Preventing diabetes by knowing your genes for a healthier lifestyle

June 11 2017

International Diabetes Symposium for
Myanmar Medical Professionals

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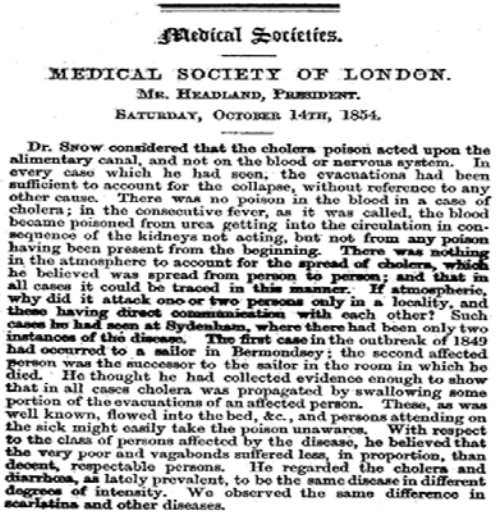
Human Genome and Epidemiology

Sequencing of the human genome offers the greatest opportunity for epidemiology since John Snow discovered the Broad Street Pump.



Medical Societies.

MEDICAL SOCIETY OF LONDON.

Mr. Headland, President.

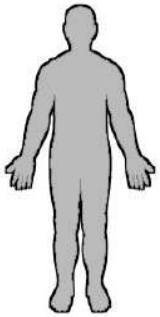
Saturday, October 14th, 1854.

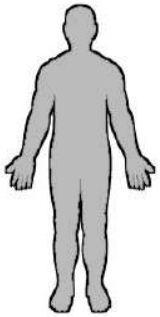
Dr. Snow considered that the cholera poison acted upon the alimentary canal, and not on the blood or nervous system. In every case which he had seen, the evacuations had been sufficient to account for the collapse, without reference to any other cause. There was no poison in the blood in a case of cholera; in the consecutive fever, as it was called, the blood became poisoned from urea getting into the circulation in consequence of the kidneys not acting, but not from any poison having been present from the beginning. There was nothing in the atmosphere to account for the spread of cholera, which he believed was spread from person to person; and that in all cases it could be traced in this manner. If atmospheric, why did it attack one or two persons only in a locality, and these having direct communication with each other? Such cases he had seen at Sydenham, where there had been only two instances of the disease. The first case in the outbreak of 1849 had occurred to a sailor in Bermondsey; the second affected person was the successor to the sailor in the room in which he died. He thought he had collected evidence enough to show that in all cases cholera was propagated by swallowing some portion of the evacuations of an affected person. These, as was well known, flowed into the bed, &c., and persons attending on the sick might easily take the poison unawares. With respect to the class of persons affected by the disease, he believed that the very poor and vagabonds suffered less, in proportion, than decent, respectable persons. He regarded the cholera and diarrhœa, as lately prevalent, to be the same disease in different degrees of intensity. We observed the same difference in scarlatina and other diseases.

19th Century

21st Century

Our genome are 99.9% identical at the DNA letter level





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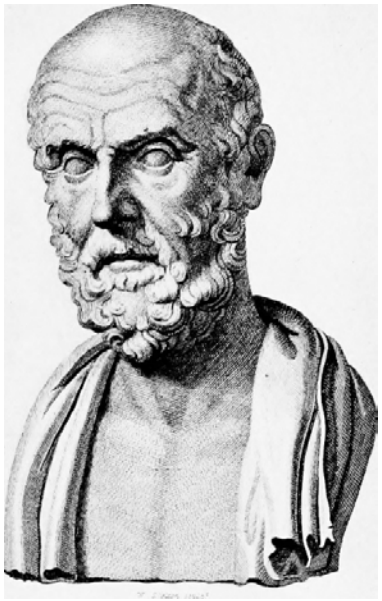
3 billion letters x 0.1%
= 3 mil letters

Most of these differences are called SNP (single nucleotide polymorphism)

