What Does Your DNA Say About You

Professor Mehmet Tevfik DORAK

School of Health Sciences
Faculty of Science

YOUR FUTURE
STARTS WITH HOPE

Liverpool Hope University EST. 1844

Outline

Primer on human genetics

You are a human being

It is You

You are from …..

You are tall, overweight, blond or not

You are male/female and your age is …..

You are a carrier for a disease gene

You are predisposed to certain diseases or not

You are protected from certain diseases

What are we doing with the current knowledge?

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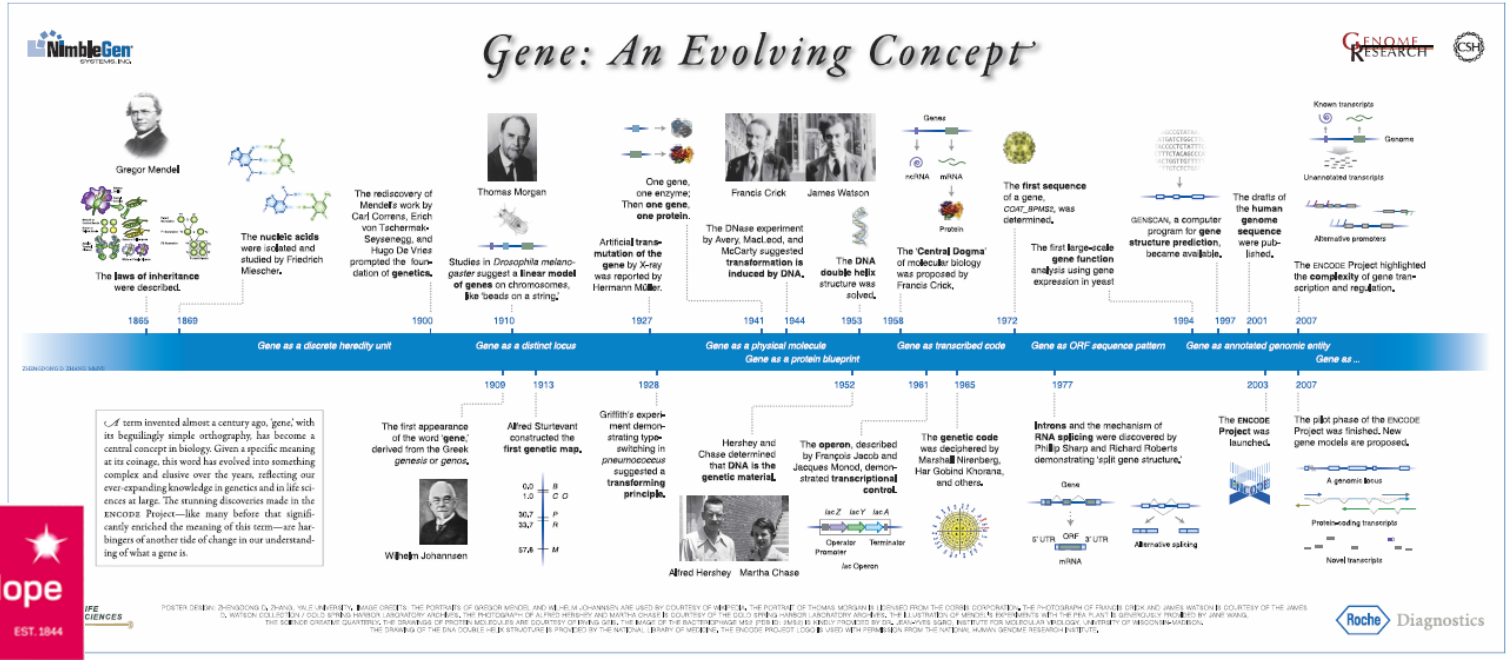
Primer on Human Genetics

From a Monastery to the Eagle
DNA, RNA and protein
Heredity and genetics
Genetic determinism
Genes and other things
Mutations and other variation



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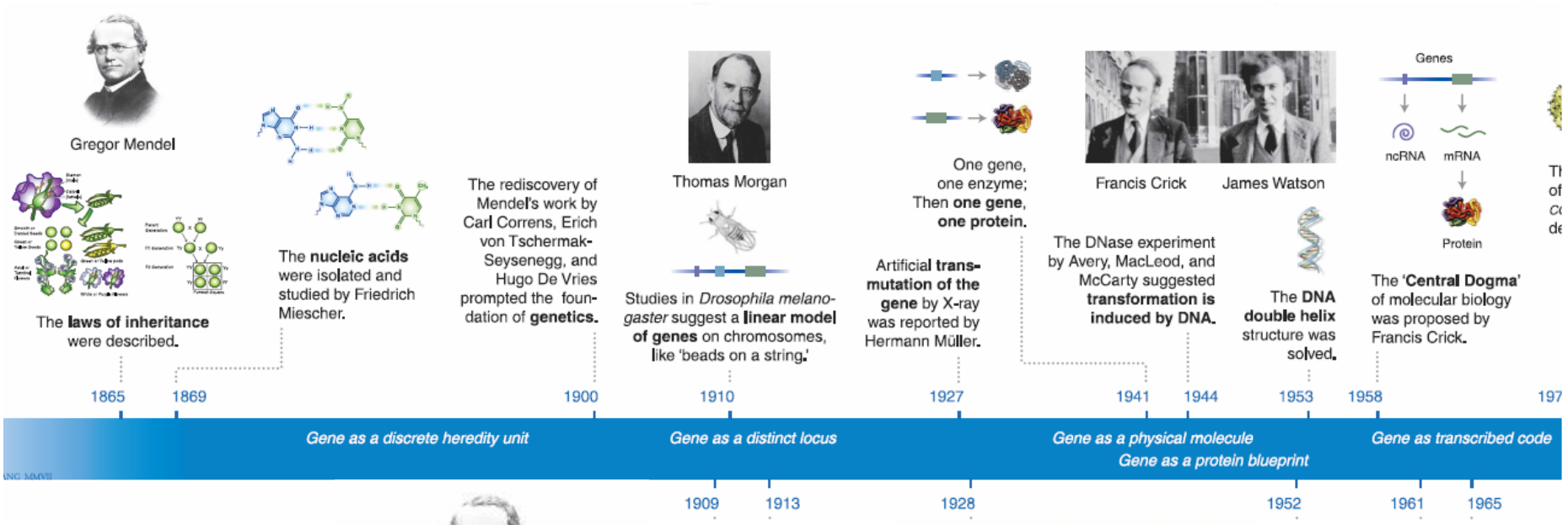

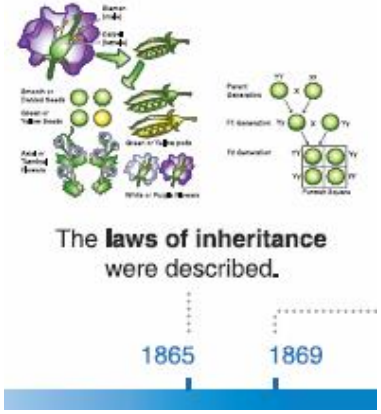

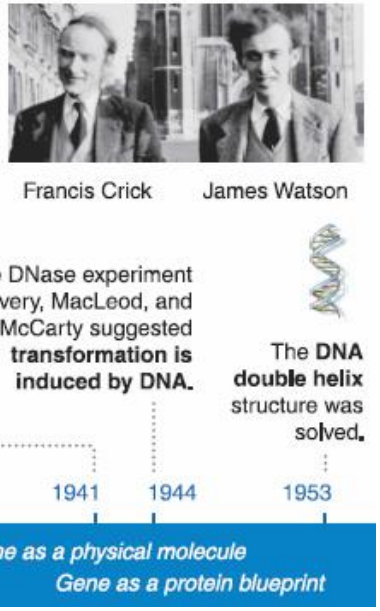

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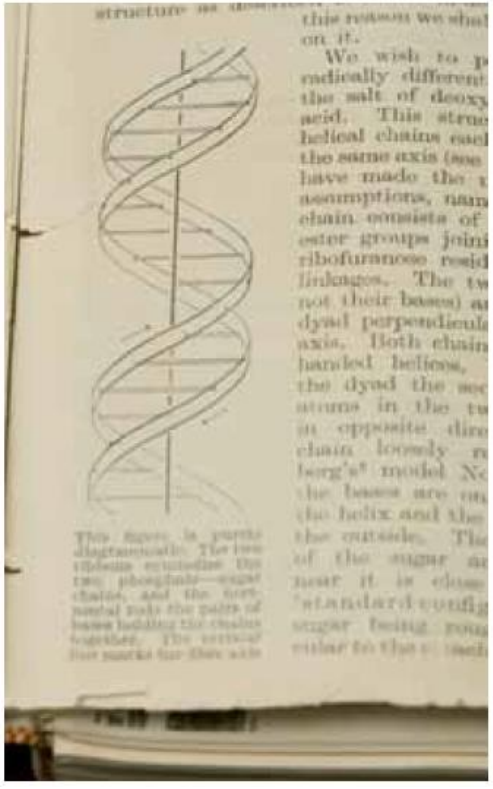
"Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid" (1953)

James D. Watson and Francis H. C. Crick

London. *Nature* 171.25 (April 1953): pp. 737–38. Printed journal, with line drawing; height 9⅞ in. (25.1 cm). Double helix DNA model. Plastic, stainless steel tube, wire, 15 ft., made by A. A. Barker, Cambridge, UK, 1969.



ABOVE: The first published illustration of the double helix. James D. Watson and Francis H. C. Crick, "Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid," *Nature* 171.25 (April 1953): pp. 737–38. The caption reads: "The figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis."

The paper is only about eight hundred words and the text is almost superfluous. The real content lies in the single unnumbered figure. It is a mere cartoon, platonic in its simplicity, "purely diagrammatic," according to the legend. Two ribbons, side by side and linked by crossbars, wrap sinuously around a thin central axis. Two arrows, one angling up, the other down, suggest polarity for the ribbons. There are no nucleotides, no As, Cs, Gs, or Ts. No hydrogen bonds, phosphates, or pentose rings.

Its meaning is conveyed in a single arrogant sentence, one of the most memorable in biology: "It has not escaped our attention that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." A with T; C with G: Chargaff's rules. Specifying the copying mechanism of course specifies cell division, which in turn specifies development and evolution. In *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (1968) James Watson reported Francis Crick as bursting into the Eagle pub, bellowing, "We have found the secret of life!"

The image was just another pretty picture until researchers elsewhere turned that "possible copying mechanism" into the foundation of the science of heredity. It happened gradually. Although well received in the scientific community, the double helix had little impact on the public consciousness until the 1960s. Watson (b. 1928), Crick (1916–2004), and Maurice Wilkins (1916–2004) won the Nobel Prize in 1962, following publication of the "operon" model of the gene and the first cracks in the genetic code.

Crick lived in the Golden Helix, his house in Cambridge, but it was Watson who transmuted the snipped tin plates of their model into gold. After the Nobel, he sat down to write the first textbook of DNA. It was a hit. Then in 1968 he published *The Double Helix*, his memoir of the discovery. The book infuriated his friends, confounded his enemies, made him rich, and made his twisting diagram famous.

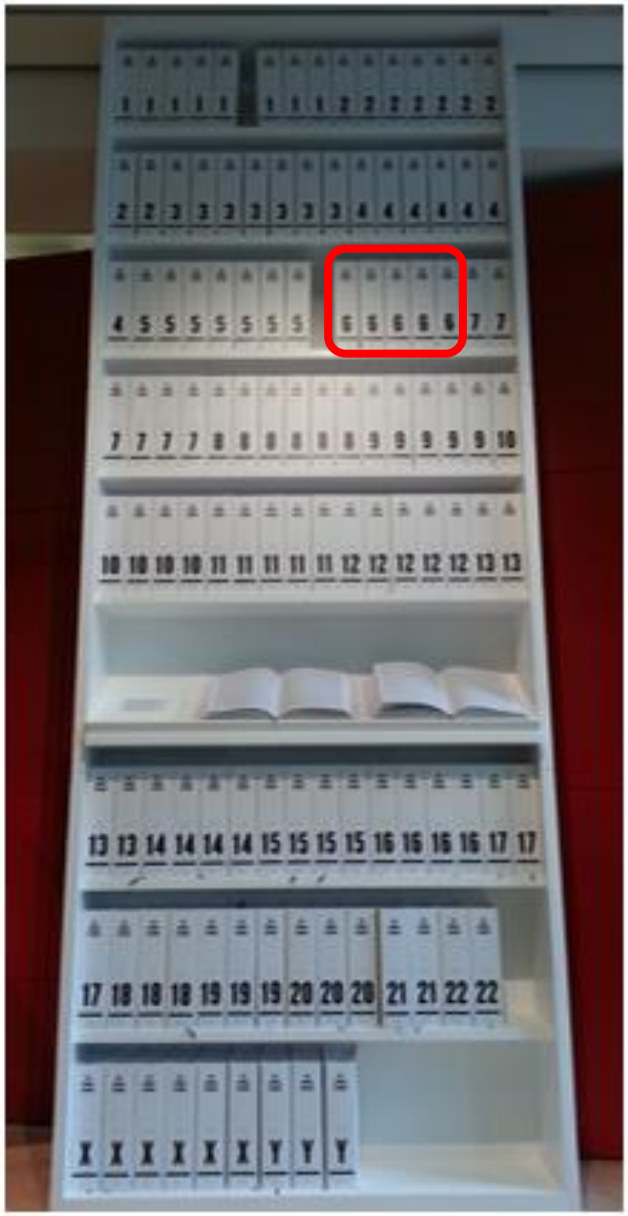
The double helix became Watson's logo. When he became director of the laboratory at Cold Spring Harbor he stamped it on the stationery, the sign at the entrance, the spines of the books published by the in-house press. Helical imagery infected the laboratory, from the hilltop bell tower to the statuary in the lobby to the wallpaper and light fixtures.

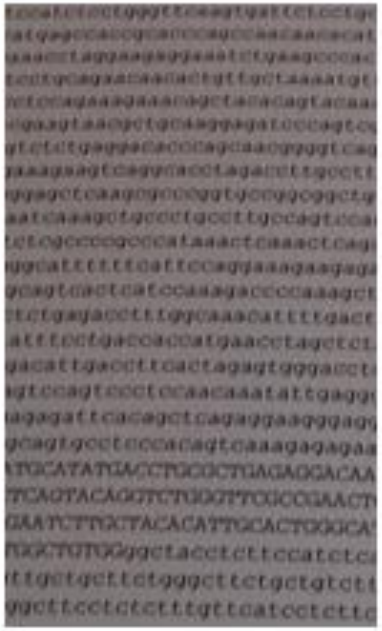
As medicine went molecular, DNA became its emblem. The double helix became as interesting to sociologists and literary theorists as it is to biologists. Since the fiftieth anniversary of the 1953 article's publication it has been commemorated federally and commercially each April 25 as DNA Day, a day of celebration of all things nucleic—including discounted subscription prices from genomics companies that provide DNA mapping to individual customers.

Where the Bohr atom represents elemental nature, the double helix stands for human nature. It is an icon of identity. In its claims to tell us who we are and how we are made, there is encoded both the power and danger of science. The double helix satisfies graphically, elegantly, the double-edged, near universal desire for determinism—for a single, simple "secret of life."

—NATHANIEL COMFORT

Primer on Human Genetics





Photos: MT Dorak

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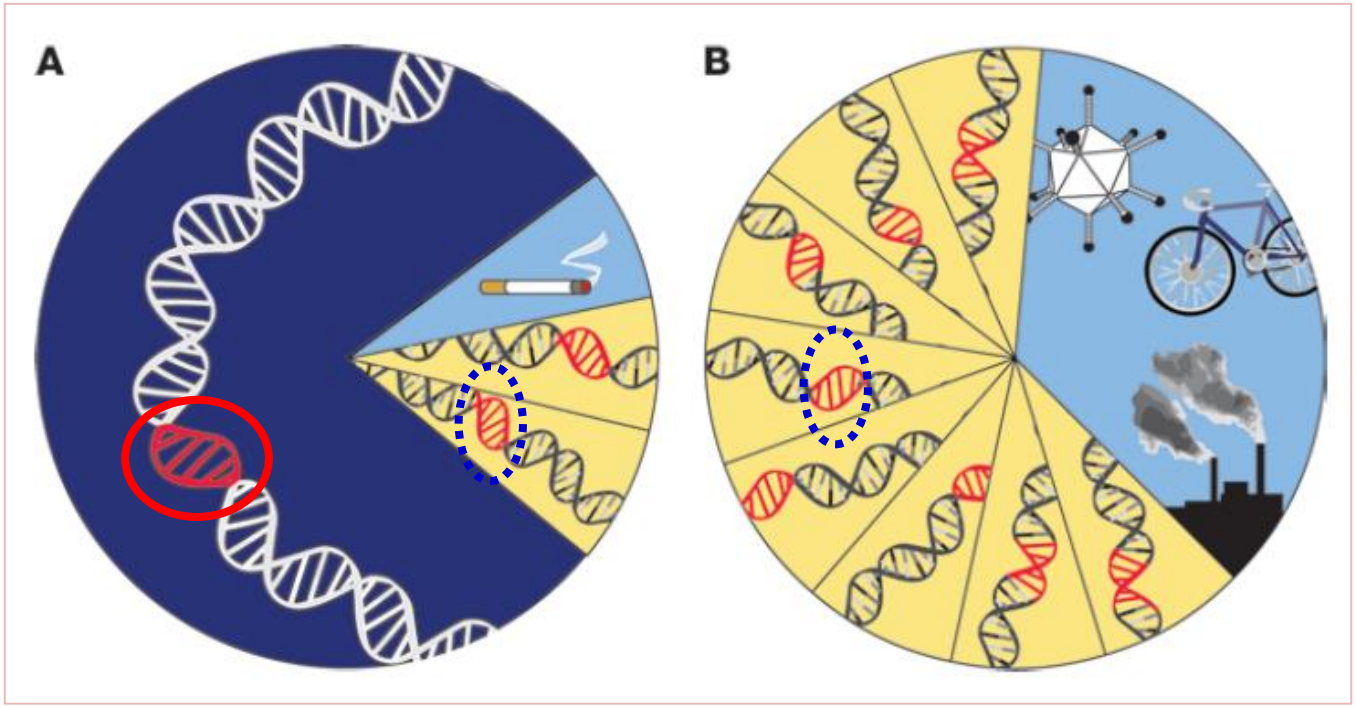


Figure 1
Genetic and environmental contributions to monogenic and complex disorders. (**A**) Monogenic disease. A variant in a single gene is the primary determinant of a monogenic disease or trait, responsible for most of the disease risk or trait variation (dark blue sector), with possible minor contributions of modifier genes (yellow sectors) or environment (light blue sector). (**B**) Complex disease. Many variants of small effect (yellow sectors) contribute to disease risk or trait variation, along with many environmental factors (blue sector).

