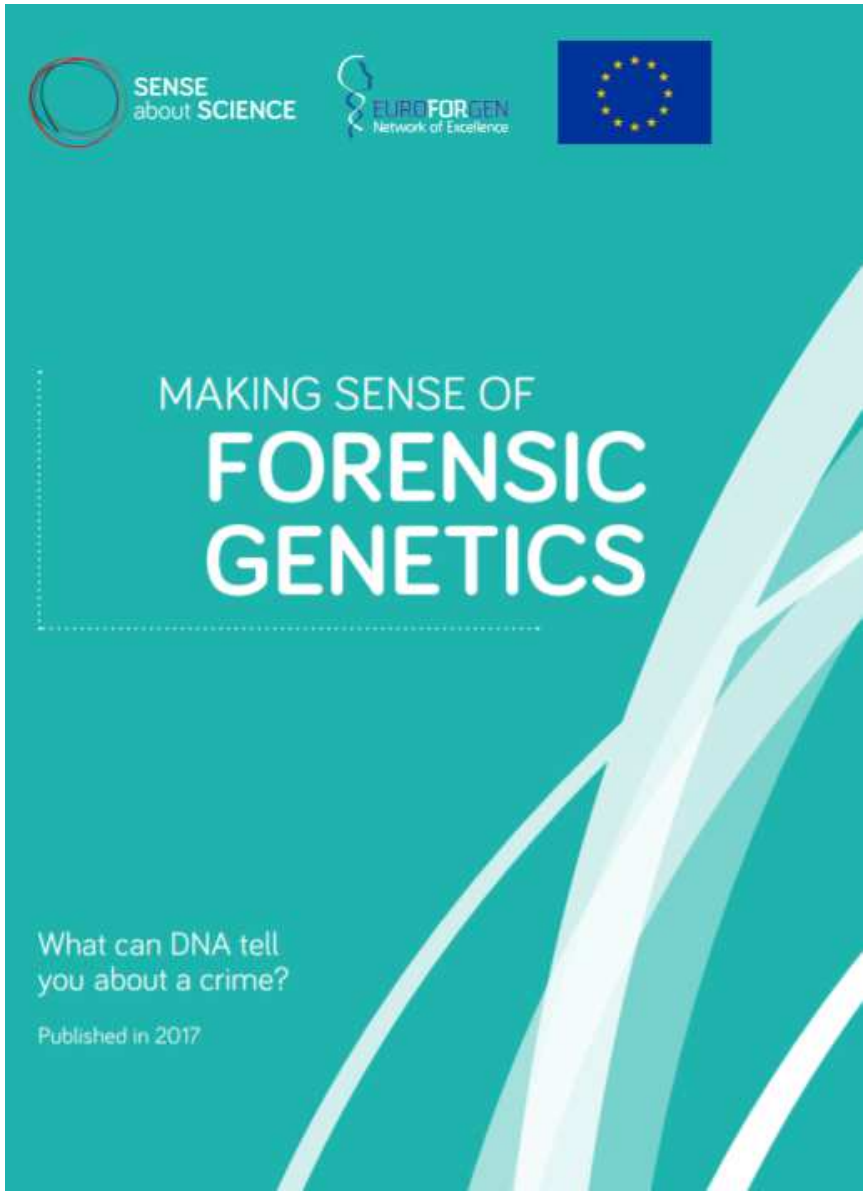
What happened then?