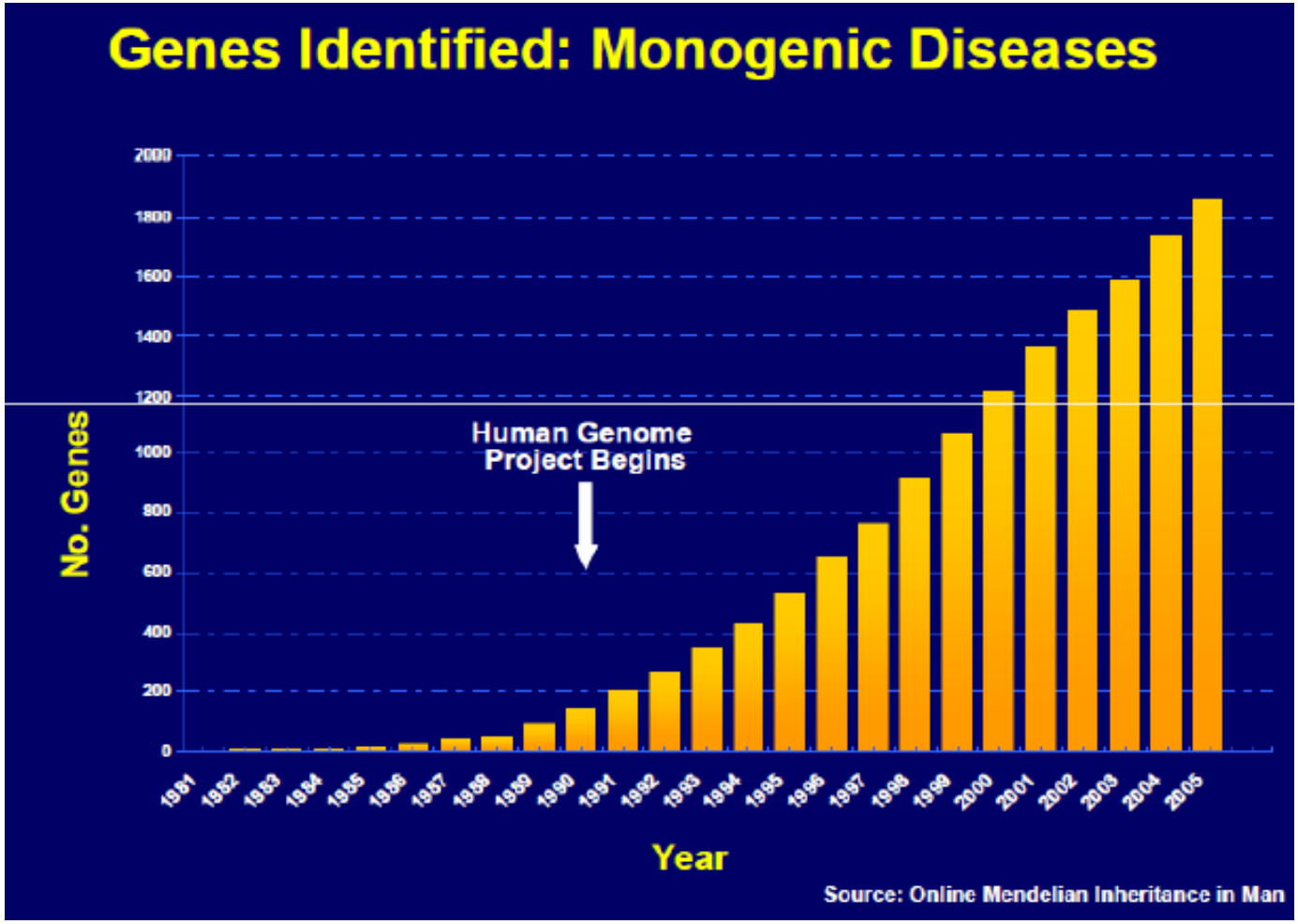
An ancient medical question

"*It's far more important to know what person the disease has than what disease the person has.*"

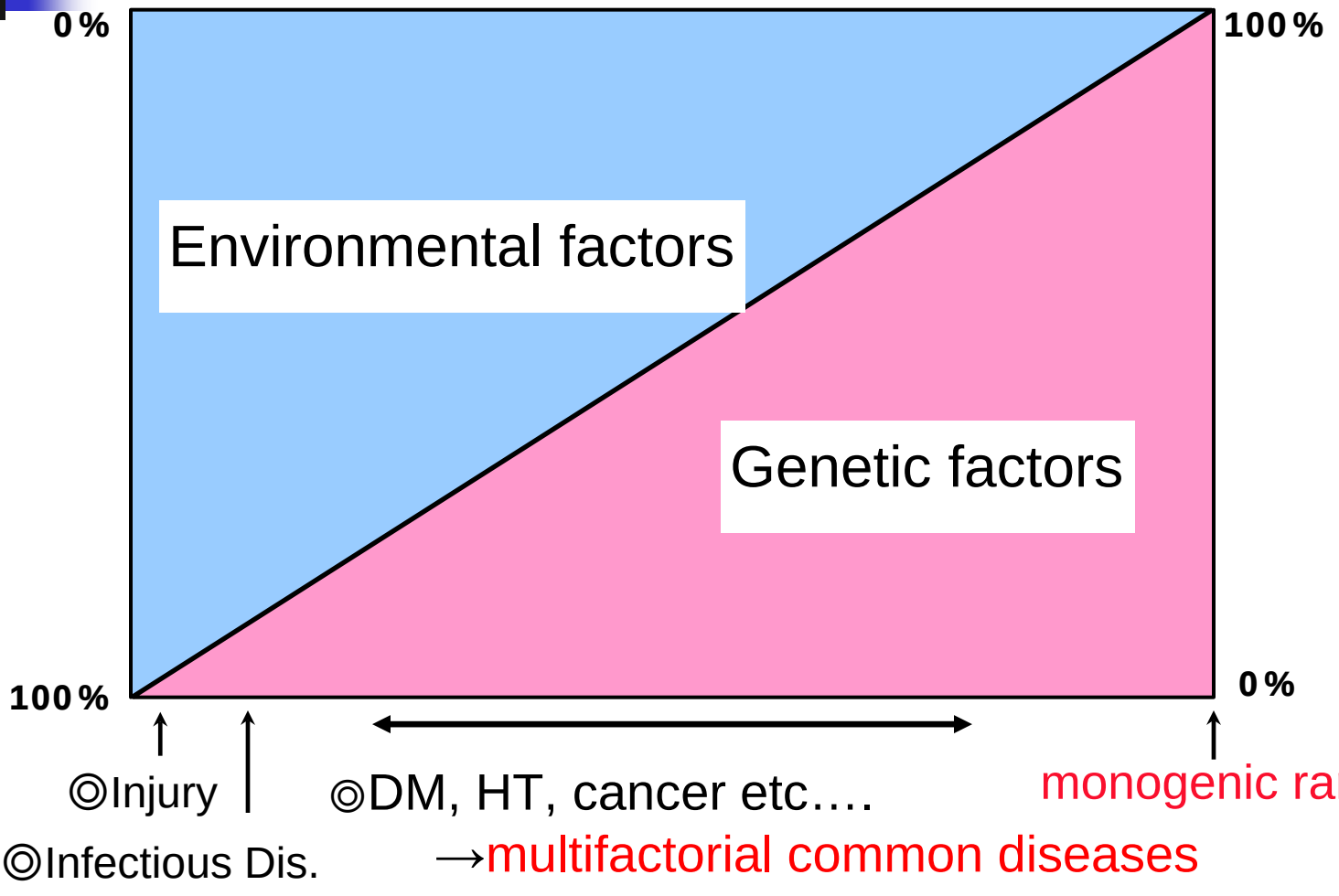


Hippocrates (BC. 400)

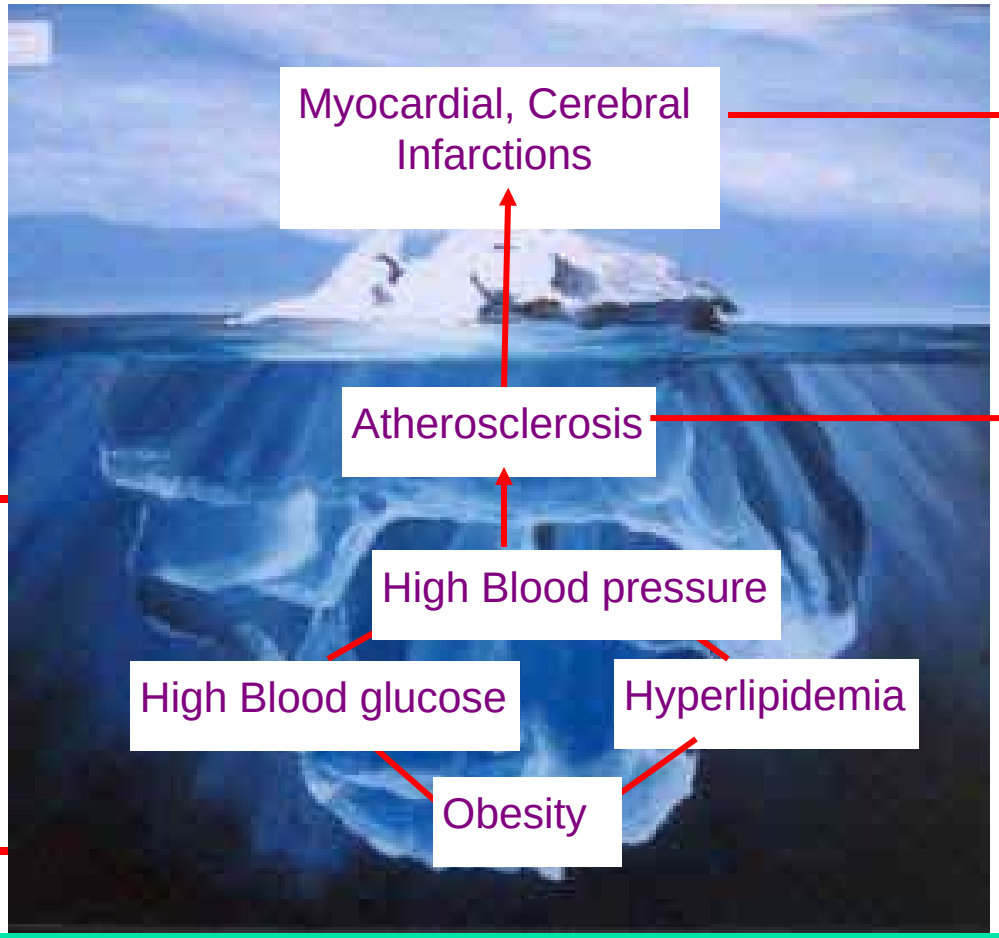
Genes account for monogenic diseases & multifactorial diseases