Monogenic vs Multifactorial

A HapMap harvest of insights into the genetics of common disease

Teri A. Manolio, Lisa D. Brooks, and Francis S. Collins

National Human Genome Research Institute, Bethesda, Maryland, USA.

The Journal of Clinical Investigation http://www.jci.org Volume 118 Number 5 May 2008

Primer on Human Genetics

When DNA Means "Do Not Ask"

As comprehensive genetic tests become more widespread, patients and experts mull how to deal with unexpected findings

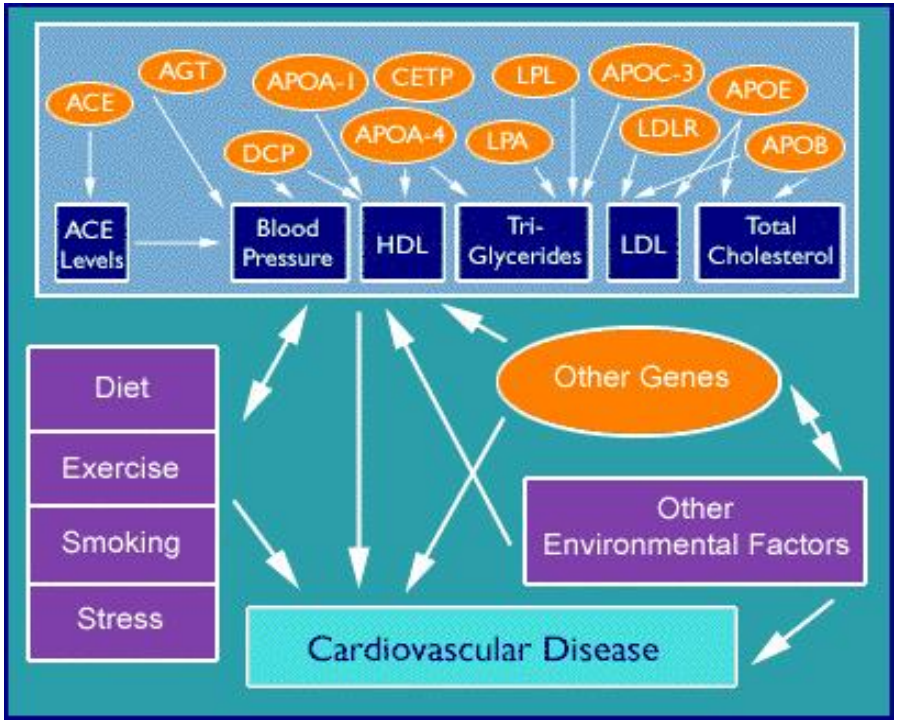
CANCERS AND PRECANCEROUS CONDITIONS
- Familial adenomatous polyposis—*APC*
- Familial medullary thyroid cancer—*RET*
- Hereditary breast and ovarian cancer—*BRCA1, BRCA2*
- Li-Fraumeni syndrome—*TP53*
- Lynch syndrome—*MLH1, MSH2, MSH6, PMS2*
- Multiple endocrine neoplasia type 1—*MEN1*
- Multiple endocrine neoplasia type 2—*RET*
- MYH-associated polyposis and related conditions—*MUTYH*
- Peutz-Jeghers syndrome—*STK11*
- PTEN hamartoma tumor syndrome—*PTEN*
- Retinoblastoma—*RB1*
- Von Hippel–Lindau syndrome—*VHL*
- WT1-related Wilms tumor—*WT1*

HEART AND VASCULAR DISORDERS
- Arrhythmogenic right ventricular cardiomyopathy—*PKP2, DSP, DSC2, TMEM43, DSG2*
- Certain other cardiomyopathies—*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
- Catecholaminergic polymorphic ventricular tachycardia—*RYR2*
- Ehlers-Danlos syndrome (vascular type)—*COL3A1*
- Long QT syndromes and Brugada syndrome—*KCNQ1, KCNH2, SCN5A*
- Marfan syndrome and related conditions—*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*

NONCANCEROUS GROWTHS
- Hereditary paraganglioma-pheochromocytoma syndrome—*SDHD, SDHAF2, SDHC, SDHB*
- Neurofibromatosis type 2—*NF2*
- Tuberous sclerosis complex—*TSC1, TSC2*

OTHER
- Familial hypercholesterolemia—*LDLR, APOB, PCSK9*
- Malignant hyperthermia susceptibility—*RYR1, CACNA1S*

Monogenic vs Multifactorial



Ethics of genetic tests

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Primer on Human Genetics

Newborn Screening

Newborn screening identifies conditions that can affect a child's long-term health or survival. Early detection, diagnosis, and intervention can prevent death or disability and enable children to reach their full potential. Each year, millions of babies in the U.S. are routinely screened, using a few drops of blood from the newborn's heel, for certain genetic, endocrine, and metabolic disorders, and are also tested for hearing loss prior to discharge from a hospital or birthing center.

U.S.A.

U.K.

Babies currently have the heel-prick test at between five and eight days old to check for:

- Phenylketonuria (PKU),
- Congenital hypothyroidism (CHT),
- Sickle cell disease
- Cystic fibrosis
- Medium-chain acyl-CoA dehydrogenase deficiency (MCADD).

The baby's heel is pricked and drops of blood are collected and analysed in a laboratory.

Detecting conditions at this stage means babies can get the treatment and support they need from the earliest stage possible.

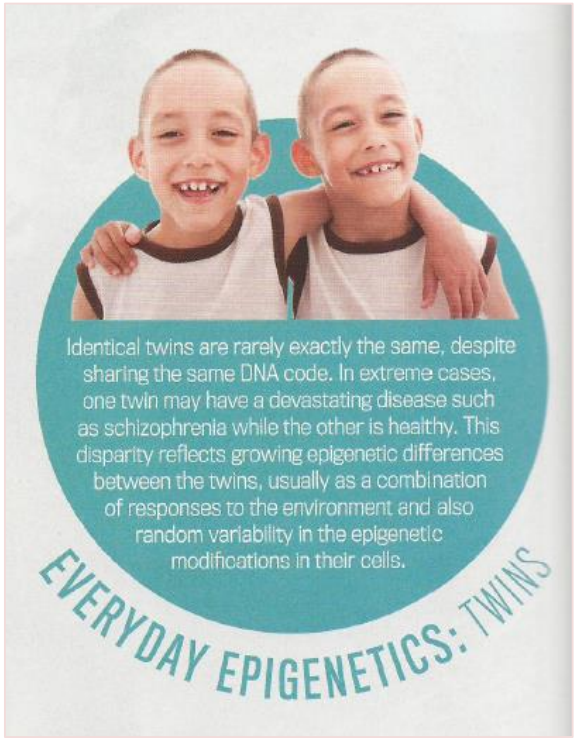
The extra conditions which will now also be tested for are:

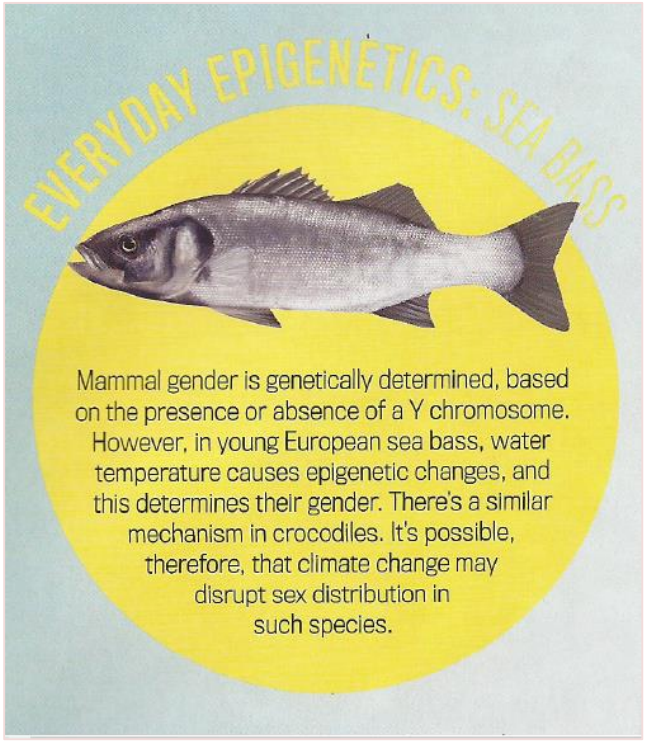
- Maple syrup urine disease
- Homocystinuria
- Glutaric acidaemia type 1
- Isovaleric acidaemia

They are all inherited conditions where babies have problems breaking down amino acids, the "building blocks" of proteins.

Primer on Human Genetics

Epigenetics:
The interface between nature and nurture





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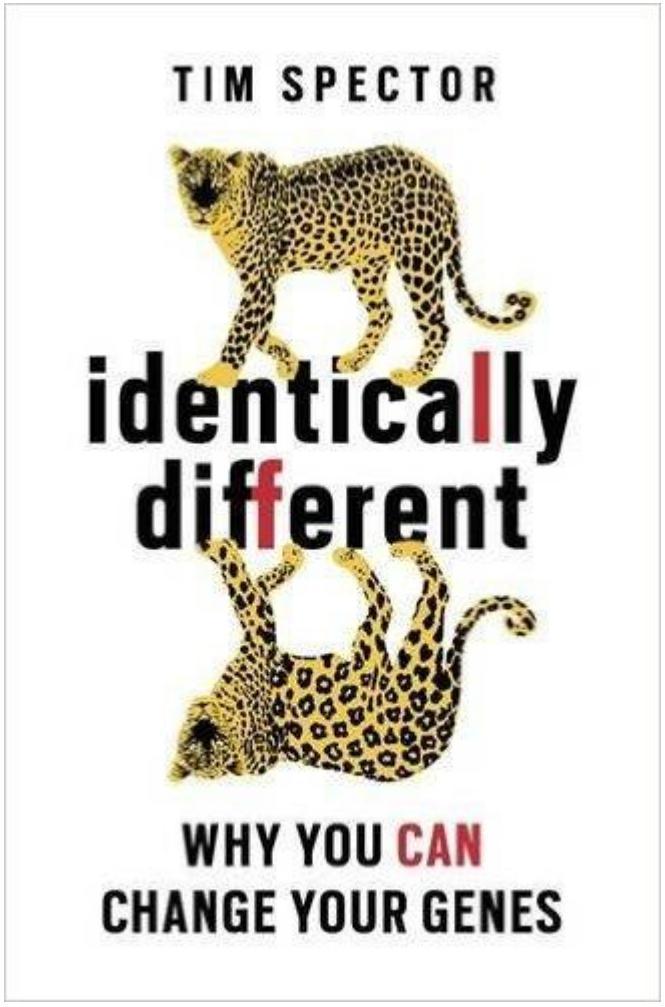

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Clones, identity and the future

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WHAT MAKES US HUMAN?

Comparisons of the genomes of humans and chimpanzees are revealing those rare stretches of DNA that are ours alone

Humans and chimpanzees have near identical genomes:

Chromosome numbers, gene counts

DNA sequence identity is 96%

Humans and fruit flies are not as different as you might think:

Nearly 75% of disease-related genes in humans have functionally similar genes in the fruit fly

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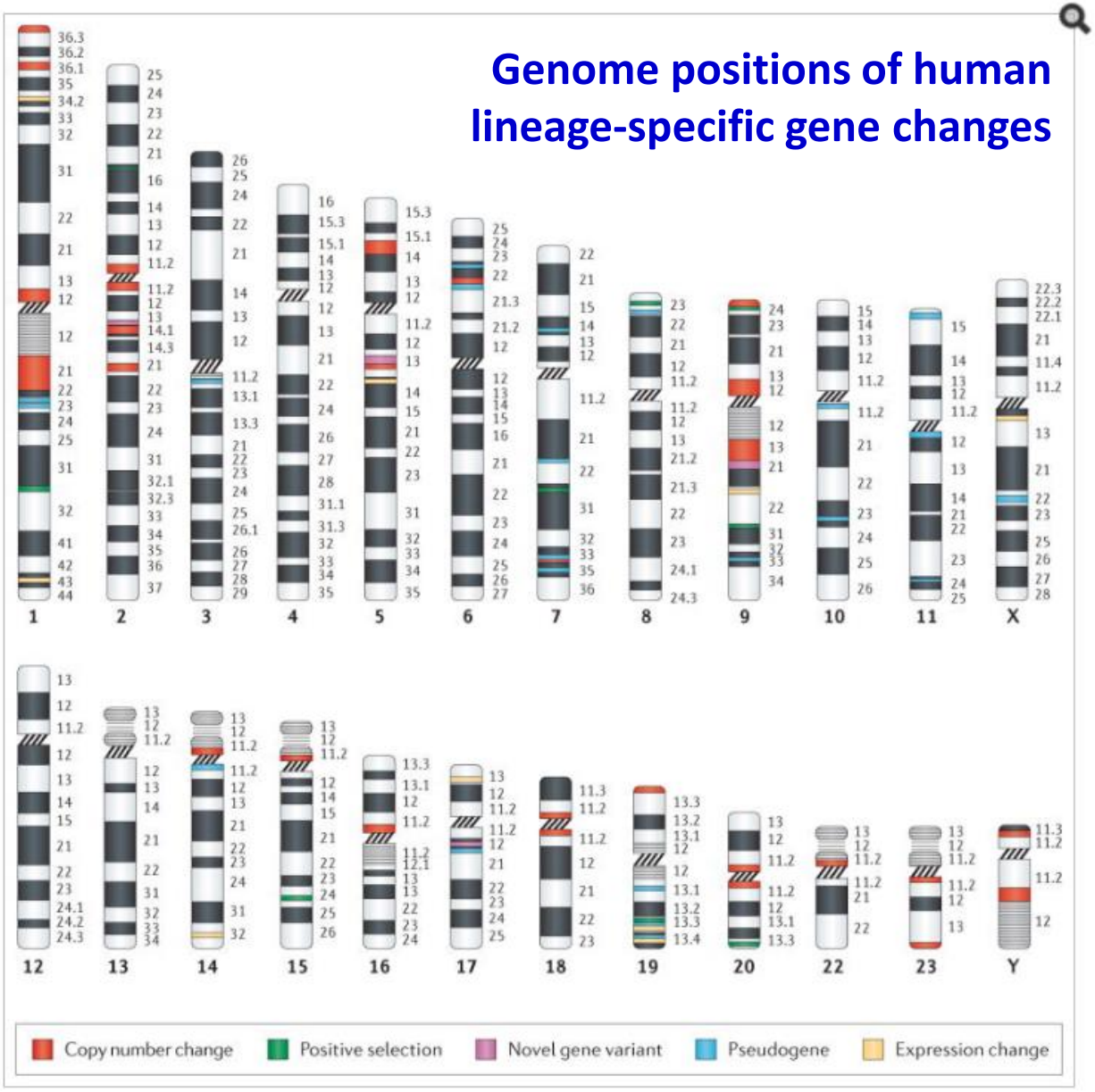
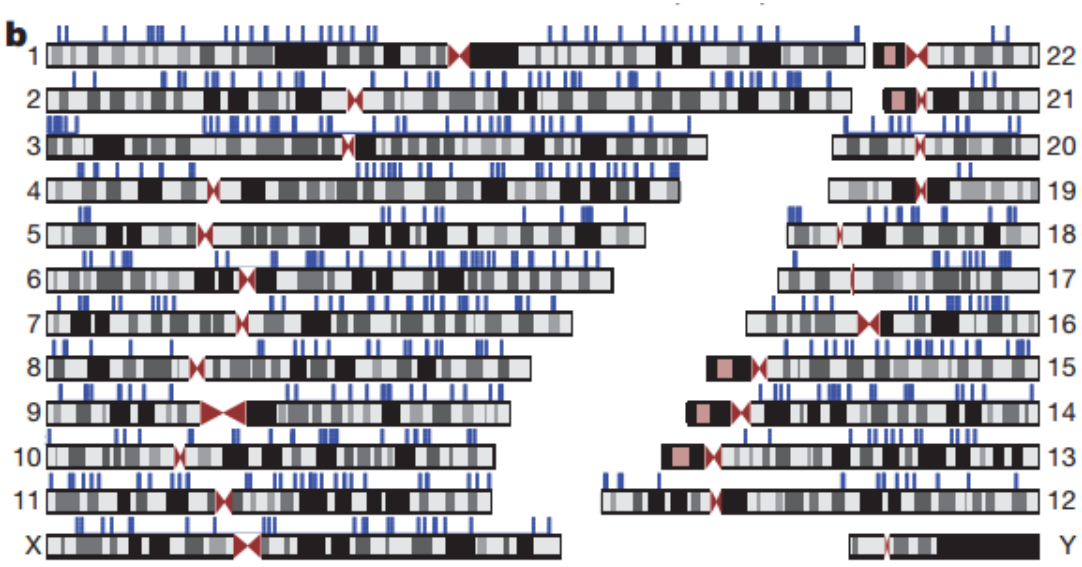
What Makes Us Human?