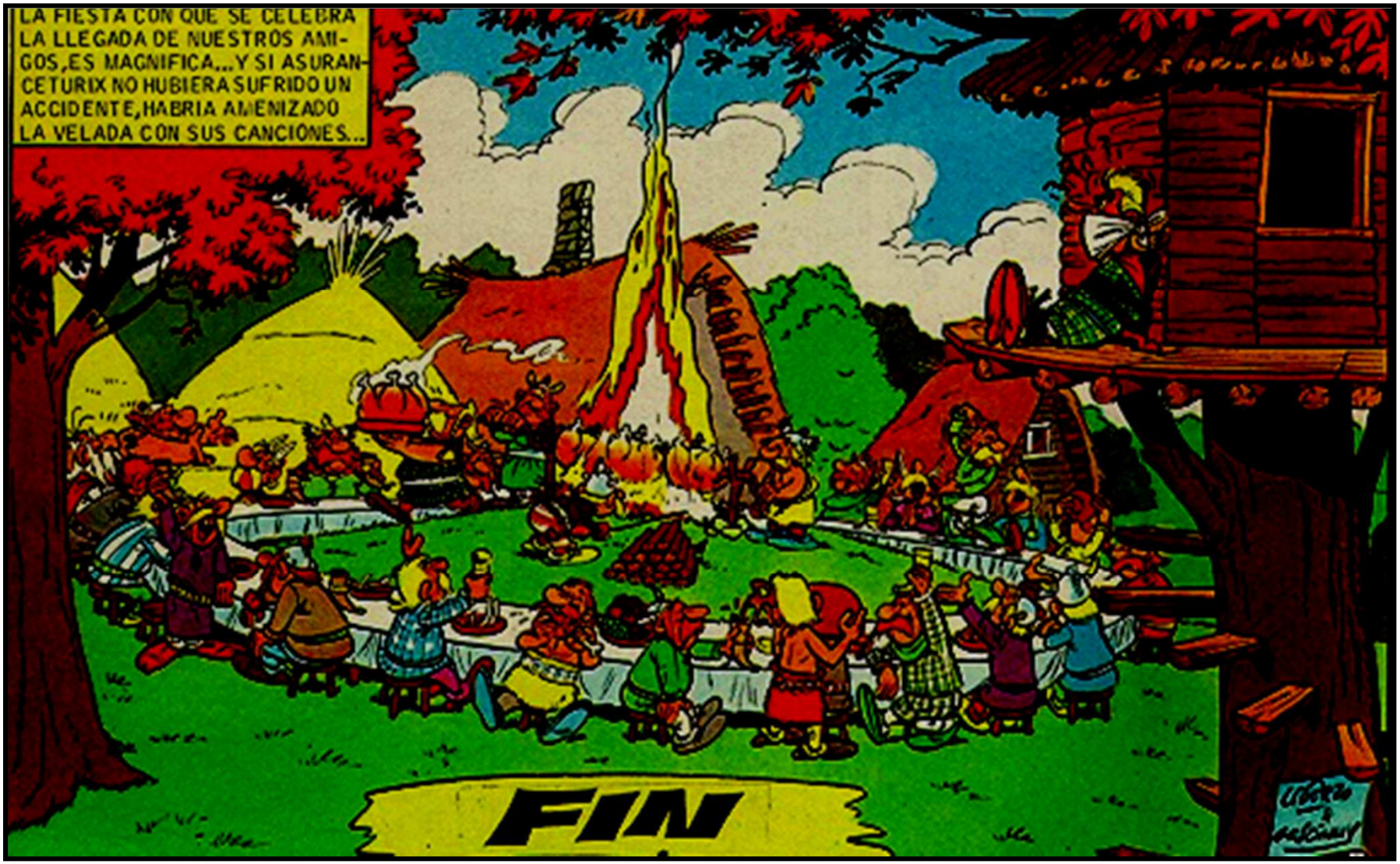
- The profile reappeared later in two more cases where the DNA source was a known male person
- Contamination was now seriously considered
- Cotton swabs were identified as potential source
- The supplier provided reference samples from the factory workers – and a retired 71-year old woman was found to match the phantom's DNA profile

It is not the science itself which is flawed but the interpretation and context in which these results may be used.





https://senseaboutscience.org


LA FIESTA CON QUE SE CELEBRA LA LLEGADA DE NUESTROS AMIGOS, ES MAGNIFICA... Y SI ASURANCETURIX NO HUBIERA SUFRIDO UN ACCIDENTE, HABRIA AMENIZADO LA VELADA CON SUS CANCIONES...
FIN