Genetic and Environmental Factors account for Common Diseases



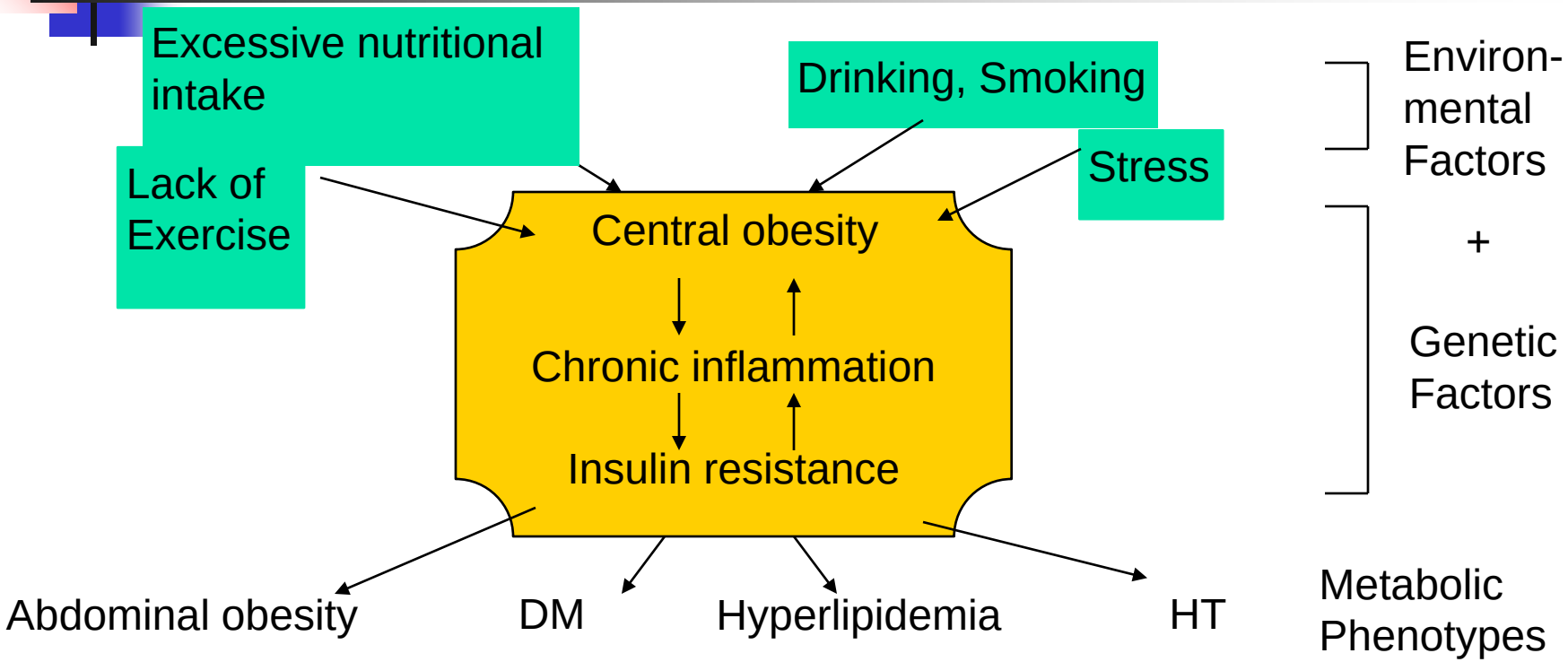
Metabolic Syndrome and Atherosclerosis



Can human genome information be used for better prevention?