What Makes Us Human?



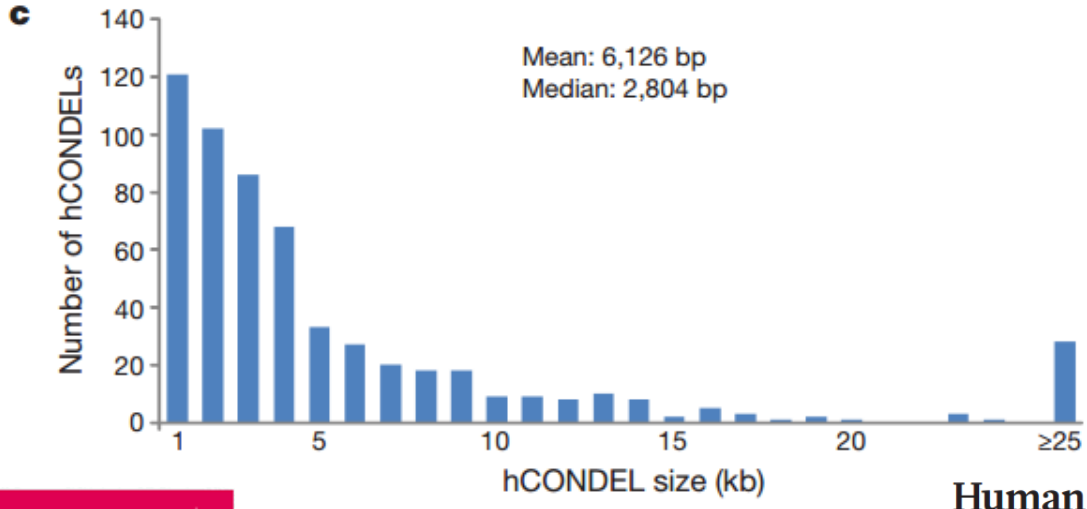


Figure 1 | Hundreds of sequences highly conserved between chimpanzee and other species are deleted in humans. **a**, Computational approach used to discover human-specific deletions of functional DNA: identification of ancestral chimpanzee genomic sequences deleted in human; discovery of chimpanzee genomic sequences highly conserved in other species; and detection of human-specific deletions that remove one or more chimpanzee conserved sequences. Total chimpanzee sequence identified in each step is displayed beneath each graphic. **b**, Human genomic locations of the 583 hCONDELs. hCONDELs are displayed as blue ticks above the many locations where they are missing. **c**, Size distribution of hCONDELs.

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Human-specific loss of regulatory DNA and the evolution of human-specific traits

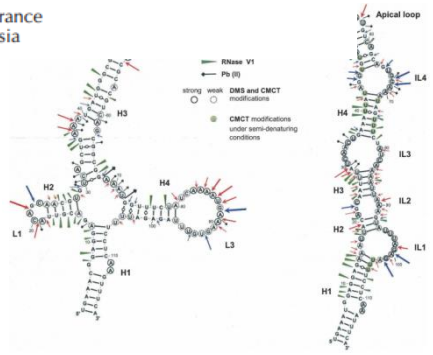
Cory Y. McLean[1]*, Philip L. Reno[2,3]*†, Alex A. Pollen[2]*, Abraham I. Bassan[2], Terence D. Capellini[2], Catherine Guenther[2,3], Vahan B. Indjeian[2,3], Xinhong Lim[2], Douglas B. Menke[2,3]†, Bruce T. Schaar[2], Aaron M. Wenger[1], Gill Bejerano[1,2] & David M. Kingsley[2,3]

What Makes Us Human?

Distinctive structures between chimpanzee and human in a brain noncoding RNA

ARTEMY BENIAMINOV,[1,2] ERIC WESTHOF,[1] and ALAIN KROL[1]

[1]Architecture et Réactivité de l'arN, Université Louis Pasteur, CNRS, IBMC, 67084 Strasbourg, France
[2]Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow 119991, Russia



HAR1A highly accelerated region 1A (non-protein coding) [*Homo sapiens* (human)]

Gene ID: 768096, updated on 7-May-2016

Summary

Official Symbol	HAR1A provided by HGNC
Official Full Name	highly accelerated region 1A (non-protein coding) provided by HGNC
Primary source	HGNC:HGNC:33117
See related	MIM:610556
Gene type	ncRNA
RefSeq status	PROVISIONAL
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	HAR1F; LINC00064; NCRNA00064

Science. 2008 Sep 5;321(5894):1346-50. doi: 10.1126/science.1159974.

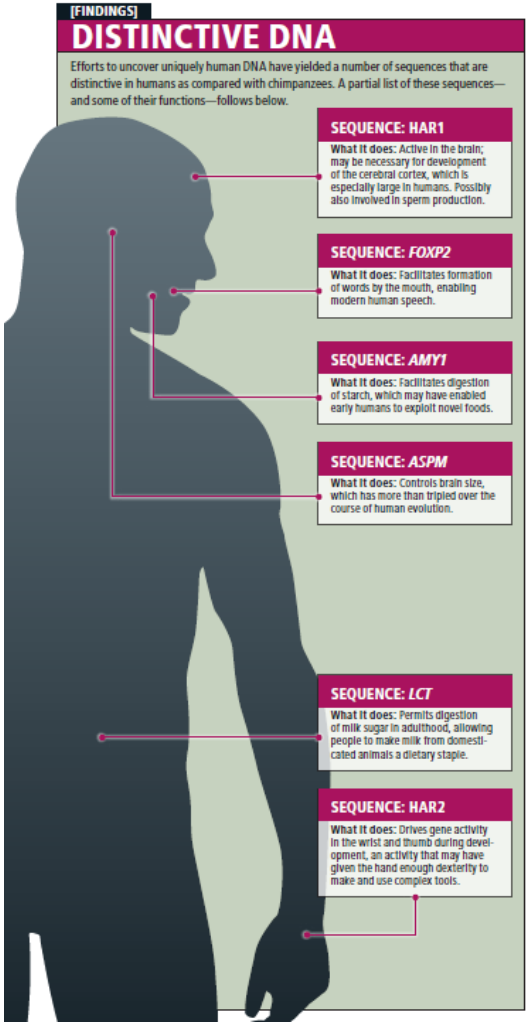
Human-specific gain of function in a developmental enhancer.

Prabhakar S[1], Visel A, Akiyama JA, Shoukry M, Lewis KD, Holt A, Plajzer-Frick I, Morrison H, Fitzpatrick DR, Afzal V, Pennacchio LA, Rubin EM, Noonan JP.

Author information

Abstract

Changes in gene regulation are thought to have contributed to the evolution of human development. However, in vivo evidence for uniquely human developmental regulatory function has remained elusive. In transgenic mice, a conserved noncoding sequence (HACNS1) that evolved extremely rapidly in humans acted as an enhancer of gene expression that has gained a strong limb expression domain relative to the orthologous elements from chimpanzee and rhesus macaque. This gain of function was consistent across two developmental stages in the mouse and included the presumptive anterior wrist and proximal thumb. In vivo analyses with synthetic enhancers, in which human-specific substitutions were introduced into the chimpanzee enhancer sequence or reverted in the human enhancer to the ancestral state, indicated that 13 substitutions clustered in an 81-base pair module otherwise highly constrained among terrestrial vertebrates were sufficient to confer the human-specific limb expression domain.



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WHAT MAKES US HUMAN?

What Makes Us Human?

Distinctive structures between chimpanzee and human in a brain noncoding RNA

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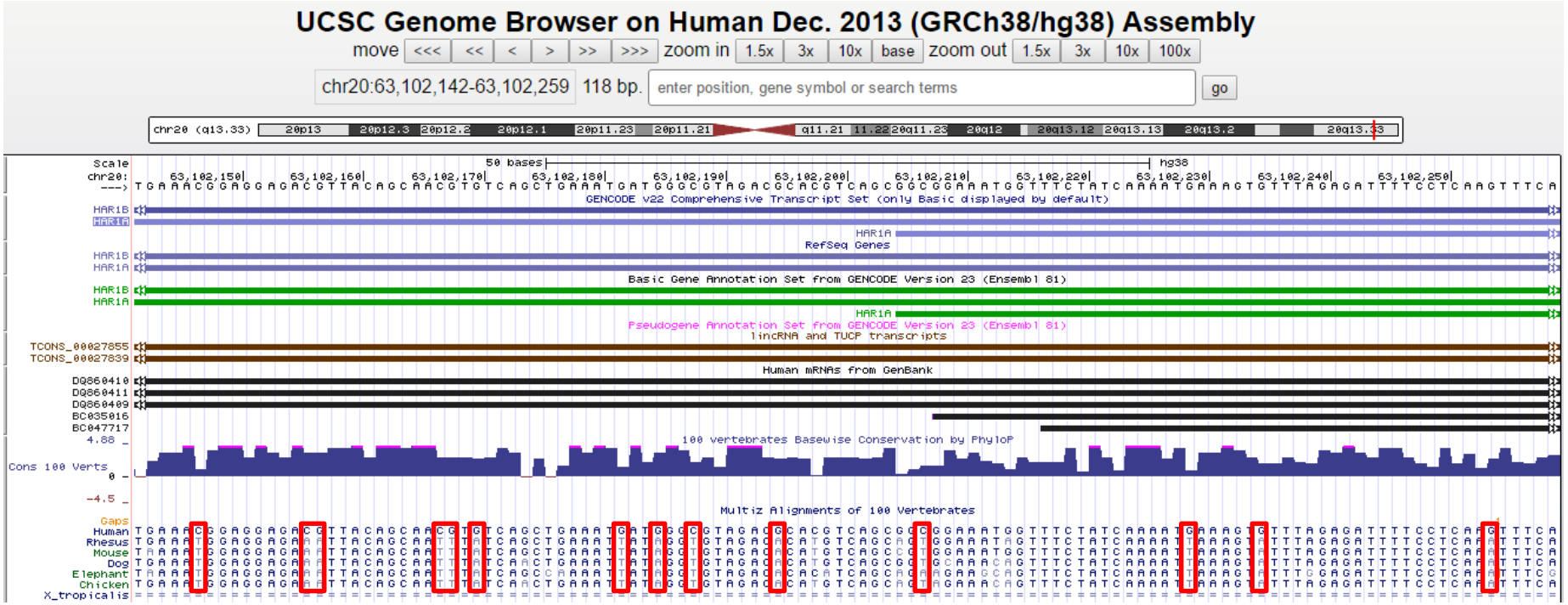

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WHAT MAKES US HUMAN?

Comparisons of the genomes of humans and chimpanzees are revealing those rare stretches of DNA that are ours alone

98.5% of the human genome does not code for a protein

80% of the non-coding genome (*junk* DNA!) has biochemical activity

Most of the non-coding DNA is not shared by other species

Human lineage-specific sequences are mainly in the non-coding regions

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Is It You?

ID testing after fire, airplane crash etc

Kinship testing

Forensic investigation

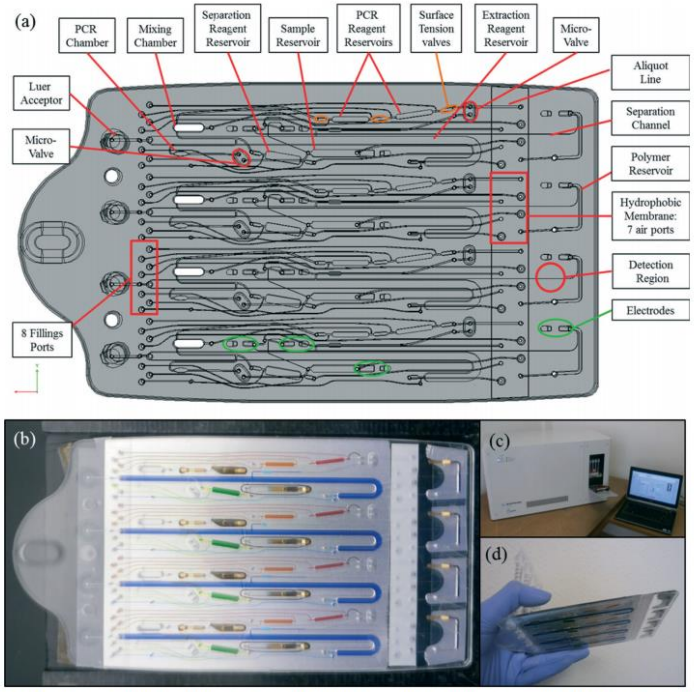


Fig. 1 Microfluidic chip for "sample-in-answer-out" integrated DNA processing. (a) Schematic representation of the microchip with major microfluidic features. (b) Bottom view of the cartridge containing the fluidic layout with blue reagents in the extraction reagent reservoir, red and orange reagents in the PCR reagent reservoirs, green reagents in the separation reagent reservoir and polymer in the polymer reservoir. (c) Microchip inside the instrument enabling its functionality with swabs attached and computer for software control. (d) View of the microchip with swabs attached to it with a hand scale.

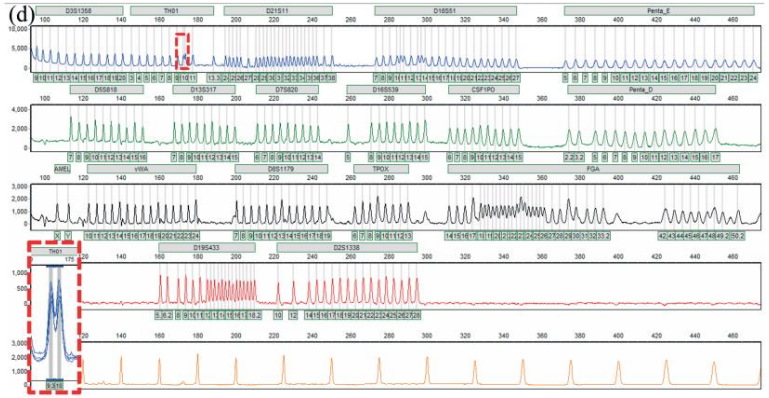
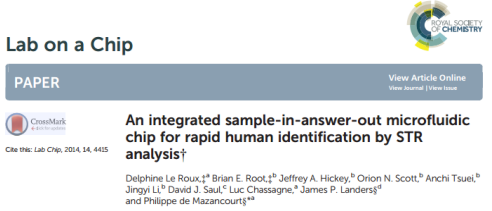


Fig. 5 PCR–ME optimization. (a) Polymer filling the microchip electrophoresis separation channel. (b) Separation reagents moving through the PCR chamber toward the sample reservoir, flushing the PCR products. Red arrows show the fluidic movement. The PCR products mixed with the separation reagents are then ready to be electrophoretically separated (cross T injection and separation microchannel shown in orange). (c) Schematic view of the polymer filling and movement to the sample reservoir. (d) Electropherogram from an allelic ladder separation in the 7 cm microchip channel with five examples of 9.3–10 alleles for the TH01 marker showing one base pair resolution (expanded in red box).



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Forensic Studies

Pets and plants play detective

DNA evidence from almost any source may provide a link between criminal and crime. For example, a particularly brutal murder in Seattle was solved entirely on the basis of DNA provided by the victim's dog. After two people and their dog were shot in their home, two suspects were arrested in the case, and blood-spattered clothing was found in their possession. The only blood on the clothing was of canine origin, and the dog's blood turned out to be the only evidence linking the suspects to the crime scene. Using markers originally designed for canine paternity analysis, investigators generated a DNA fingerprint from the dog's blood and compared it with DNA tests from the bloodstained clothing. A perfect match resulted in a conviction.

Practically any sort of biological material can provide enough DNA to match a suspect to a crime. In one murder case, the perpetrator stepped in a pile of dog feces near the scene. DNA fingerprinting matched the evidence on a suspect's shoe to the evidence at the scene, leading to a conviction. In another case, a rape victim's dog urinated on the attacker's vehicle, allowing investigators to match the pup to the truck; the suspect promptly confessed his guilt.

Even plants have a space in the DNA evidence game. The very first time DNA evidence from plants was used was in an Arizona court case in 1992. A murder victim was found near a desert tree called Paloverde. Seeds from that type of tree were found in the bed of a pickup truck that belonged to a suspect in the case, but the suspect denied ever having been in the area. The seeds in the truck were matched to the exact tree where the victim was found using DNA fingerprinting. The seeds couldn't prove the suspect's presence, but they provided a link between his truck and the tree where the body was found. The DNA evidence was convincing enough to obtain a conviction in the case.