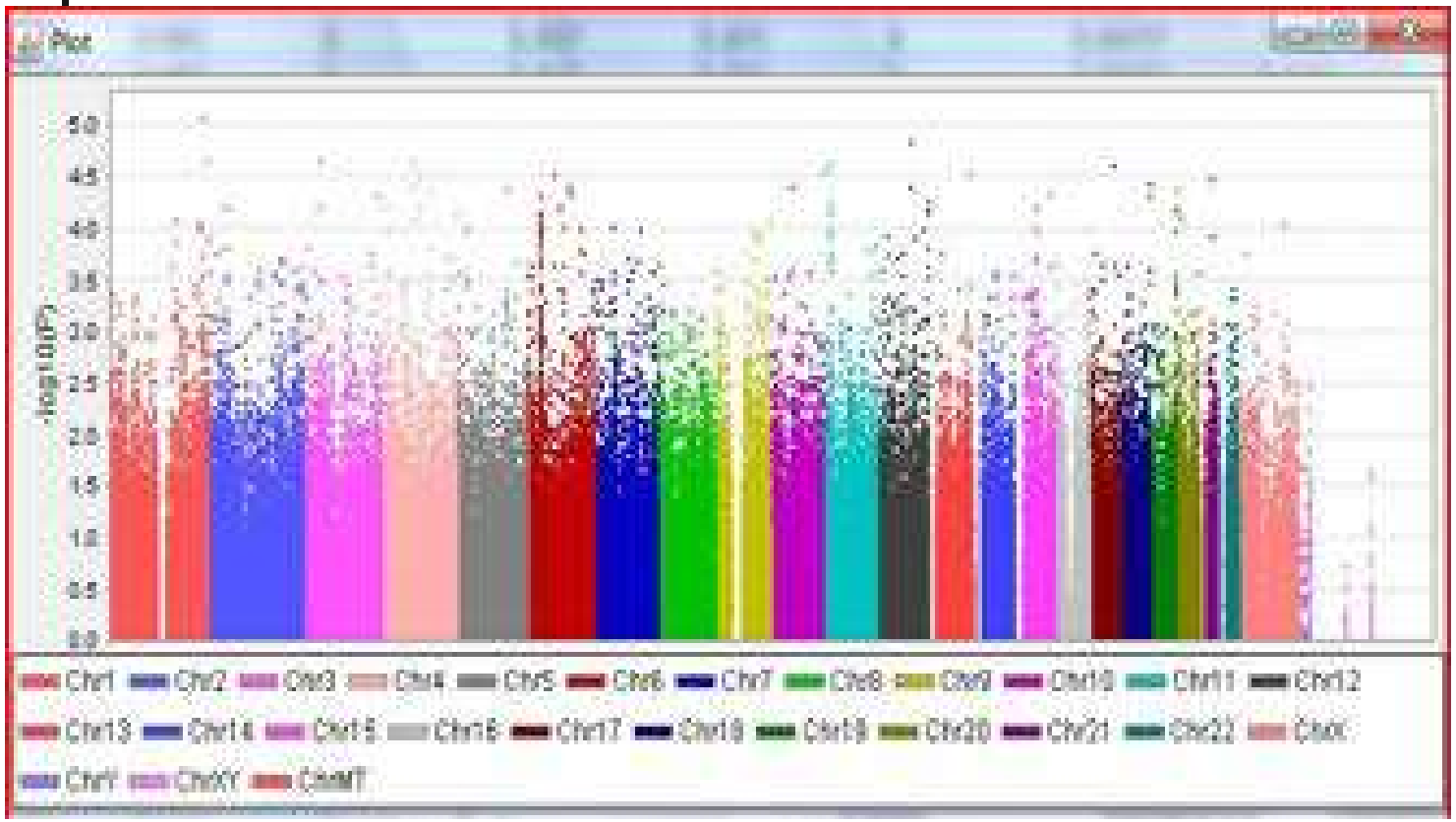
Metabolic Syndrome (MS)

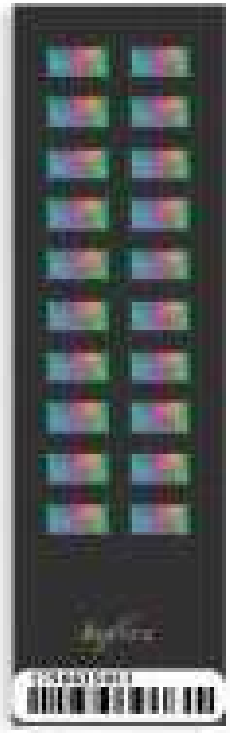
:A typical multifactorial disease



- Insulin Resistance
- Low grade chronic inflammation
- Developmental Origin of Health and Diseases (DOHaD)

Genome Wide Association Study（GWAS) of multifactorial diseases





Millions of SNPs analyzed on a DNA chip

→Manhattan Plot

GWAS of T2DM

- Confirmed to be polygenic
  - ~80 SNPs were identified for T2DM susceptibility
- Effect of each SNP is small.
  - One SNP increases 5~20% of disease risk
  - There are combinatorial effects
- Only a part of genetic factors can explained.
  - The problem of missing heritability remains

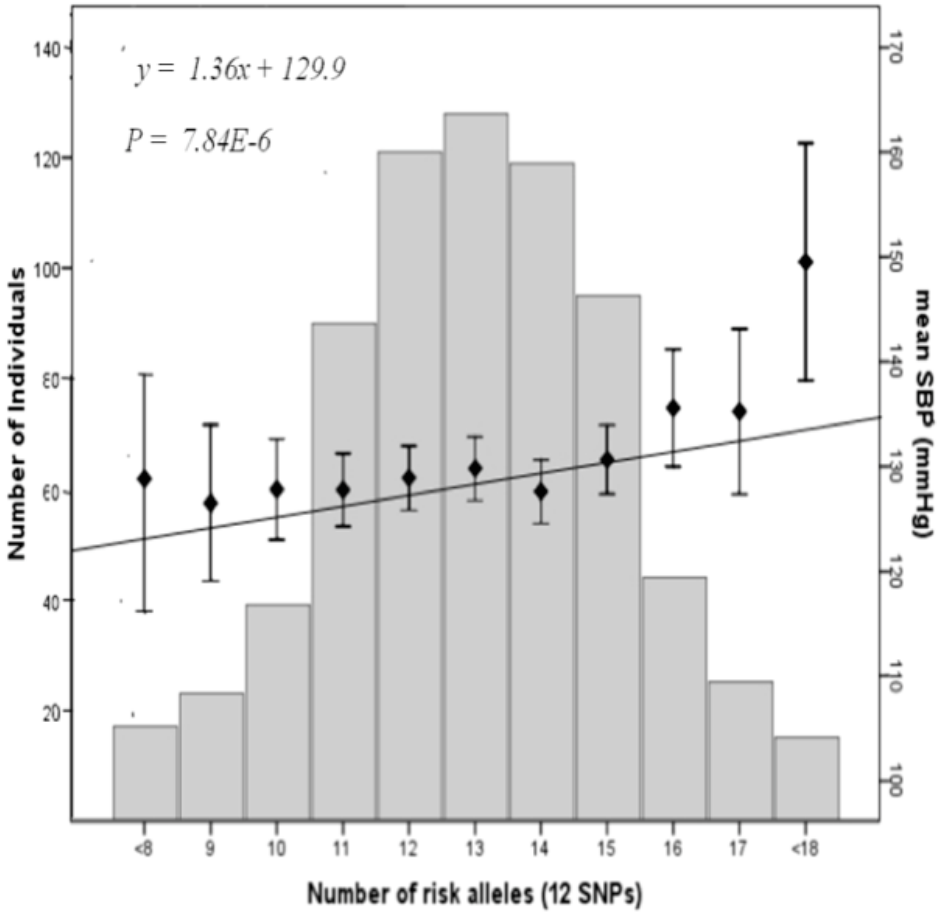
Gene-Environment interaction in MS phenotypes

- NOS3 SNP X daily physical activity→BP (Kimura, 2003)
- ADH SNP X alcohol intake →BP (Saito, 2004)
- ACE In/del X salt intake→BP (Zhang, 2006)
- IL6R SNP X energy intake→obesity（Song, 2007)
- NNMT SNP X folate uptake→serum homocys(Zhang, 2008)
- CYP3A5, CYP11B2 SNP X salt intake→BP (Song, 2009)
- CDKAL1 SNP X energy intake→ HbA1c（Miyaki, 2010)
- COMT SNP X energy intake →BP (Htun, 2011)