Forensic Studies

To find a criminal using DNA

The FBI's CODIS system works because it contains hundreds of thousands of cataloged samples for comparison. All 50 U.S. states require DNA samples to be collected from persons convicted of sex offenses and murder. Laws vary from state to state on which other convictions require DNA sampling, but so far, CODIS has cataloged over 300,000 offender samples, with at least that many more awaiting analysis. But what if no sample has been collected from the guilty party? What happens then?

Some law enforcement agencies have conducted mass collection efforts to obtain DNA samples for comparison. The most famous of these collection efforts occurred in Great Britain in the mid-1980s. After two teenaged girls were murdered, every male in the entire neighborhood around the crime scene was asked to donate a sample for comparison. In all, nearly 4,000 men complied with the request to donate their DNA. The actual murderer was captured after he bragged about how he had gotten someone else to volunteer a sample for him.

DNA evidence is also sometimes used to extend the statute of limitations on crimes when no arrest has been made. (The *statute of limitations* is the amount of time prosecutors have to bring charges against a suspect.) Crimes involving murder have no statute of limitations, but most states have a statute of limitations on other crimes such as rape. To allow prosecution of such crimes, DNA evidence can be used to file an arrest warrant or make an indictment against "John Doe" — the unknown person possessing the DNA fingerprint of the perpetrator. The arrest warrant extends the statute of limitations indefinitely until a suspect is captured.

Ancient DNA Studies

Nature. 2010 Feb 11;463(7282):757-62. doi: 10.1038/nature08835.

Ancient human genome sequence of an extinct Palaeo-Eskimo.

Rasmussen M[1], Li Y, Lindgreen S, Pedersen JS, Albrechtsen A, Moltke I, Metspalu M, Metspalu E, Kivisild T, Gupta R, Bertalan M, Nielsen K, Gilbert MT, Wang Y, Raghavan M, Campos PF, Kamp HM, Wilson AS, Gledhill A, Tridico S, Bunce M, Lorenzen ED, Binladen J, Guo X, Zhao J, Zhang X, Zhang H, Li Z, Chen M, Orlando L, Kristiansen K, Bak M, Tommerup N, Bendixen C, Pierre TL, Grønnow B, Meldgaard M, Andreasen C, Fedorova SA, Osipova LP, Higham TF, Ramsey CB, Hansen TV, Nielsen FC, Crawford MH, Brunak S, Sicheritz-Pontén T, Villems R, Nielsen R, Krogh A, Wang J, Willerslev E.

Author information

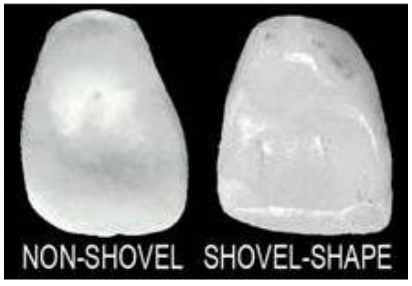
Abstract

We report here the genome sequence of an ancient human. Obtained from approximately 4,000-year-old permafrost-preserved hair, the genome represents a male individual from the first known culture to settle in Greenland. Sequenced to an average depth of 20x, we recover 79% of the diploid genome, an amount close to the practical limit of current sequencing technologies. We identify 353,151 high-confidence single-nucleotide polymorphisms (SNPs), of which 6.8% have not been reported previously. We estimate raw read contamination to be no higher than 0.8%. We use functional SNP assessment to assign possible phenotypic characteristics of the individual that belonged to a culture whose location has yielded only trace human remains. We compare the high-confidence SNPs to those of contemporary populations to find the populations most closely related to the individual. This provides evidence for a migration from Siberia into the New World some 5,500 years ago, independent of that giving rise to the modern Native Americans and Inuit.

A 4,000 years old Saqqaq person!

Ancient DNA Studies

Given the A1 antigen allele plus encoding of the rhesus factor in combination with lack of B antigen and the O antigen frameshift mutation, we conclude that the Saqqaq individual had blood type A+[24]. Although common in all ethnic groups, this has very high frequencies in populations of the east coast of Siberia down to mid China[25]. Furthermore, we find a combination of four SNPs at the *HERC2-OCA2* locus, which among Asians is strongly associated with brown eyes[26]. SNPs on chromosomes 2, 5, 15 and X suggest that he probably did not have a European light skin colour[27], had dark and thick hair[28,29] (in agreement with the morphological examination (Fig. 1b–d)), and an increased risk of baldness[30,31]. The same SNP that is characteristic of hair thickness also suggests that he probably had shovel-graded front teeth—a characteristic trait of Asian and Native American populations[32]. An AA genotype SNP (forward strand) on chromosome 16 is consistent with the Saqqaq individual having earwax of the dry type that is typical of Asians and Native Americans, rather than the wet earwax type dominant in other ethnic groups[33]. In addition, the combined influence of 12 SNPs on metabolism and body mass index indicates that the Saqqaq individual was adapted to a cold climate (see Supplementary information and Supplementary Table 14).



Nature. 2010 Feb 11;463(7282):757-62. doi: 10.1038/nature08835.

Ancient human genome sequence of an extinct Palaeo-Eskimo.

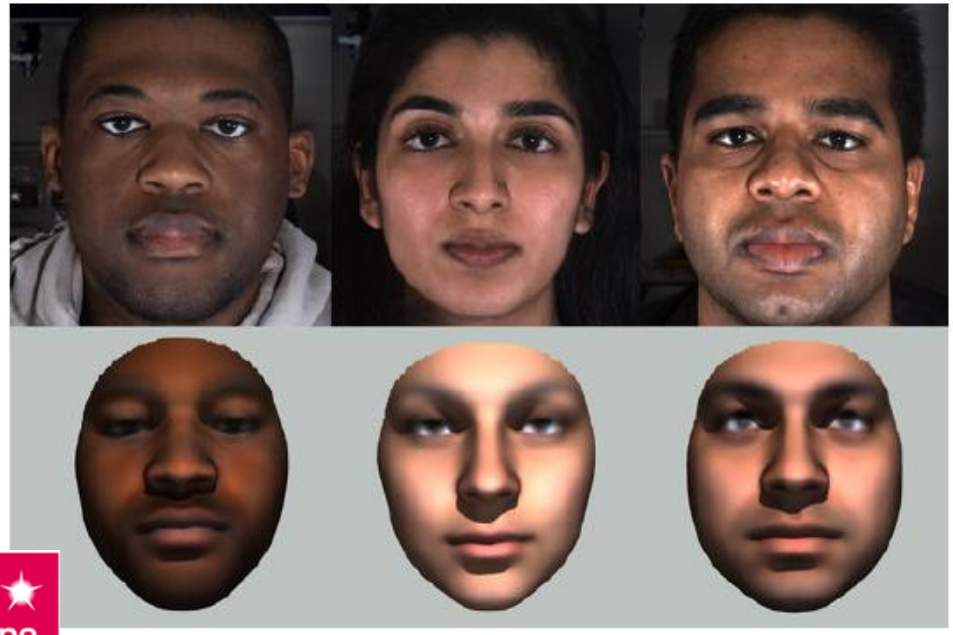
Rasmussen M[1], Li Y, Lindgreen S, Pedersen JS, Albrechtsen A, Moltke I, Metspalu M, Metspalu E, Kivisild T, Gupta R, Bertalan M, Nielsen K, Gilbert MT, Wang Y, Raghavan M, Campos PF, Kamp HM, Wilson AS, Gledhill A, Tridico S, Bunce M, Lorenzen ED, Binladen J, Guo X, Zhao J, Zhang X, Zhang H, Li Z, Chen M, Orlando L, Kristiansen K, Bak M, Tommerup N, Bendixen C, Pierre TL, Grønnow B, Meldgaard M, Andreasen C, Fedorova SA, Osipova LP, Higham TF, Ramsey CB, Hansen TV, Nielsen FC, Crawford MH, Brunak S, Sicheritz-Pontén T, Villems R, Nielsen R, Krogh A, Wang J, Willerslev E.

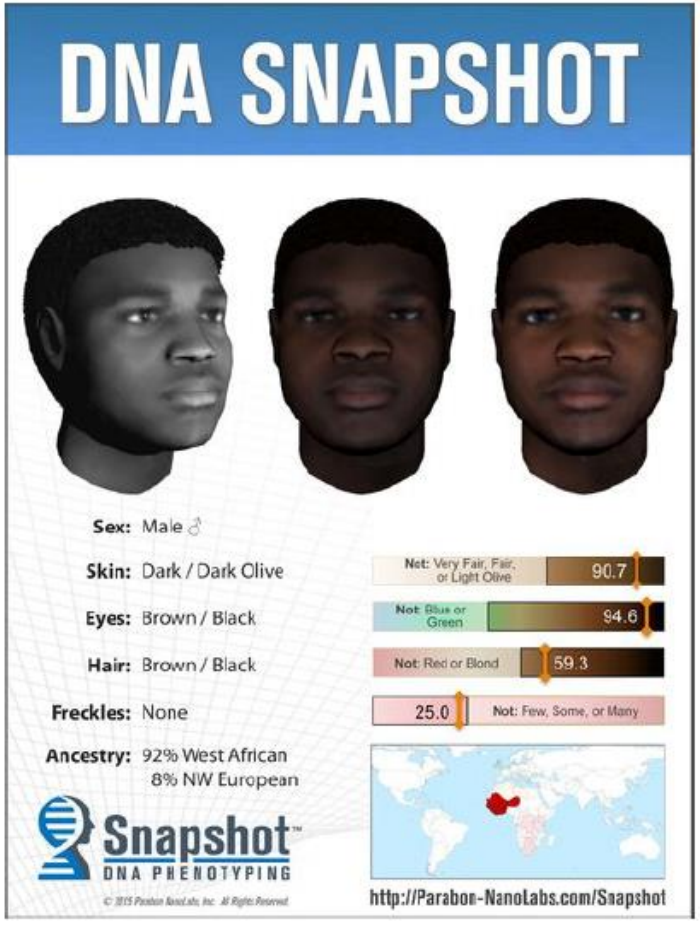
Portrait of DNA?

Modeling 3D Facial Shape from DNA

Peter Claes[1], Denise K. Liberton[2], Katleen Daniels[1], Kerri Matthes Rosana[2], Ellen E. Quillen[2], Laurel N. Pearson[2], Brian McEvoy[3], Marc Bauchet[2], Arslan A. Zaidi[2], Wei Yao[2], Hua Tang[4], Gregory S. Barsh[4,5], Devin M. Absher[5], David A. Puts[2], Jorge Rocha[6,7], Sandra Beleza[4,8], Rinaldo W. Pereira[9], Gareth Baynam[10,11,12], Paul Suetens[1], Dirk Vandermeulen[1], Jennifer K. Wagner[13], James S. Boster[14], Mark D. Shriver[2]*

Human facial diversity is substantial, complex, and largely scientifically unexplained. We used spatially dense quasi-landmarks to measure face shape in population samples with mixed West African and European ancestry from three locations (United States, Brazil, and Cape Verde). Using bootstrapped response-based imputation modeling (BRIM), we uncover the relationships between facial variation and the effects of sex, genomic ancestry, and a subset of craniofacial candidate genes. The facial effects of these variables are summarized as response-based imputed predictor (RIP) variables, which are validated using self-reported sex, genomic ancestry, and observer-based facial ratings (femininity and proportional ancestry) and judgments (sex and population group). By jointly modeling sex, genomic ancestry, and genotype, the independent effects of particular alleles on facial features can be uncovered. Results on a set of 20 genes showing significant effects on facial features provide support for this approach as a novel means to identify genes affecting normal-range facial features and for approximating the appearance of a face from genetic markers.





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Portrait of DNA?

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NATURE COMMUNICATIONS | ARTICLE OPEN

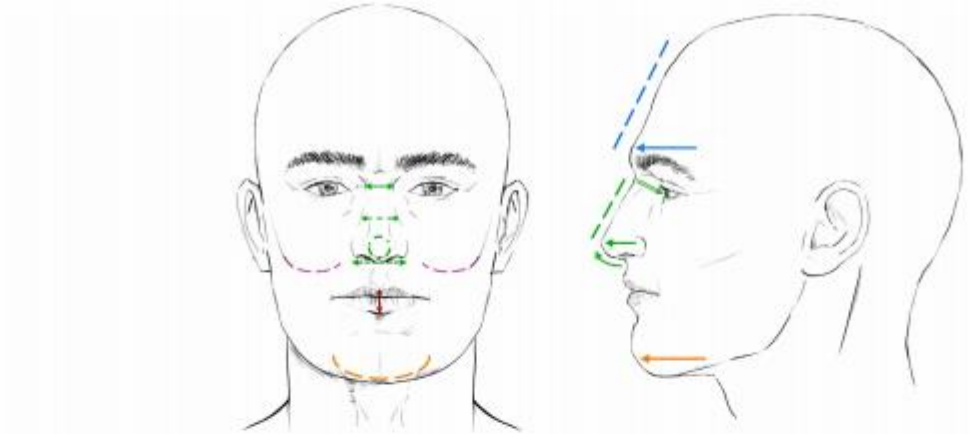
A genome-wide association scan implicates *DCHS2*, *RUNX2*, *GLI3*, *PAX1* and *EDAR* in human facial variation

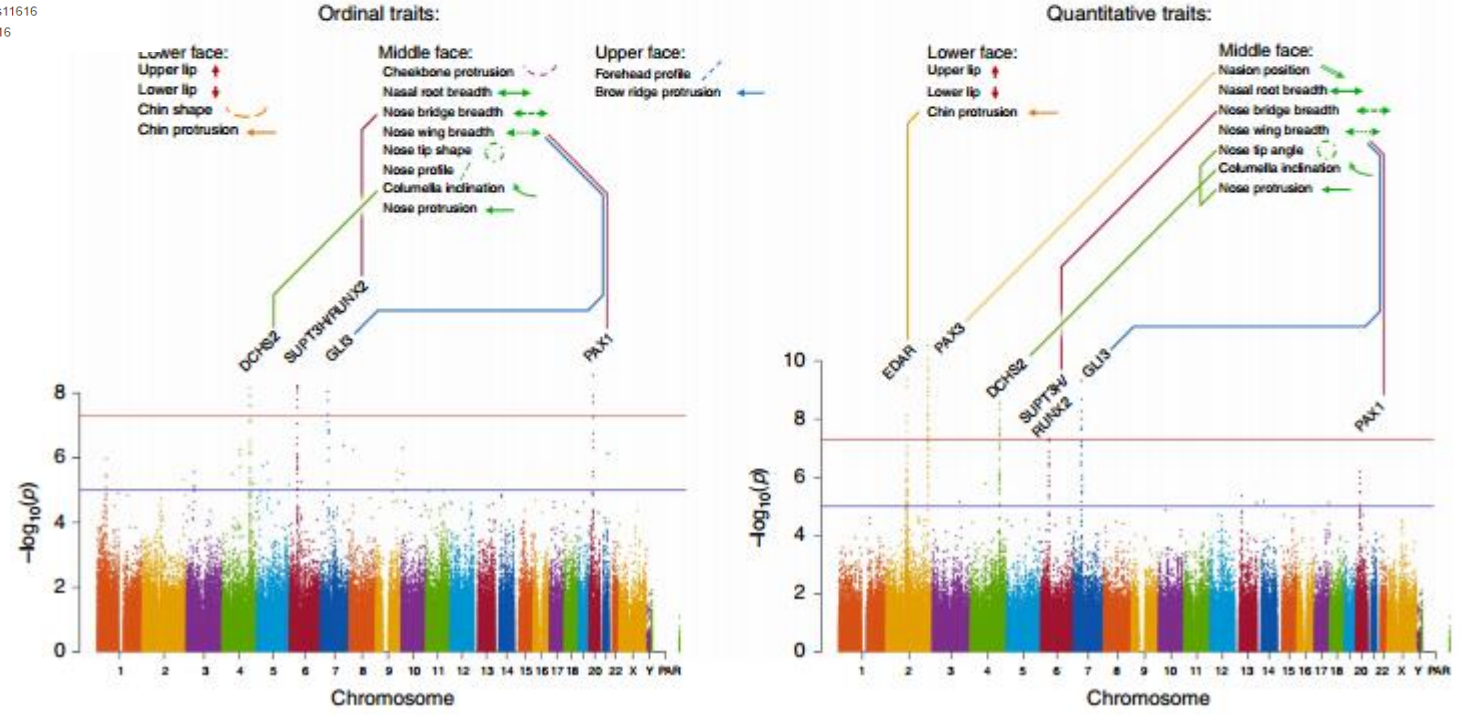
Kaustubh Adhikari, Macarena Fuentes-Guajardo, Mirsha Quinto-Sánchez, Javier Mendoza-Revilla, Juan Camilo Chacón-Duque, Victor Acuña-Alonzo, Claudia Jaramillo, William Arias, Rodrigo Barquera Lozano, Gastón Macín Pérez, Jorge Gómez-Valdés, Hugo Villamil-Ramírez, Tábita Hunemeier, Virginia Ramallo, Caio C. Silva de Cerqueira, Malena Hurtado, Valeria Villegas, Vanessa Granja, Carla Gallo, Giovanni Poletti + *et al.*

Affiliations | Contributions | Corresponding author

Nature Communications 7, Article number: 11616 | doi:10.1038/ncomms11616

Received 03 July 2015 | Accepted 14 April 2016 | Published 19 May 2016





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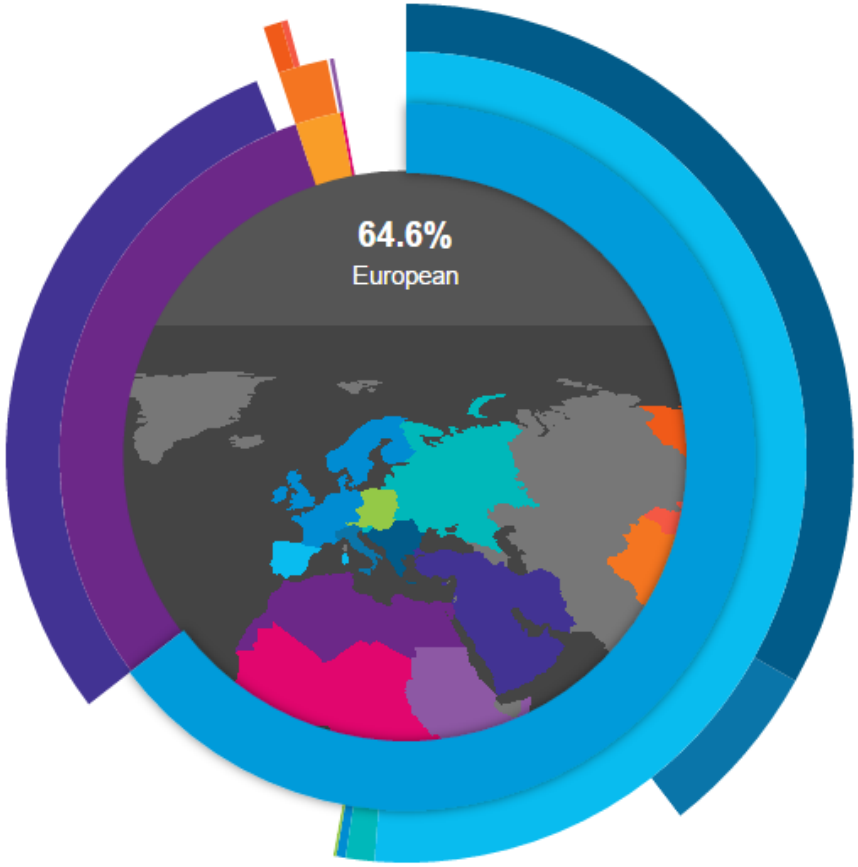
Where Are You From?

Map View ▾ | Sub-regional Resolution



Ancestry Composition tells you what percent of your DNA comes from each of 31 populations worldwide. This analysis includes DNA you received from all of your recent ancestors, on both sides of your family. The results reflect where your ancestors lived before the widespread migrations of the past few hundred years.

64.6%	European
	Southern European
33.2%	Balkan
6.3%	Italian
11.7%	Broadly Southern European
1.2%	Eastern European
	Northwestern European
0.4%	Broadly Northwestern European
0.1%	Ashkenazi
11.6%	Broadly European
30.3%	Middle Eastern & North African
29.3%	Middle Eastern
0.9%	Broadly Middle Eastern & North Afric...
2.1%	East Asian & Native American
	East Asian
0.6%	Yakut
0.2%	Mongolian
1.1%	Broadly East Asian
0.1%	Broadly East Asian & Native American
0.2%	Sub-Saharan African
0.2%	East African
2.9%	Unassigned
100%	

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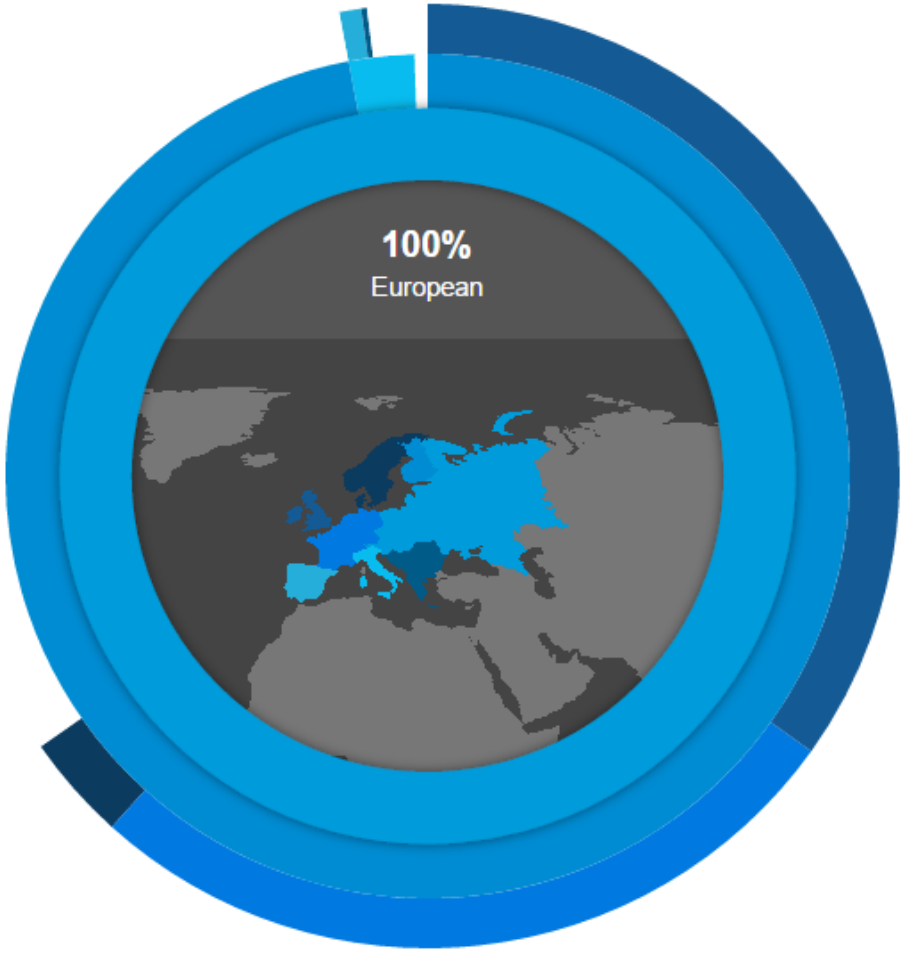
Where Are You From?

Map View ▾ | Sub-regional Resolution



Ancestry Composition tells you what percent of your DNA comes from each of 31 populations worldwide. This analysis includes DNA you received from all of your recent ancestors, on both sides of your family. The results reflect where your ancestors lived before the widespread migrations of the past few hundred years.

100%	European
	Northwestern European
34.9%	British & Irish
26.8%	French & German
3.6%	Scandinavian
31.7%	Broadly Northwestern European
	Southern European
0.8%	Iberian
0.2%	Balkan
1.6%	Broadly Southern European
0.5%	Broadly European
100%	

show all populations

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Where Are You From?

Allele*Frequencies
in Worldwide Populations

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IMMUNOGENOMICS DATA ANALYSIS WORKING GROUP

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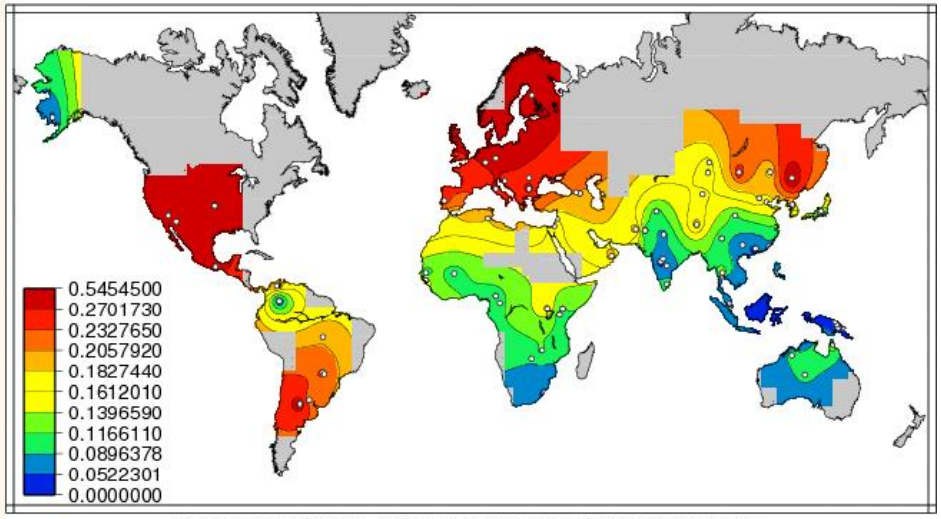

Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.

HLA-A ▾ | A*0201 ▾ | A*02:01 ▾ | Previous Allele | Next Allele | Show Maps

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Human Traits and Genetics

Chapter 5

Genetics and Human Traits

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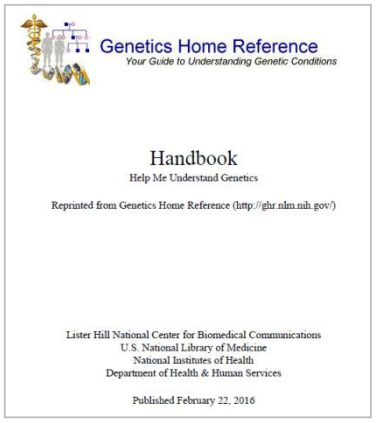

Are You a Morning Person?

There is a genetic variant for it!

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NATURE COMMUNICATIONS | ARTICLE OPEN

GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person

Youna Hu, Alena Shmygelska, David Tran, Nicholas Eriksson, Joyce Y. Tung & David A. Hinds

Affiliations | Contributions | Corresponding authors

Nature Communications **7**, Article number: 10448 | doi:10.1038/ncomms10448

Received 08 August 2014 | Accepted 11 December 2015 | Published 02 February 2016

DNA can tell early bird from night owl - see if one is better

Are you a morning person or a night owl? In a study published in Nature Communications, researchers report that our preference for mornings or evenings is determined by the phase of our circadian rhythms. The researchers identified 15 genetic loci significantly associated with morningness, including 7 near established circadian genes. To arrive at these findings, the researchers conducted a genome-wide association study (GWAS) of self-reported morningness, followed by analyses of biological pathways and related phenotypes, using the 23andMe cohort.

Morning people are more likely to be female, and were significantly less likely than evening people to have insomnia or sleep apnea. They are also less likely to require >8 hours of sleep/day, to sleep soundly, to sweat while sleeping and to sleep walk. Morning people were associated with lower prevalence of depression and they are less prevalent in extreme Body Mass Index (BMI) groups such as the underweight and the obese. The findings from this study reinforce current understanding of circadian biology.

GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person (Feb 2016)

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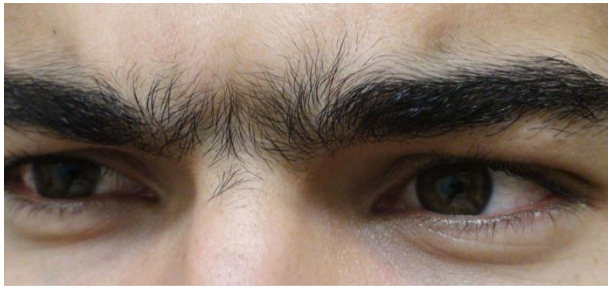
Do You Have Unibrows?



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NATURE COMMUNICATIONS | ARTICLE OPEN

A genome-wide association scan in admixed Latin Americans identifies loci influencing facial and scalp hair features

Kaustubh Adhikari, Tania Fontanil, Santiago Cal, Javier Mendoza-Revilla, Macarena Fuentes-Guajardo, Juan-Camilo Chacón-Duque, Farah Al-Saadi, Jeanette A. Johansson, Mirsha Quinto-Sanchez, Victor Acuña-Alonzo, Claudia Jaramillo, William Arias, Rodrigo Barquera Lozano, Gastón Macín Pérez, Jorge Gómez-Valdés, Hugo Villamil-Ramírez, Tábita Hunemeier, Virginia Ramallo, Caio C. Silva de Cerqueira, Malena Hurtado + *et al.*

We report a genome-wide association scan in over 6,000 Latin Americans for features of scalp hair (shape, colour, greying, balding) and facial hair (beard thickness, monobrow, eyebrow thickness). We found 18 signals of association reaching genome-wide significance (P values 5×10^{-8} to 3×10^{-119}), including 10 novel associations. These include novel loci for scalp hair shape and balding, and the first reported loci for hair greying, monobrow, eyebrow and beard thickness. A newly identified locus influencing hair shape includes a Q30R substitution in the Protease Serine S1 family member 53 (*PRSS53*). We demonstrate that this enzyme is highly expressed in the hair follicle, especially the inner root sheath, and that the Q30R substitution affects enzyme processing and secretion. The genome regions associated with hair features are enriched for signals of selection, consistent with proposals regarding the evolution of human hair.

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Are You Likely To Go Bald?

Prediction of male-pattern baldness from genotypes

Fan Liu[1,2], Merel A Hamer[3], Stefanie Heilmann[4,5], Christine Herold[6], Susanne Moebus[7], Albert Hofman[8], André G Uitterlinden[9,8], Markus M Nöthen[4,5], Cornelia M van Duijn[8], Tamar EC Nijsten[3] and Manfred Kayser[1]

The global demand for products that effectively prevent the development of male-pattern baldness (MPB) has drastically increased. However, there is currently no established genetic model for the estimation of MPB risk. We conducted a prediction analysis using single-nucleotide polymorphisms (SNPs) identified from previous GWASs of MPB in a total of 2725 German and Dutch males. A logistic regression model considering the genotypes of 25 SNPs from 12 genomic loci demonstrates that early-onset MPB risk is predictable at an accuracy level of 0.74 when 14 SNPs were included in the model, and measured using the area under the receiver-operating characteristic curves (AUC). Considering age as an additional predictor, the model can predict normal MPB status in middle-aged and elderly individuals at a slightly lower accuracy (AUC 0.69–0.71) when 6–11 SNPs were used. A variance partitioning analysis suggests that 55.8% of early-onset MPB genetic liability can be explained by common autosomal SNPs and 23.3% by X-chromosome SNPs. For normal MPB status in elderly individuals, the proportion of explainable variance is lower (42.4% for autosomal and 9.8% for X-chromosome SNPs). The gap between GWAS findings and the variance partitioning results could be explained by a large body of common DNA variants with small effects that will likely be identified in GWAS of increased sample sizes. Although the accuracy obtained here has not reached a clinically desired level, our model was highly informative for up to 19% of Europeans, thus may assist decision making on early MPB intervention actions and in forensic investigations.

Can genetics make you a vegan?

May 9, 2016

You may think that your choice of meat or vegetables for dinner is a personal taste. But a new study suggests that genetics may play a role in conferring an advantage or disadvantage of a vegan diet in individuals.

Long chain polyunsaturated fatty acids (LCPUFAs) are a part of the cell membrane and play an important role in signaling in neural development. LCPUFAs are either synthesized from 18 carbon molecule precursors by the FADS2 enzyme or can be obtained from animal foods. Vegans have to synthesize all LCPUFAs, so scientists hypothesized that vegans may have gene variants that help them to better synthesize LCPUFAs endogenously. Researchers studied the genomes of 234 Indian vegans in the US and found that a specific FADS2 variant (w/ 22 bp insertion-deletion) was found in 68%.The variant occurred at 18% in randomly selected US individuals. Data analysis using the 1000 Genomes Project confirmed the finding, revealing a global genotype of 70% in South Asians, 53% in Africans, 29% in East Asians, and 17% in Europeans. In addition, *in vitro* expression of the FADS2 mutant enhanced FADS2 synthesis of LCPUFAs, suggesting that FADS2 is a gene that confers an advantage for veganism in some individuals.

Kothapalli KSD *et al.* Positive selection on a regulatory insertion-deletion polymorphism in FADS2 influences apparent endogenous synthesis of arachidonic acid. *Molecular Biology and Evolution* (2016). doi: 10.1093/molbev/msw049.

Liverpool Hope University EST. 1844

What is Your Ear Wax type?

Gene Expression

« Finding out who your "ancestors" were via DNA

Blogs of the Union »

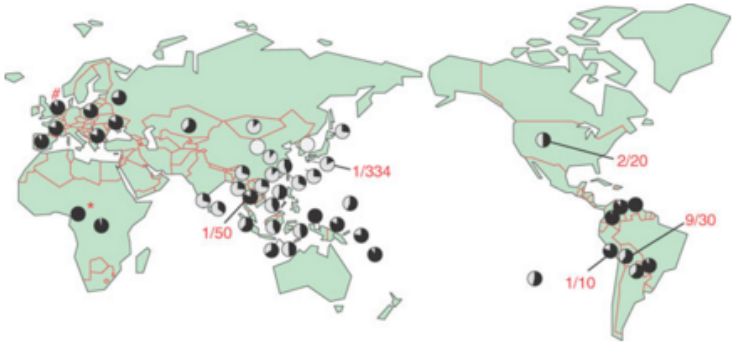
Wet or dry ear wax?