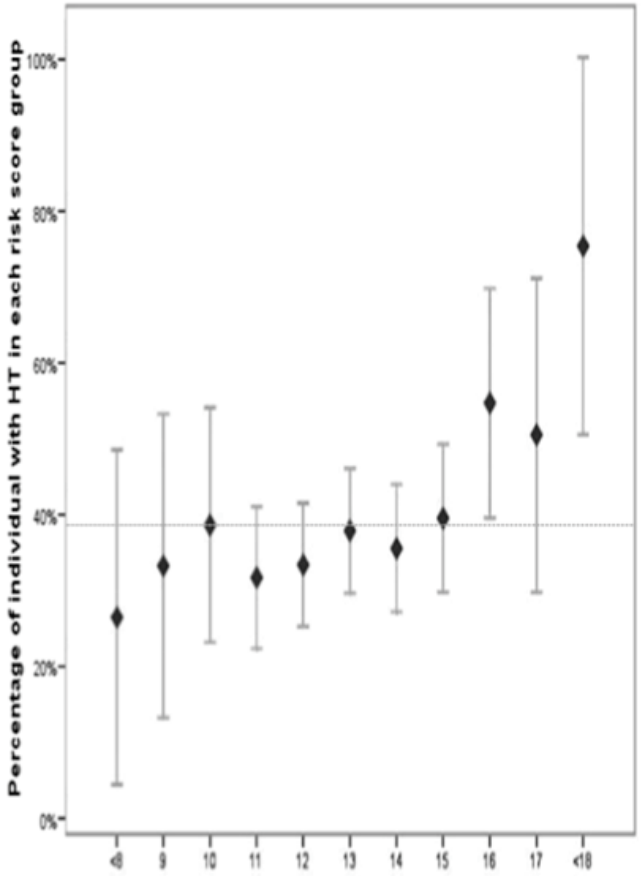
Genetic Risk Score (GRS) of 12 SNPs and HT

- Twelve SNPs in ABCA1, ACADSB, ATP2B, CDH13, COMT, CSK, CYP11B2, CYP17A1, GREB1, HPCAL1, PTGIS, PTK2B genes were analyzed.
- Number of risk alleles were counted.
- Population was grouped according to risk point.
  - 0~24points (Approx. normal distribution)
- BP and HT prevalence was calculated for each group