By Razib Khan | January 30, 2006 2:20 pm

50

Life can be really funny. When I was in college I was incorrigibly curious and I asked a Korean American friend if his ear wax was dry (I'd read that East Asians had dry ear wax once) and his response was, "Isn't everybody's?" When it comes to interpersonal differences there are many things we take for granted and extrapolate to others that aren't necessarily true.[1] Nick Wade in *The New York Times* has an interesting write up about the genetics of the ear wax phenotype. While the populations of Europe and Africa have wet ear wax, those of East Asia have dry ear wax. Other populations are somewhere in between. *Nature Genetics* has the original paper (don't be surprised if the link takes a while to load).

Here are the worldwide distribution of the alleles:



Nature Genetics **38**, 324 - 330 (2006)
Published online: 29 January 2006; | doi:10.1038/ng1733

A SNP in the *ABCC11* gene is the determinant of human earwax type

Koh-ichiro Yoshiura[1, 2], Akira Kinoshita[1, 2], Takafumi Ishida[3], Aya Ninokata[3], Toshihisa Ishikawa[4], Tadashi Kaname[2, 5], Makoto Bannai[6], Katsushi Tokunaga[6], Shunro Sonoda[7], Ryoichi Komaki[8], Makoto Ihara[9], Vladimir A Saenko[10], Gabit K Alipov[11], Ichiro Sekine[11], Kazuki Komatsu[12], Haruo Takahashi[12], Mitsuko Nakashima[1, 2, 13], Nadiya Sosonkina[1, 2], Christophe K Mapendano[1, 2], Mohsen Ghadami[1, 2], Masayo Nomura[1, 2, 14], De-Sheng Liang[2, 15], Nobutomo Miwa[1, 2], Dae-Kwang Kim[16], Ariuntuul Garidkhuu[17], Nagato Natsume[17], Tohru Ohta[2, 18], Hiroaki Tomita[19], Akira Kaneko[20], Mihoko Kikuchi[21], Graciela Russomando[22], Kenji Hirayama[21], Minaka Ishibashi[23], Aya Takahashi[23], Naruya Saitou[23], Jeffery C Murray[24], Susumu Saito[25], Yusuke Nakamura[25, 26] & Norio Niikawa[1, 2]

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Musical Ability

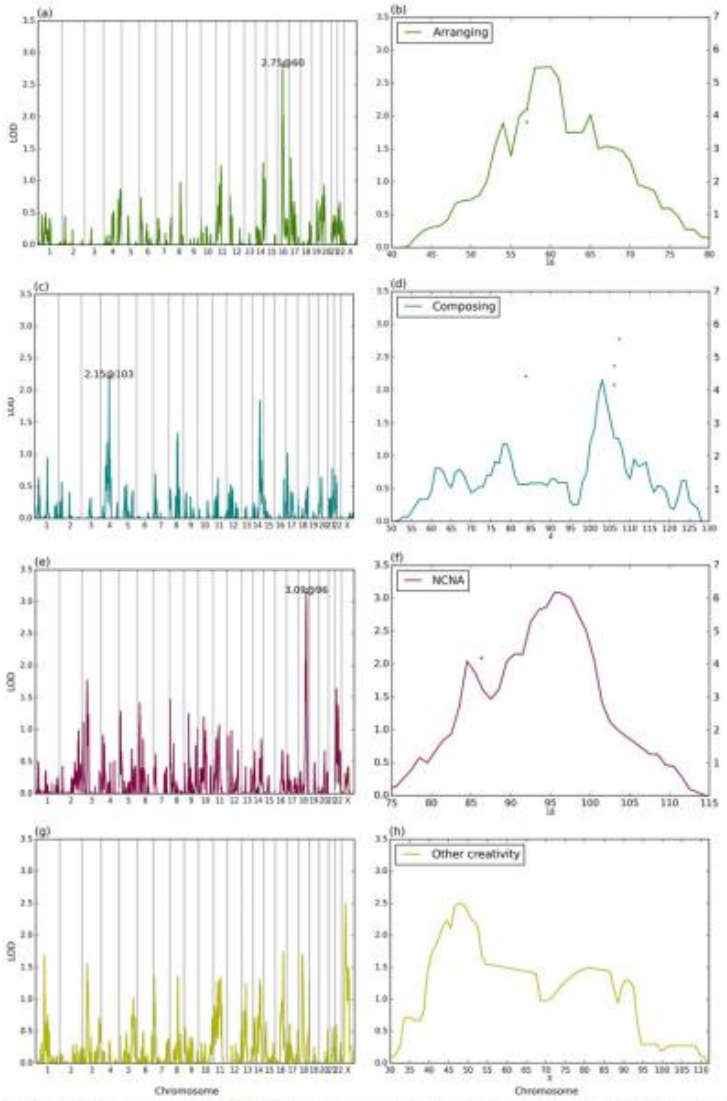

Fig 2. Merlin linkage results. Multipoint linkage LOD scores for arranging (a), composing (c) NCNA (e) and other creativity (g). The chromosomal region around the best LOD score is depicted for each phenotype (b, d, f and h for arranging, composing, NCNA and other creativity, respectively). On the best regions, multipoint linkages are illustrated by curves (scale on the left) and the best joint linkage and LD results by points as negative logarithmic values (scale on the right). The X-scale shows positions as centimorgans.

doi:10.1371/journal.pone.0148679.g002

Table 3. Best joint LD and linkage results. Only the results with p-value < $5x10^{-6}$ are shown. The nearest genes were obtained from the RefSeq database and the main functions from UCSC (http://genome-euro.ucsc.edu/) and NCBI (http://www.ncbi.nlm.nih.gov/gene/). NA, not available; TF, transcription factor; lcRNA, long non-coding RNA; rec, recessive; dom, dominant

Region	Marker	Phenotype	Model	LOD	Joint p-value	Nearest genes	Main gene function
10q22.1	rs1417940	Other creativity	rec	1.90	$1.5x10^{-7}$	*STOX1*	Pre-eclampsia
2p24.3	rs6531144	Arranging	rec	2.68	$1.7x10^{-7}$	*FAM49A*	Paralog of *FAM49B*
						MYCN	TF, Feingold syndrome, neuroblastoma
2q31.1	rs4972527	Other creativity	rec	3.97	$3.4x10^{-7}$	*RAPGEF4*	Energy metabolism, Ras signalling pathway
6q15	rs1528983	NCNA	dom	0.34	$9.3x10^{-7}$	*MAP3K7*	Cell response to environmental stress
7p21.1	rs518136	Composing	dom	0.36	$1.0x10^{-6}$	*AGR3*	Breast cancer
						AHR	TF, aromatic hydrocarbon effects
3p14.3	rs1375515	Other creativity	dom	0.12	$1.0x10^{-6}$	*CACNA2D3*	Brain specific calcium-channel
20q13.2	rs1293430	NCNA	dom	0.08	$2.0x10^{-6}$	*TSHZ2*	TF, cancer
8p23.2	rs4242493	Composing	rec	0.50	$2.0x10^{-6}$	*CSMD1*	Carcinoma suppressor
4q22.3	rs10856917	Composing	dom	1.87	$2.0x10^{-6}$	*UNC5C*	Cell migration, axon extension
14q13.1	rs737401	Composing	dom	2.56	$2.0x10^{-6}$	*EGLN3*	Oxygen censor, hypoxia, pre-eclampsia
						NPAS3	TF, possibly neurogenesis, schizophrenia
16p12.1	rs4073229	Other creativity	rec	0.08	$2.0x10^{-6}$	*HS3ST4*	Brain specific sulfotransferase
14q21.3	rs2225994	NCNA	rec	0.02	$4.0x10^{-6}$	*LINC00648*	lcRNA
4p14	rs4833107	NCNA	dom	0.18	$4.0x10^{-6}$	*ARAP2*	Actin cytoskeleton remodelling
						DTHD1	Signalling, apoptosis
12p12.2	rs2728554	Arranging	rec	0.00	$4.0x10^{-6}$	*LOC100506393*	lcRNA
6q25.3	rs9397906	Other creativity	rec	1.85	$4.0x10^{-6}$	*NOX3*	Inner ear structures
						ARID1B	Neural development and dendrite growth
17q11.2	rs8064530	Other creativity	dom	3.47	$4.0x10^{-6}$	*PIPOX*	NA
						SEZ6	Neuronal membrane signalling
7q34	rs12667802	Arranging	dom	1.87	$4.0x10^{-6}$	*PRSS37*	Protease
						OR9A4	Olfactory receptor
						CLEC5A	Inflammatory response

RESEARCH ARTICLE

Creative Activities in Music – A Genome-Wide Linkage Analysis

Jaana Oikkonen[1]*, Tuire Kuusi[2], Petri Peltonen[1], Pirre Raijas[3], Liisa Ukkola-Vuoti[1¤], Kai Karma[2], Päivi Onkamo[4], Irma Järvelä[1]

Educational Attainment

GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment

All authors with their affiliations appear at the end of this paper.

A genome-wide association study (GWAS) of educational attainment was conducted in a discovery sample of 101,069 individuals and a replication sample of 25,490. Three independent single-nucleotide polymorphisms (SNPs) are genome-wide significant (rs9320913, rs11584700, rs4851266), and all three replicate. Estimated effects sizes are small (coefficient of determination $R^2 \approx 0.02\%$), approximately 1 month of schooling per allele. A linear polygenic score from all measured SNPs accounts for ≈2% of the variance in both educational attainment and cognitive function. Genes in the region of the loci have previously been associated with health, cognitive, and central nervous system phenotypes, and bioinformatics analyses suggest the involvement of the anterior caudate nucleus. These findings provide promising candidate SNPs for follow-up work, and our effect size estimates can anchor power analyses in social-science genetics.

Table 1. The results of the GWAS meta-analysis for the independent signals reaching $P < 10^{-6}$ in the discovery stage. The rows in bold are the independent signals reaching $P < 5 \times 10^{-8}$ in the discovery stage. "Frequency" refers to allele-frequency in the combined-stage meta-analysis. "Beta/OR" refers to the effect size in the EduYears analysis and to the odds ratio in the College analysis. All *P* values are from the sample-size–weighted meta-analysis (fixed effects). The *P* value in the replication-stage meta-analysis was calculated from a one-sided test. I^2 represents the percent heterogeneity of effect size between the discovery-stage studies. P_{het} is the heterogeneity *P* value. bp, base pair.

SNP	Chr	Position (bp)	Nearest gene	Reference allele	Frequency	Discovery stage				Replication stage		Combined stage			Combined stage–sex-specific analysis			
						Beta/OR	*P* value	I^2	P_{het}	Beta/OR	*P* value	Beta/OR	*P* value	P_{het}	Beta/OR (males)	*P* value (males)	Beta/OR (females)	*P* value (females)
						EduYears												
rs9320913	**6**	**98691454**	**LOC100129158**	**A**	**0.483**	**0.106**	**4.19×10^{-9}**	**18.3**	**0.097**	**0.077**	**0.012**	**0.101**	**3.50×10^{-10}**	**0.350**	**0.095**	**1.87×10^{-4}**	**0.100**	**1.43×10^{-6}**
rs3783006	13	97909210	STK24	C	0.454	0.096	2.29×10^{-7}	0	0.982	0.056	0.055	0.088	8.45×10^{-8}	0.959	0.064	1.44×10^{-2}	0.108	3.35×10^{-7}
rs8049439	16	28745016	ATXN2L	T	0.581	0.090	7.12×10^{-7}	10.7	0.229	0.065	0.026	0.086	1.15×10^{-7}	0.205	0.097	1.43×10^{-4}	0.078	1.90×10^{-4}
rs13188378	5	101958587	SLCO6A1	A	0.878	−0.136	7.49×10^{-7}	0	0.791	0.091	0.914	−0.097	1.37×10^{-4}	0.646	−0.134	8.21×10^{-3}	-0.080	5.92×10^{-3}
						College												
rs11584700	**1**	**202843606**	**LRRN2**	**A**	**0.780**	**0.921**	**2.07×10^{-9}**	**13.8**	**0.179**	**0.912**	**4.86×10^{-4}**	**0.919**	**8.24×10^{-12}**	**0.221**	**0.934**	**6.11×10^{-4}**	**0.911**	**2.12×10^{-9}**
rs4851266	**2**	**100184911**	**LOC150577**	**T**	**0.396**	**1.050**	**2.20×10^{-9}**	**23.7**	**0.049**	**1.049**	**0.003**	**1.050**	**5.33×10^{-11}**	**0.072**	**1.054**	**1.55×10^{-5}**	**1.052**	**6.74×10^{-8}**
rs2054125	2	199093966	PLCL1	T	0.064	1.468	5.55×10^{-8}	7	0.325	1.098	0.225	1.376	2.12×10^{-7}	0.268	1.264	1.74×10^{-2}	1.503	1.95×10^{-7}
rs3227	6	33770273	ITPR3	C	0.498	1.043	6.02×10^{-8}	5	0.363	1.010	0.280	1.037	3.24×10^{-7}	0.415	1.046	9.44×10^{-5}	1.029	1.37×10^{-3}
rs4073894	7	104254200	LHFPL3	A	0.207	1.076	4.41×10^{-7}	0	0.765	1.003	0.467	1.062	5.55×10^{-6}	0.513	1.050	2.18×10^{-2}	1.073	1.74×10^{-5}
rs12640626	4	176863266	GPM6A	A	0.580	1.041	4.94×10^{-7}	10.9	0.234	1.000	0.495	1.034	7.48×10^{-6}	0.420	1.038	1.59×10^{-3}	1.031	7.61×10^{-4}

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Childhood Trauma

Suderman *et al. BMC Medical Genomics* 2014, **7**:13
http://www.biomedcentral.com/1755-8794/7/13

BMC Medical Genomics

RESEARCH ARTICLE Open Access

Childhood abuse is associated with methylation of multiple loci in adult DNA

Matthew Suderman[1,2,3†], Nada Borghol[1,2†], Jane J Pappas[1,2†], Snehal M Pinto Pereira[4], Marcus Pembrey[5], Clyde Hertzman[6^], Chris Power[4] and Moshe Szyf[1,2*]

Abstract

Background: Childhood abuse is associated with increased adult disease risk, suggesting that processes acting over the long-term, such as epigenetic regulation of gene activity, may be involved. DNA methylation is a critical mechanism in epigenetic regulation. We aimed to establish whether childhood abuse was associated with adult DNA methylation profiles.

Methods: In 40 males from the 1958 British Birth Cohort we compared genome-wide promoter DNA methylation in blood taken at 45y for those with, versus those without, childhood abuse (n = 12 vs 28). We analysed the promoter methylation of over 20,000 genes and 489 microRNAs, using MeDIP (methylated DNA immunoprecipitation) in triplicate.

Results: We found 997 differentially methylated gene promoters (311 hypermethylated and 686 hypomethylated) in association with childhood abuse and these promoters were enriched for genes involved in key cell signaling pathways related to transcriptional regulation and development. Using bisulfite-pyrosequencing, abuse-associated methylation (MeDIP) at the metalloproteinase gene, *PM20D1*, was validated and then replicated in an additional 27 males. Abuse-associated methylation was observed in 39 microRNAs; in 6 of these, the hypermethylated state was consistent with the hypomethylation of their downstream gene targets. Although distributed across the genome, the differentially methylated promoters associated with child abuse clustered in genome regions of at least one megabase. The observations for child abuse showed little overlap with methylation patterns associated with socioeconomic position.

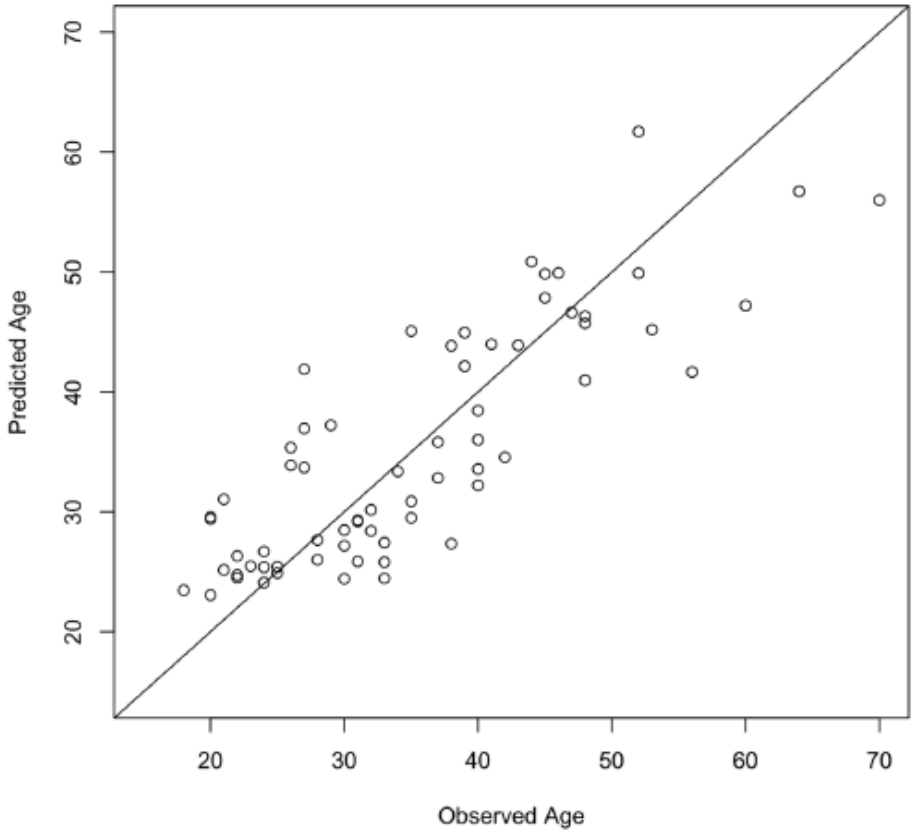
Conclusions: Our observed genome-wide methylation profiles in adult DNA associated with childhood abuse justify the further exploration of epigenetic regulation as a mediating mechanism for long-term health outcomes.

Keywords: Epigenetics, Childhood abuse, Early life environment, Epigenome, DNA methylation, Biomarker

Genetic Prediction of Traits

NAME	CONFIDENCE ▲	OUTCOME
Alcohol Flush Reaction	★★★★	Does Not Flush
Bitter Taste Perception	★★★★	Can Taste
Blond Hair	★★★★	28% Chance
Earwax Type	★★★★	Wet
Eye Color	★★★★	Likely Brown
Hair Curl	★★★★	Straighter Hair on Average
Lactose Intolerance	★★★★	Likely Intolerant
Malaria Resistance (Duffy Antigen)	★★★★	Likely Not Resistant to One Form of Malaria
Male Pattern Baldness ♂	★★★★	Increased Odds
Muscle Performance	★★★★	Likely Sprinter
Non-ABO Blood Groups	★★★★	See Report
Norovirus Resistance	★★★★	Not Resistant to the Most Common Strain
Red Hair	★★★★	<1% Chance
Resistance to HIV/AIDS	★★★★	Not Resistant

How Old Are You?



Epigenetic Predictor of Age

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Abstract

From the moment of conception, we begin to age. A decay of cellular structures, gene regulation, and DNA sequence ages cells and organisms. DNA methylation patterns change with increasing age and contribute to age related disease. Here we identify 88 sites in or near 80 genes for which the degree of cytosine methylation is significantly correlated with age in saliva of 34 male identical twin pairs between 21 and 55 years of age. Furthermore, we validated sites in the promoters of three genes and replicated our results in a general population sample of 31 males and 29 females between 18 and 70 years of age. The methylation of three sites—in the promoters of the EDARADD, TOM1L1, and NPTX2 genes—is linear with age over a range of five decades. Using just two cytosines from these loci, we built a regression model that explained 73% of the variance in age, and is able to predict the age of an individual with an average accuracy of 5.2 years. In forensic science, such a model could estimate the age of a person, based on a biological sample alone. Furthermore, a measurement of relevant sites in the genome could be a tool in routine medical screening to predict the risk of age-related diseases and to tailor interventions based on the epigenetic bio-age instead of the chronological age.

Figure 3. Predicted versus observed age of all subjects using a leave-one-out model. A multivariate regression model was fit on all but one sample and its predicted age (y-axis) was related to the truly observed age of the left out sample (x-axis). The predicted values are highly correlated with the observed ages ($r = 0.83$, $p = 2.2 \times 10^{-16}$, $n = 66$), and the average absolute difference between the predicted and the observed age is 5.2 years.

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Genetic Associations with Disease

	A	B	C	D	E	F	G	H	I	J	K	L
1	NHLBI key	Snp Id	Pvalue	PMID	Location	Phenotype	Phenotype Category	chr	pos	InGene	Journal	DatePub
2	2.31436E+14	rs4406273	4.5E-723	23143594	Table1	Psoriasis	Skin-related	6	31298313		Nat Genet	11/11/2012 0:00
3	2.17577E+14	rs9472159	1.61E-557	21757650	Table 2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43951958		Circ Res	7/14/2011 0:00
4	2.17385E+14	rs2814778	1E-524	21738479	Table 2	White blood cell count (WBC)	Quantitative trait(s),Blood-related,Immune-related	1	159204893	(DARC)	PLoS Genet	6/30/2011 0:00
5	2.17577E+14	rs6921438	4.44E-524	21757650	Table 2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43957870		Circ Res	7/14/2011 0:00
6	2.19264E+14	rs12913832	7.68E-523	21926416	Table 3	Eye color (blue versus brown)	Cancer,Skin cancer,Skin-related,Melanoma	15	28120472	(HERC2)	Hum Mol Genet	9/17/2011 0:00
7	2.17577E+14	rs9369434	1.18E-504	21757650	Table S4	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43950670		Circ Res	7/14/2011 0:00
8	2.16769E+13	rs561241	8.0E-495	21676895	Table S3	FVII activity	Quantitative trait(s),Blood-related,Plasma	13	113105720		Hum Mol Genet	6/23/2011 0:00
9	2.16769E+13	rs493833	1.8E-494	21676895	Table S3	FVII activity	Quantitative trait(s),Blood-related,Plasma	13	113115325	(F7)	Hum Mol Genet	6/23/2011 0:00
10	2.16769E+13	rs561241	6.78E-485	21676895	Table 2	FVII	Quantitative trait(s),Blood-related,Plasma	13	113105720		Hum Mol Genet	6/23/2011 0:00
11	2.17577E+14	rs7767396	1.71E-482	21757650	Table S2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43959313		Circ Res	7/14/2011 0:00
12	2.17577E+14	rs4513773	2.08E-482	21757650	Table S2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43957789		Circ Res	7/14/2011 0:00
13	2.30566E+14	rs4644	4.97E-465	23056639	Table2	Circulating galectin-3 levels	Quantitative trait(s),Blood-related	14	55138217	(LGALS3)	PLoS One	10/9/2012 0:00
14	2.34556E+14	rs10737680	1E-434	23455636	Table 2	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration	1	196710325	(CFH)	Nat Genet	3/3/2013 0:00
15	2.30566E+14	rs4652	1.50E-421	23056639	Table2	Circulating galectin-3 levels	Quantitative trait(s),Blood-related	14	55138318	(LGALS3)	PLoS One	10/9/2012 0:00
16	2.17577E+14	rs9472158	6.22E-400	21757650	Table S2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43951160		Circ Res	7/14/2011 0:00
17	2.06866E+14	rs3764261	7E-380	20686565	Table 1	HDL cholesterol	CVD risk factor (CVD RF),Lipids	16	56959412		Nature	8/5/2010 0:00
18	2.06866E+12	rs173539	2.50E-379	20686565	FullScan	HDL cholesterol	CVD risk factor (CVD RF),Lipids	16	56954132		Nature	8/5/2010 0:00
19	2.06866E+13	rs247616	8.54E-378	20686565	FullScan	HDL cholesterol	CVD risk factor (CVD RF),Lipids	16	56955678		Nature	8/5/2010 0:00
20	2.17577E+14	rs9472173	1.16E-355	21757650	Table S2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43965519		Circ Res	7/14/2011 0:00
21	2.17577E+13	rs729391	7.17E-355	21757650	Table S2	Serum vascular endothelial growth factor (VEGF)	Quantitative trait(s),Blood-related,Serum	6	43950155		Circ Res	7/14/2011 0:00
22	2.34556E+14	rs10490924	4.2851E-353	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration	10	122454932	(ARMS2)	Nat Genet	3/3/2013 0:00
23	2.34556E+14	rs3750848	8.787E-353	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration	10	122455799	(ARMS2)	Nat Genet	3/3/2013 0:00
24	2.34556E+14	rs3750847	1.4435E-352	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration	10	122455905	(ARMS2)	Nat Genet	3/3/2013 0:00
25	2.34556E+14	rs3793917	3.4613E-346	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration	10	122459759		Nat Genet	3/3/2013 0:00
26	2.06866E+14	rs7205804	2.00E-329	20686565	FullScan	HDL cholesterol	CVD risk factor (CVD RF),Lipids	16	56970977	(CETP)	Nature	8/5/2010 0:00
27	2.06866E+14	rs1532624	2.93E-327	20686565	FullScan	HDL cholesterol	CVD risk factor (CVD RF),Lipids	16	56971567	(CETP)	Nature	8/5/2010 0:00
28	2.34556E+14	rs932275	3.9455E-327	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration	10	122471948	(HTRA1)	Nat Genet	3/3/2013 0:00
29	1.94145E+14	rs28899170	5.0E-324	19414484	Table S3	Total serum bilirubin	Quantitative trait(s),Blood-related,Hepatic,Serum	2	233695584	6)(UGT1A7)(	Hum Mol Genet	5/4/2009 0:00

Genetic Associations with Disease

Nat Genet. 2012 Dec;44(12):1341-8. doi: 10.1038/ng.2467. Epub 2012 Nov 11.

Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity.

Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, Ding J, Li Y, Tejasvi T, Gudjonsson JE, Kang HM, Allen MH, McManus R, Novelli G, Samuelsson L, Schalkwijk J, Ståhle M, Burden AD, Smith CH, Cork MJ, Estivill X, Bowcock AM, Krueger GG, Weger W, Worthington J, Tazi-Ahnini R, Nestle FO, Hayday A, Hoffmann P, Winkelmann J, Wijmenga C, Langford C, Edkins S, Andrews R, Blackburn H, Strange A, Band G, Pearson RD, Vukcevic D, Spencer CC, Deloukas P, Mrowietz U, Schreiber S, Weidinger S, Koks S, Kingo K, Esko T, Metspalu A, Lim HW, Voorhees JJ, Weichenthal M, Wichmann HE, Chandran V, Rosen CF, Rahman P, Gladman DD, Griffiths CE, Reis A, Kere J; Collaborative Association Study of Psoriasis (CASP); Genetic Analysis of Psoriasis Consortium; Psoriasis Association Genetics Extension; Wellcome Trust Case Control Consortium 2, Nair RP, Franke A, Barker JN, Abecasis GR, Elder JT, Trembath RC.

⊕ **Collaborators (133)**

Abstract

To gain further insight into the genetic architecture of psoriasis, we conducted a meta-analysis of 3 genome-wide association studies (GWAS) and 2 independent data sets genotyped on the Immunochip, including 10,588 cases and 22,806 controls. We identified 15 new susceptibility loci, increasing to 36 the number associated with psoriasis in European individuals. We also identified, using conditional analyses, five independent signals within previously known loci. The newly identified loci shared with other autoimmune diseases include candidate genes with roles in regulating T-cell function (such as RUNX3, TAGAP and STAT3). Notably, they included candidate genes whose products are involved in innate host defense, including interferon-mediated antiviral responses (DDX58), macrophage activation (ZC3H12C) and nuclear factor (NF)-kB signaling (CARD14 and CARM1). These results portend a better understanding of shared and distinctive genetic determinants of immune-mediated inflammatory disorders and emphasize the importance of the skin in innate and acquired host defense.

Table 1

Meta-analysis results for psoriasis loci. For known loci, the most significant SNP within 500kb (3Mb for MHC region) of the previously published SNP is shown. rs34536443 was the most strongly associated SNP in the *TYK2* region, but found to be independent of the previously published SNP (rs12720356). 'GWAS P value': P value from the meta-analysis of the 3 GWAS datasets. 'Immunochip P value': the result of the meta-analysis of the two Immunochip datasets. 'Combined P-value': the P-value from the meta-analysis including all 5 datasets, RAF: Risk allele frequency, 'Notable genes': genes most likely to have an effect on the development of psoriasis.

SNP	Chr.	Position (bp)	GWAS P-value (meta)	Immunochip p-value (meta)	Combined P-value	Risk/ Non-risk allele	RAF (Case)	RAF (Ctrls)	OR[a] (meta)	Notable genes	No. of genes +/− 500kb
Known Loci											
rs7552167	1	24,518,643	2.3×10^{-5}	8.4×10^{-8}	8.5×10^{-12}	G/A	0.878	0.858	1.21	*IL28RA*	*26*
rs9988642	1	67,726,104	2.5×10^{-13}	3.5×10^{-15}	1.1×10^{-26}	T/C	0.952	0.929	1.52	*IL23R*	*17*
rs6677595	1	152,590,187	8.1×10^{-15}	2.7×10^{-20}	2.1×10^{-33}	T/C	0.689	0.640	1.26	*LCE3B, LCE3D*	*43*
rs62149416	2	61,083,506	3.4×10^{-10}	3.2×10^{-9}	1.8×10^{-17}	T/C	0.671	0.635	1.17	*FLJ16341, REL*	*9*
rs17716942	2	163,260,691	4.1×10^{-9}	1.0×10^{-10}	3.3×10^{-18}	T/C	0.891	0.863	1.27	*KCNH7, IFIH1*	*7*
rs27432	5	96,119,273	4.4×10^{-8}	7.5×10^{-14}	1.9×10^{-20}	A/G	0.309	0.274	1.20	*ERAP1*	*7*
rs1295685	5	131,996,445	8.5×10^{-6}	6.7×10^{-6}	3.4×10^{-10}	G/A	0.807	0.798	1.18	*IL13, IL4*	*21*
rs2233278	5	150,467,189	4.9×10^{-17}	5.2×10^{-27}	2.2×10^{-42}	C/G	0.090	0.058	1.59	*TNIP1*	*17*
rs12188300	5	158,829,527	7.5×10^{-23}	3.3×10^{-32}	3.2×10^{-53}	T/A	0.132	0.095	1.58	*IL12B*	*5*
rs4406273	6	31,266,090	5.3×10^{-300}	3.6×10^{-427}	4.5×10^{-723}	A/G	0.259	0.092	4.32	*HLA-B, HLA-C*	*56*
rs33980500	6	111,913,262	4.3×10^{-20}	7.6×10^{-27}	4.2×10^{-45}	T/C	0.108	0.074	1.52	*TRAF3IP2*	*8*
rs582757	6	138,197,824	2.0×10^{-14}	3.7×10^{-13}	2.2×10^{-25}	C/T	0.315	0.273	1.23	*TNFAIP3*	*5*

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Genetic Associations with Disease

Population Diversity (Alleles in RefSNP orientation) . See additional population frequency from 1000Genome [here]

	Sample Ascertainment				Genotype Detail				Alleles	
ss#	Population	Individual Group	Chrom. Sample Cnt.	Source	A/A	A/G	G/G	HWP	A	G
ss1319547016	EAS		1008	AF					0.03670000	0.96329999
	EUR		1006	AF					0.09840000	0.90160000
	AFR		1322	AF					0.07260000	0.92739999
	AMR		694	AF					0.05480000	0.94520003
	SAS		978	AF					0.14309999	0.85690004
ss22459490	HapMap-HCB	Asian	90	IG	0.02222222	0.13333334	0.84444445	0.25059200	0.08888889	0.91111112
	HapMap-JPT	Asian	90	IG		0.02222222	0.97777778	1.00000000	0.01111111	0.98888886
	HapMap-YRI	Sub-Saharan African	120	IG		0.01666667	0.98333335	1.00000000	0.00833333	0.99166667
	ENSEMBL_Watson		2	IG			1.00000000			1.00000000
ss23137281	POPU2		96	IG	0.06250000		0.93750000	0.00100000	0.06250000	0.93750000
ss233394026	pilot_1_CEU_low_coverage_panel		120	AF					0.05833333	0.94166666
ss98378719	J. Craig Venter		2	IG	1.00000000				1.00000000	

Summary	Average Het.+/- std err:	Individual Count	Founders Count	Individual Overlap	Genotype Conflict
	0.150+/-0.229	401	343	0	0

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Genetic Predisposition to Disease

Health Risks (122)

ELEVATED RISKS	YOUR RISK	AVERAGE RISK
Venous Thromboembolism	17.9%	12.3%
Psoriasis	16.8%	11.4%
Lung Cancer	11.6%	8.5%
Chronic Kidney Disease	4.2%	3.4%
Restless Legs Syndrome	2.5%	2.0%

See all 122 risk reports...

Inherited Conditions (53)

REPORT	RESULT
Familial Mediterranean Fever	Variant Present
ARSACS	Variant Absent
Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)	Variant Absent
Alpha-1 Antitrypsin Deficiency	Variant Absent
Autosomal Recessive Polycystic Kidney Disease	Variant Absent

See all 53 carrier status...