Combinatorial effect of SNPs on BP and HT



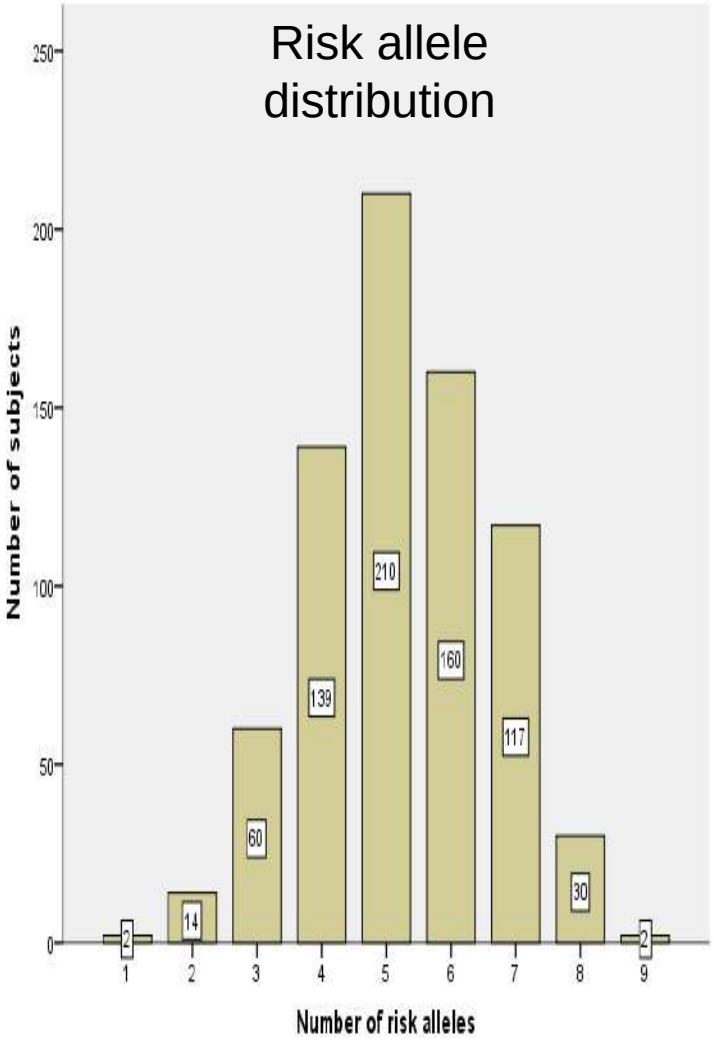
Systolic BP

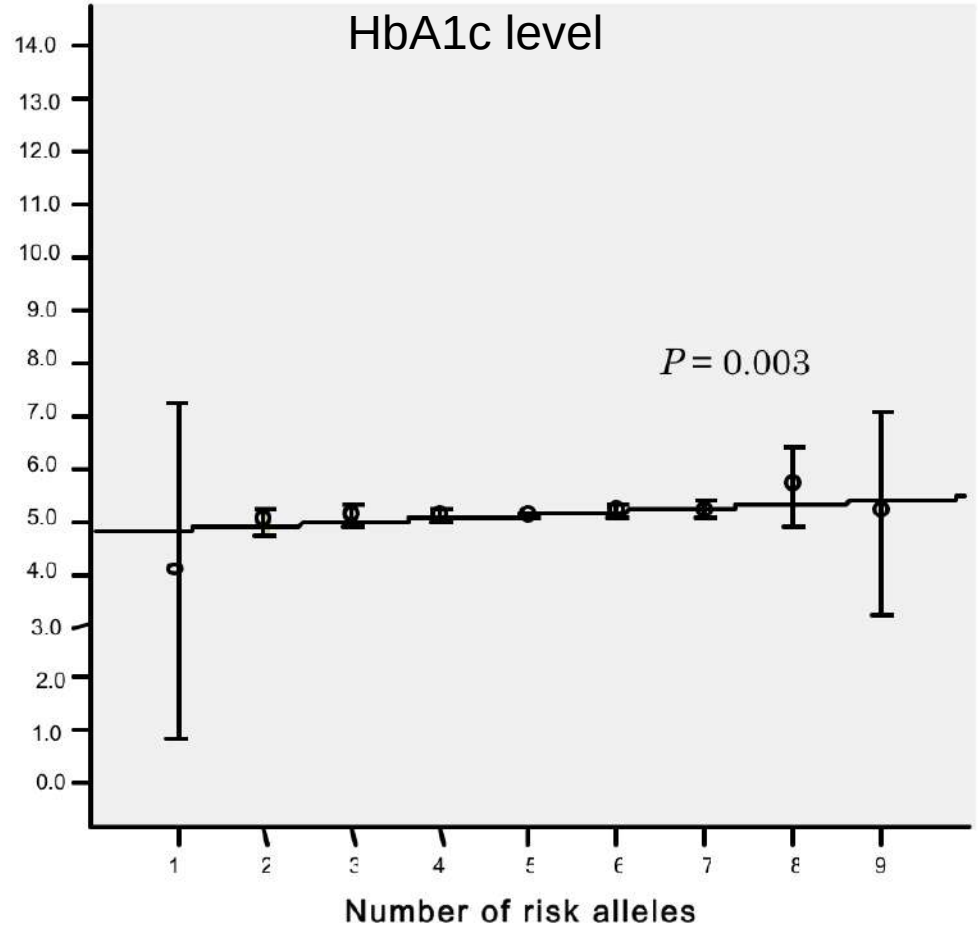


Prevalence of HT

Miyaki et al. Am. J. Hyperten.2011

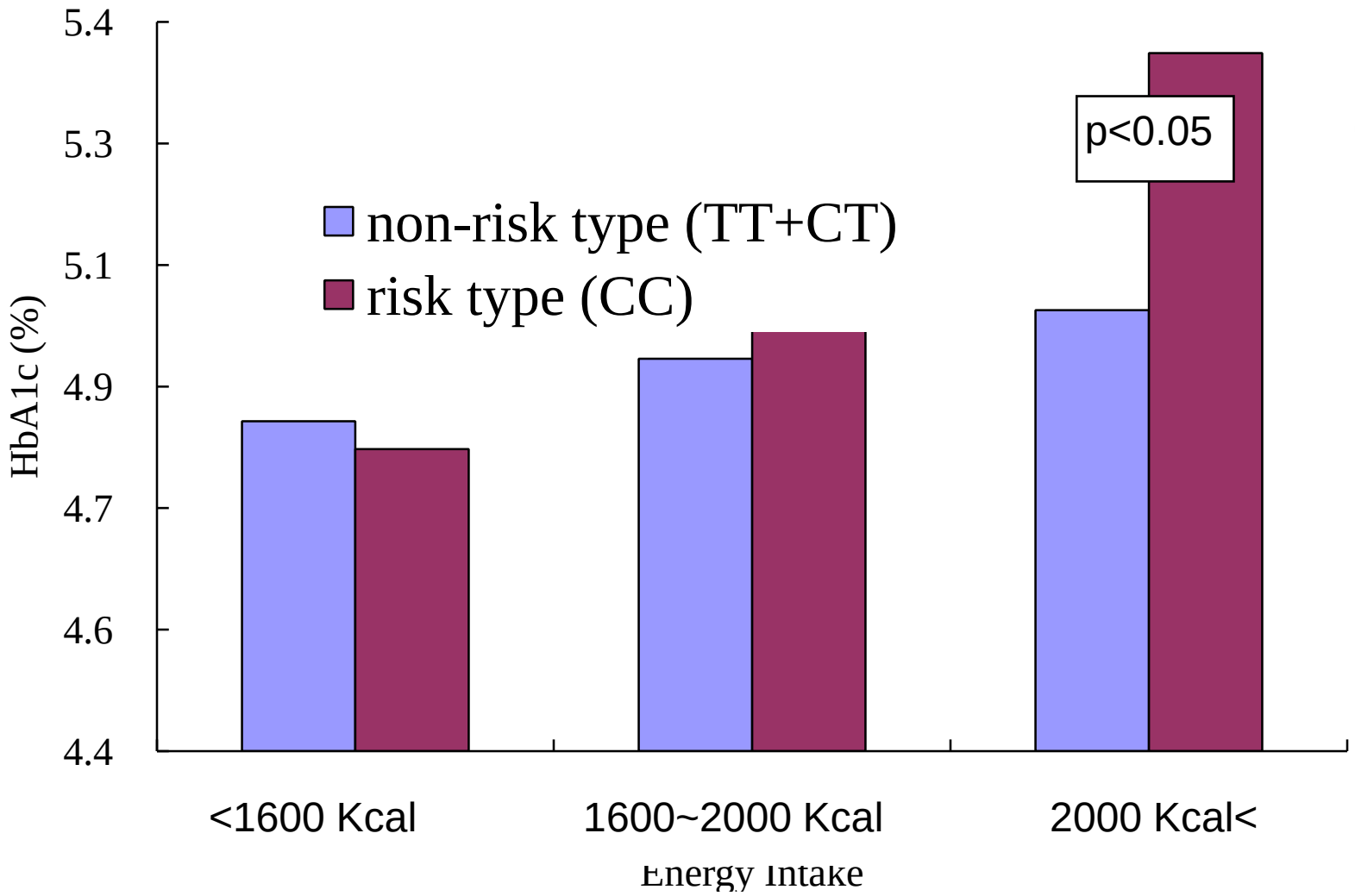
5 DM risk SNPs and HbA1c





HbA1c increases with the risk score.

GxE Interaction: CDKAL1 genotype X energy intake



The genetic effect is apparent only in high intake group

(Miyaki et al. Am. J. Epidemiol. 2010)

Home | Health Watch Results | Ancestry Results | Friends | Community | Advanced

Welcome Masaaki Muramatsu

- 10.10.11: NEWS - Not only Size Matters: Genetic Megastudies Draw out Distinctions between Obesity and Waist-Hip Ratio.
- 10.10.11: Kidney Stones updated in the Complete Scan.
- 10.09.29: Type 1 Diabetes updated in the Complete Scan.
- 10.09.27: Crohn's Disease updated in the Complete Scan.

Health Results

Ancestry Results

- ✓ Go to Condition
- All Conditions
- Abdominal Aortic Aneurysm
- Age Related Macular Degeneration
- Alcohol Flush Reaction
- Alzheimer's Disease
- Asthma
- Atrial Fibrillation
- Basal Cell Carcinoma
- Bitter Taste Perception
- Bladder Cancer
- Brain Aneurysm
- Brain Cancer-Glioma
- Breast Cancer
- Celiac Disease
- Chronic Kidney Disease
- Chronic Lymphocytic Leukemia
- Chronic Obstructive Pulmonary Disease
- Colorectal Cancer
- Crohn's Disease
- Essential Tremor
- Exfoliation Glaucoma
- Eye Color
- Gallstones

Ancestry Results

Your results are based on the deCODEme Complete Scan.

riend sharing

are yourself to others.

Visit the forum

Discuss your results.

Advanced options

Including the genome browser.

More options

> View our FAQ
> Genome Browser guide
> Sitemap

Your account
> Change settings
> Private messages

Feedback
> Edit answers

Type 2 Diabetes

Type 2 diabetes (T2D) (also called non-insulin dependent diabetes mellitus or adult-onset diabetes) is the most common form of diabetes.

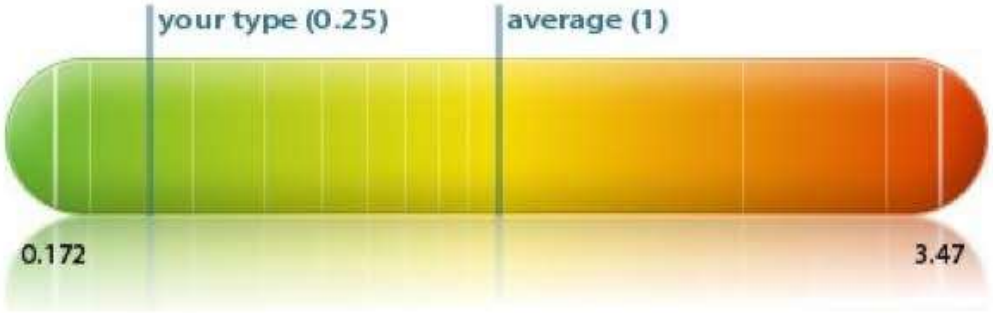
Results can vary according to population and/or gender. Results currently based on:

East Asian ancestry

CHANGE

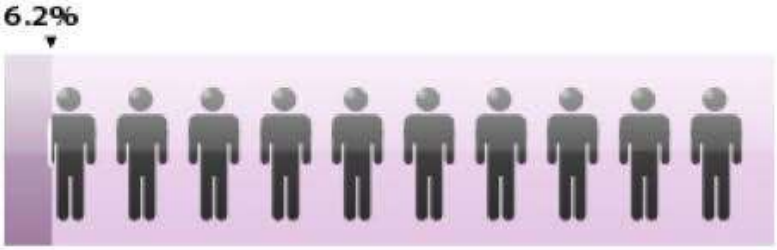
Male

CHANGE

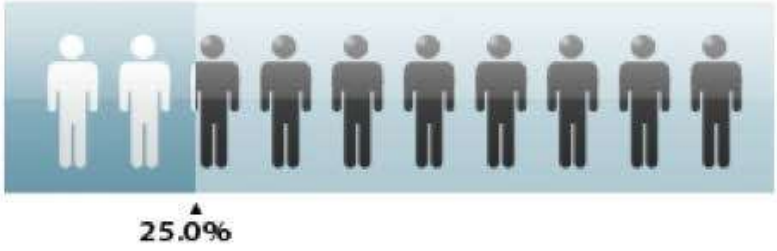


According to the selected literature, the relative genetic risk calculated from your genotype for males of East Asian ancestry is **0.25**. This corresponds to a **6.2% lifetime risk** of developing type 2 diabetes, which is **75% less than** for males of East Asian ancestry in general (source) . Note that these calculations may not include all risk factors.

The lifetime risk of your type
It is estimated that **6 of every 100** males of East Asian ancestry with your genotype variants develop this disease in their lifetime.



The average lifetime risk
On average, about **25 of every 100** males of East Asian ancestry develop this disease in their lifetime.



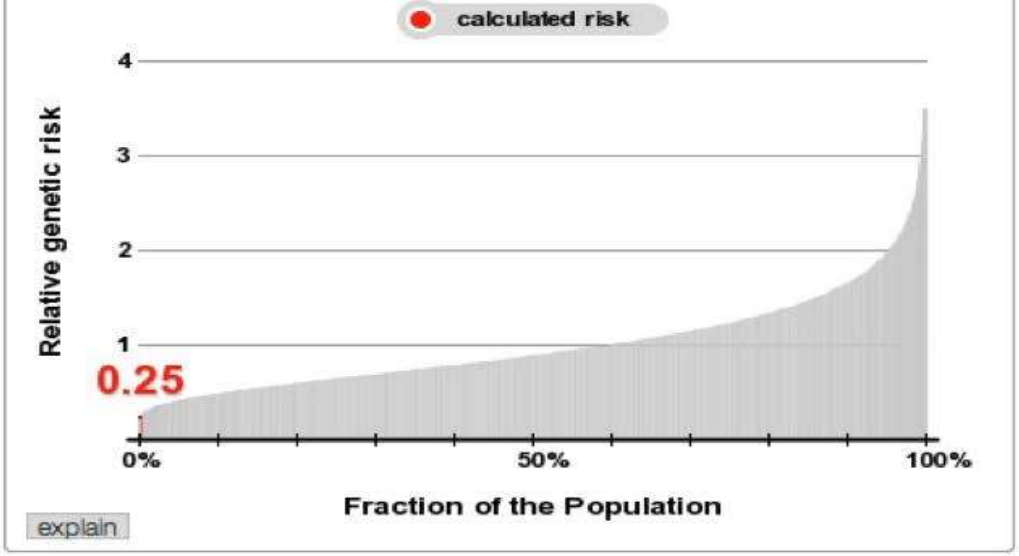
These are the results of calculations comparing your genetic sequence to sequence of participants in studies published in the world literature on genetic risk for this disease.

▸ HOW DECODEME CALCULATES GENETIC RISK

Consult with our experts

Need something clarified? If so, please feel free to contact our experts. Based on the nature of your questions, we may refer you to a genetic counselor.

▸ ASK A QUESTION ABOUT TYPE 2 DIABETES



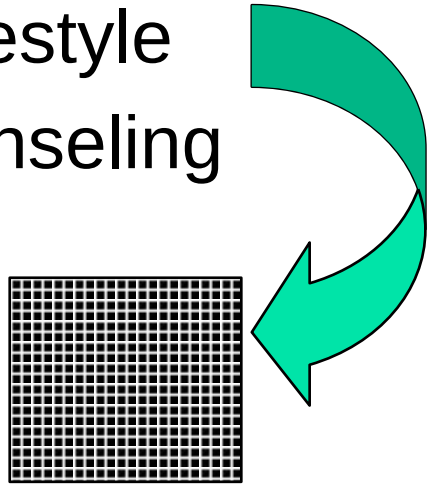
Relevant risk variants from the literature