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Genetic Predisposition to Disease

Elevated Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Venous Thromboembolism	★★★★	17.9%	12.3%	1.45x
Psoriasis	★★★★	16.8%	11.4%	1.48x
Lung Cancer	★★★★	11.6%	8.5%	1.37x
Chronic Kidney Disease	★★★★	4.2%	3.4%	1.22x
Restless Legs Syndrome	★★★★	2.5%	2.0%	1.25x

Decreased Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Age-related Macular Degeneration	★★★★	4.5%	6.5%	0.69x
Alzheimer's Disease	★★★★	4.3%	7.2%	0.60x
Melanoma	★★★★	2.2%	2.9%	0.75x
Type 1 Diabetes	★★★★	0.46%	1.02%	0.45x
Crohn's Disease	★★★★	0.39%	0.53%	0.74x
Esophageal Squamous Cell Carcinoma (ESCC)	★★★★	0.29%	0.36%	0.80x
Multiple Sclerosis	★★★★	0.24%	0.34%	0.69x
Stomach Cancer (Gastric Cardia Adenocarcinoma)	★★★★	0.18%	0.23%	0.77x
Exfoliation Glaucoma	★★★★	0.16%	0.75%	0.22x
Primary Biliary Cirrhosis	★★★★	0.05%	0.08%	0.66x
Celiac Disease	★★★★	0.04%	0.12%	0.36x

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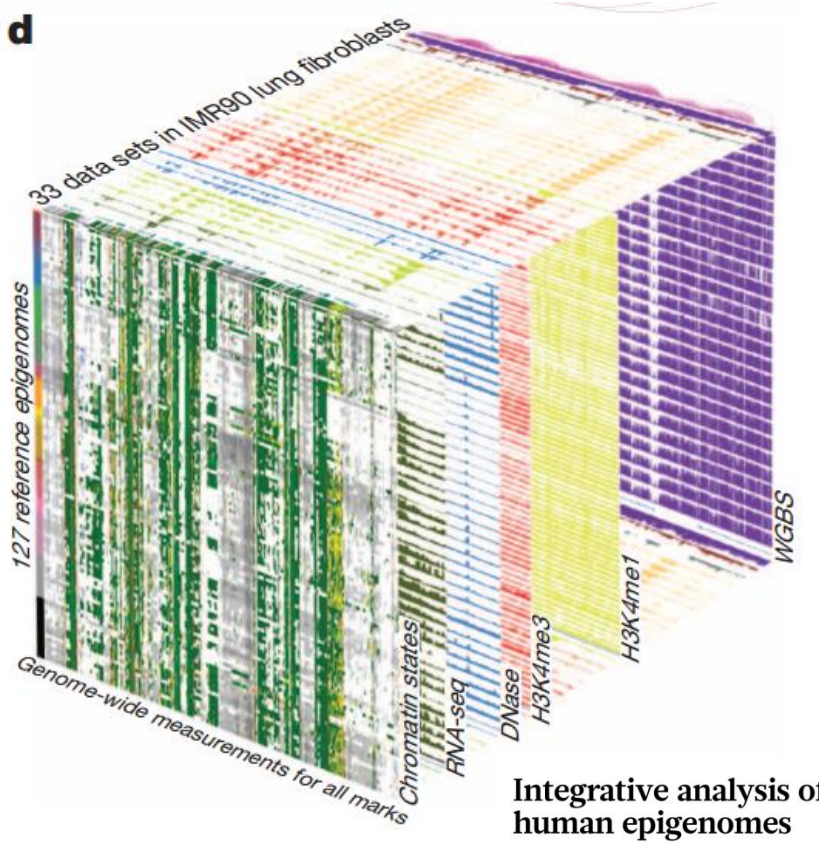
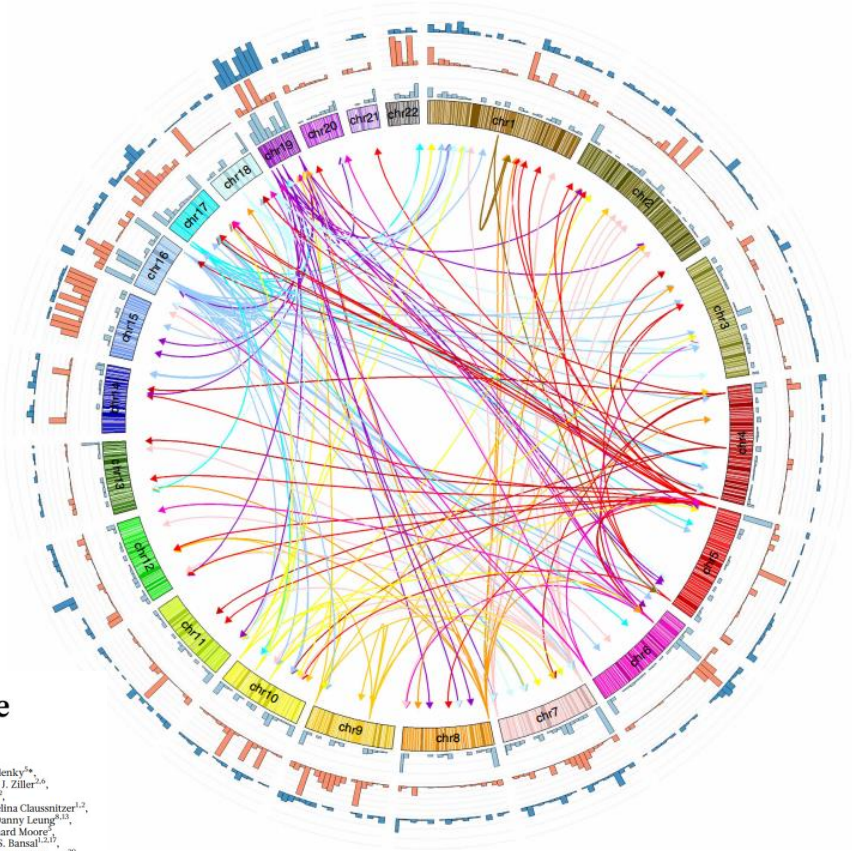
What Are We Doing with the Current Knowledge

Genome Biology



Integrative analysis of 111 reference human epigenomes

Roadmap Epigenomics Consortium†, Anshul Kundaje[1,2,3]*, Wouter Meuleman[1,2]*, Jason Ernst[1,2,4]*, Misha Bilenky[5]*, Angela Yen[1,2], Alireza Heravi-Moussavi[5], Pouya Kheradpour[1,2], Zhizhuo Zhang[1,2], Jianrong Wang[1,2], Michael J. Ziller[2,6], Viren Amin[7], John W. Whitaker[8], Matthew D. Schultz[9], Lucas D. Ward[1,2], Abhishek Sarkar[1,2], Gerald Quon[1,2], Richard S. Sandstrom[10], Matthew L. Eaton[1,2], Yi-Chieh Wu[1,2], Andreas R. Pfenning[1,2], Xinchen Wang[1,2,11], Melina Claussnitzer[1,2], Yaping Liu[1,2], Cristian Coarfa[7], R. Alan Harris[7], Noam Shoresh[2], Charles B. Epstein[2], Elizabeta Gjoneska[2,12], Danny Leung[8,13], Wei Xie[8,13], R. David Hawkins[8,13], Ryan Lister[5], Chibo Hong[14], Philippe Gascard[15], Andrew J. Mungall[16], Richard Moore[16], Eric Chuah[16], Angela Tam[16], Theresa K. Canfield[10], R. Scott Hansen[10], Rajinder Kaul[16], Peter J. Sabo[10], Mukul S. Bansal[2,17], Annaick Carles[18], Jesse R. Dixon[8,13], Kai-How Farh[2], Soheil Feizi[1,2], Rosa Karlic[19], Ah-Ram Kim[1,2], Ashwinikumar Kulkarni[20], Daofeng Li[21], Rebecca Lowdon[21], GiNell Elliott[21], Tim R. Mercer[22], Shane J. Neph[10], Vitor Onuchic[7], Paz Polak[2,23], Nisha Rajagopal[8,13], Pradipta Ray[20], Richard C. Sallari[1,2], Kyle T. Siebenthall[10], Nicholas A. Sinnott-Armstrong[1,2], Michael Stevens[21,42], Robert E. Thurman[10], Jie Wu[24,25], Bo Zhang[21], Xin Zhou[21], Arthur E. Beaudet[26], Laurie A. Boyer[11], Philip L. De Jager[2,23,27], Peggy J. Farnham[28], Susan J. Fisher[29], David Haussler[30], Steven J. M. Jones[5,31,32], Wei Li[33], Marco A. Marra[5,32], Michael T. McManus[34], Shamil Sunyaev[2,23,27], James A. Thomson[35,41], Thea D. Tlsty[15], Li-Huei Tsai[2,12], Wei Wang[8], Robert A. Waterland[36], Michael Q. Zhang[20,37], Lisa H. Chadwick[38], Bradley E. Bernstein[2,39,40]§, Joseph F. Costello[14]§, Joseph R. Ecker[9]§, Martin Hirst[5,18]§, Alexander Meissner[2,6]§, Aleksandar Milosavljevic[7]§, Bing Ren[8,13]§, John A. Stamatoyannopoulos[10]§, Ting Wang[21]§ & Manolis Kellis[1,2]§



Long-range epigenetic regulation is conferred by genetic variation located at thousands of independent loci

Mathieu Lemire[1], Syed H.E. Zaidi[1], Maria Ban[2], Bing Ge[3], Dylan Aïssi[4,5,6], Marine Germain[4,5,6], Irfahan Kassam[7], Mike Wang[1], Brent W. Zanke[8], France Gagnon[7], Pierre-Emmanuel Morange[9,10,11], David-Alexandre Trégouët[4,5,6], Philip S. Wells[8], Stephen Sawcer[2], Steven Gallinger[12,13], Tomi Pastinen[3] & Thomas J. Hudson[1,14,15]

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What Are We Doing with the Current Knowledge

Disease Biology

Potential Mediation of HLA and Cancer Associations via Non-coding RNAs

Izabela Stasik [1], Ken I. Mills [2], Mehmet Tevfik Dorak [1]

[1] School of Health Sciences, Liverpool Hope University, Liverpool, U.K.;
[2] Centre for Cancer Research and Cell Biology, Queen's University Belfast, U.K.

ASHI 2015, Savannah, GA

YOUR FUTURE STARTS WITH HOPE

A Survey of Cancer Somatic Mutations in the HLA Region

Amy E. Kennedy[1], Ximena V. Qadir[1], Crystal Lane[1], Mehmet Tevfik Dorak[2]

[1] National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.;
[2] School of Health Sciences, Liverpool Hope University, Liverpool, U.K.

ASHI 2015, Savannah, GA

YOUR FUTURE STARTS WITH HOPE

Largest Copy Number Variation Regions in the Extended HLA Show Correlations with Ancestral HLA Haplotypes

Çağla YAVUZ*, Fatma Savran OĞUZ*, Mehmet Tevfik DORAK**

*Dept of Medical Biology, Istanbul University, Istanbul Faculty of Medicine, Turkey
**School of Health Sciences, Liverpool Hope University, Liverpool, U.K.

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What Are We Doing with the Current Knowledge

What Makes Boys More Susceptible to Childhood Leukaemia?

A genome-wide association study in collaboration with Baylor College of Medicine

Analysis is being done in collaboration with the Dept of Math & Computer Science (Hope and JMU)

children with cancer uk

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What Are We Doing with the Current Knowledge

Summary of the Recommendation

- **The U.S. Preventive Services Task Force (USPSTF) recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population.**
  Rating: D recommendation.

Rationale

Importance: There is fair evidence that disease due to hereditary hemochromatosis is rare in the general population. (Select for a description of the USPSTF classification of levels of evidence.)

Detection: The USPSTF found fair evidence that a low proportion of individuals with a high-risk genotype (C282Y homozygote at the *HFE* locus, a mutation common among white populations presenting with clinical symptoms) manifest the disease.

Benefits of detection and early treatment: There is poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically detected individuals.

Harms of detection and early treatment: Screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance, labeling, unnecessary invasive work-up, anxiety, and, potentially, unnecessary treatments.

USPSTF assessment: The USPSTF concludes that the potential harms of genetic screening for hereditary hemochromatosis outweigh the potential benefits.

What Are We Doing with the Current Knowledge

Why Can We Not Use the Disease Markers Anyway?

A genetic test with 99% accuracy and with only 1% false-positive rate.
Sounds good…

Disease occurs 1 in 1000 people
1,000,000 tests are done

99% accuracy: 990 of 1,000 people have been detected (with the disease gene)
1% false-positivity: 10,000 people have been wrongly detected as positive

* * * * * * *

Accuracy of currently existing tests is around 70-75%

What Are We Doing with the Current Knowledge

ACCE Principles for Genomic Tests

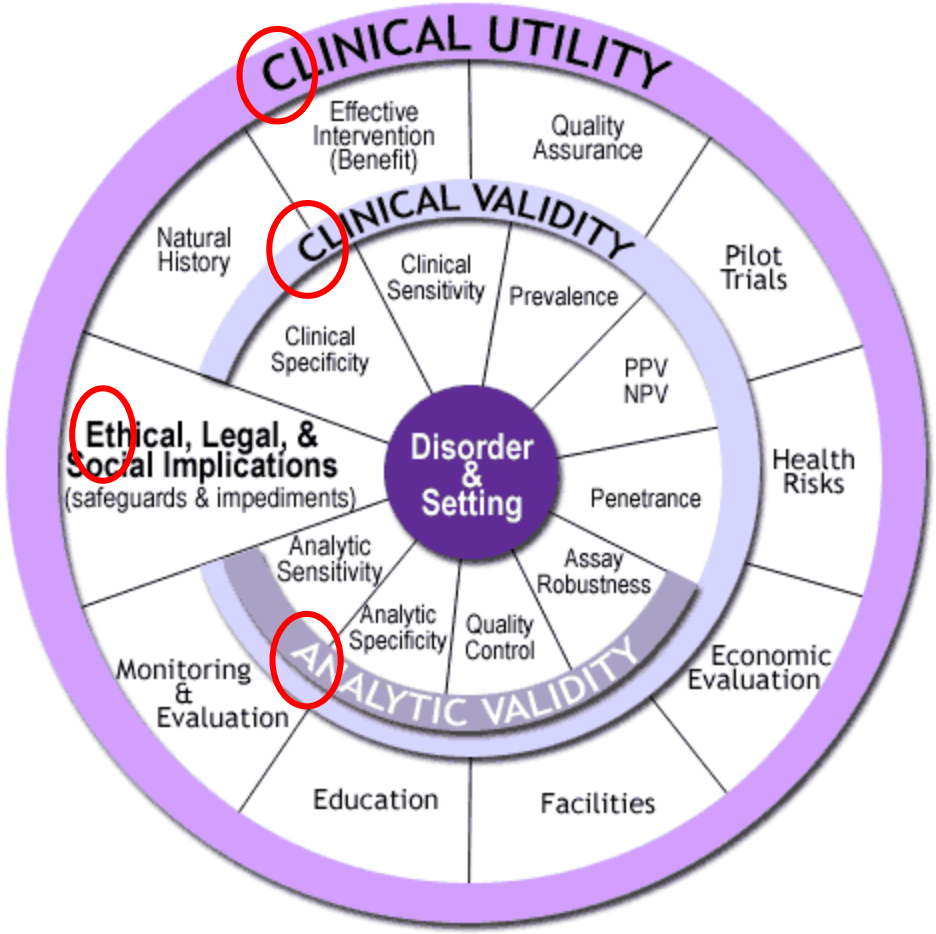

Figure 5: The ACCE Wheel
(from CDC-ACCE at http://www.cdc.gov/genomics/gtesting/ACCE)

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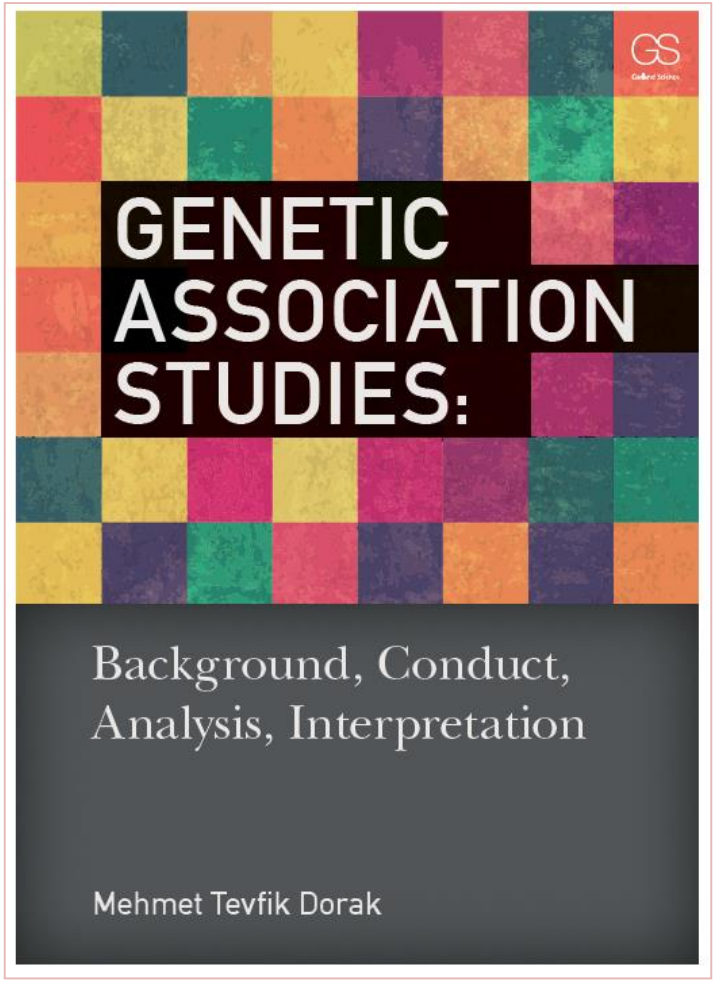
What Are We Doing with the Current Knowledge



Release Date: 25 September 2016

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What Are We Doing with the Current Knowledge

Your DNA can tell how your risk compares to the population average

It cannot tell whether you will have a particular disease or not

The same applies to non-disease traits

Almost all genetic effect can be controlled by environmental and behavioural modifications

Your DNA can reveal whether you will have any of the rare, very serious monogenic diseases, adverse effects of certain drugs, blood group and tissue type

Conclusions

Traditionally, the emphasis has been on protein-coding genes, and on mutations changing their function

Recent findings emphasise the importance of non-coding regions of the genome

Only a few very rare, but very strong mutations can be used as deterministic biomarkers

Most disease risk markers have very weak non-exclusive correlations, and cannot be used to assess risk with high confidence

Almost every trait has some genetic basis, but the environment almost always has a dominant effect

Conclusions

Genetics is not necessarily destiny.

Your genes are up to chance;
but your lifestyle is up to you!

Secret to Long and Healthy Life:
Social Life

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