Population: Males of East Asian ancestry

Locus	Chromosome	Variant / SNP	My Codes	Relative Risk	Genotype frequency	Num. Cases / Num. Controls
CDKAL1	6	▸ rs7756992	AG	1.00	49.7%	1457 / 986
▸ STEINTHORSDOTTIR, V ET AL. NAT GENET. 2007 JUN;39(6):770-5. EPUB 2007 APR 26.						
CDKN2A / B	9	▸ rs2383208	GG	0.77	19.4%	1630 / 1064
▸ OMORI, S ET AL. DIABETES. 2008 MAR;57(3):791-5. EPUB 2007 DEC 27.						
HHEX	10	▸ rs1111875	AA	0.88	51.8%	1630 / 1064
▸ OMORI, S ET AL. DIABETES. 2008 MAR;57(3):791-5. EPUB 2007 DEC 27.						
IGF2BP2	3	▸ rs4402960	GG	0.82	50.4%	1630 / 1064
▸ OMORI, S ET AL. DIABETES. 2008 MAR;57(3):791-5. EPUB 2007 DEC 27.						
KCNJ11	11	▸ rs5219	CC	0.84	42.2%	1630 / 1064
▸ OMORI, S ET AL. DIABETES. 2008 MAR;57(3):791-5. EPUB 2007 DEC 27.						
KCNQ1	11	▸ rs2237892	TT	0.63	15.2%	6552 / 6621
▸ YASUDA, K ET AL. NATURE GENETICS 2008 SEPT; 40:1092-1097.						
SLC30A8	8	▸ rs13266634	TT	0.83	23.0%	1457 / 986
▸ STEINTHORSDOTTIR, V ET AL. NAT GENET. 2007 JUN;39(6):770-5. EPUB 2007 APR 26.						
TCF2	17	▸ rs4430796	AG	1.06	40.3%	1859 / 1785

Gene test for common diseases

- By analyzing multiple SNPs disease risk information can be conveyed.
- Since not all genetic factors are covered, the results should be conveyed with caution.
- Motivate to improve (not deteriorate) lifestyle
- Needs genome literacy and proper counseling



DM related genes in Japanese

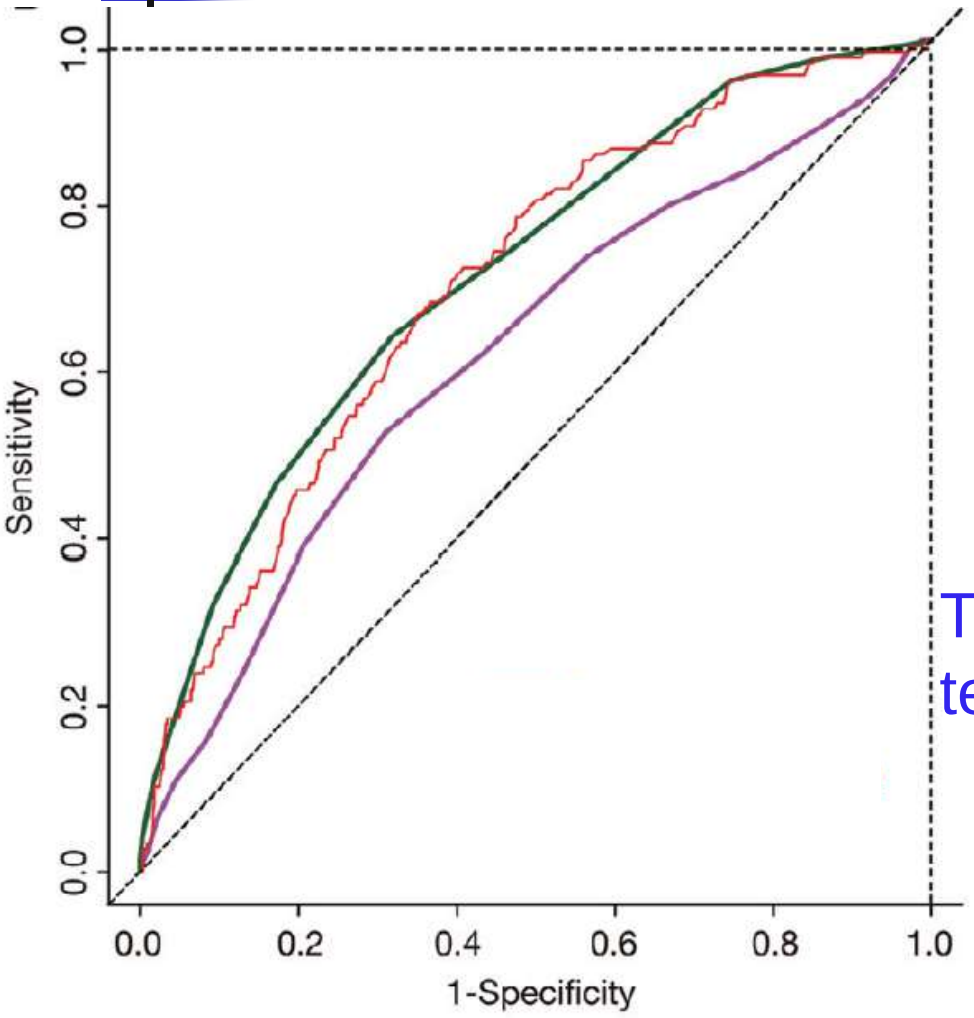
信頼度順	信頼性	人種	rs番号	ゲノム上の位置
1	高い	共通	rs7903146	*TCF7L2*
2	高い	共通	rs1111875	*near_HHEX*
3	高い	共通	rs13266634	*SLC30A8*
4	高い	共通	rs10811661 [rs2383208]	*near_CDKN2A/B*
5	高い	共通	rs4402960	*IGF2BP2*
6	高い	共通	rs7754840	*CDKAL1*
7	高い	共通	rs2237892	*KCNQ1*
8	高い	共通	rs5219	*KCNJ11*
9	高い	共通	rs8050136	*FTO*
10	高い	共通	rs864745 [rs917117]	*JAZF1*
11	高い	共通	rs780094	*GCKR*
12	高い	東アジア	rs1359790 [rs1215451]	*near_SPRY2*
13	高い	共通	rs340874	*PROX1*
14	高い	共通	rs7501939	*HNF1B*
15	高い	共通	rs5945326	*near_DUSP9*
16	高い	共通	rs1436955	*C2CD4B-C2CD4A*
17	高い	共通	rs10425678	*PEPD*
18	高い	東アジア	rs10906115	*CDC123-CAMK1D*
19	高い	共通	rs7612463	*UBE2E2*
20	高い	共通	rs7178572	*HMG20A*
21	低い	共通	rs2943641	*near_IRS1*
22	低い	共通	rs1801282 [rs6802898]	*PPARG*
23	低い	共通	rs1552224	*ARAP1*
24	低い	共通	rs1802295	*VPS26A*
25	低い	共通	rs896854	*TP53INP1*
26	低い	共通	rs16861329	*ST6GAL1*
27	低い	東アジア	rs6467136	*near_GCC1*
28	低い	東アジア	rs7041847	*GLIS3*
29	低い	東アジア	rs831571	*near_PSMD6*
30	低い	東アジア	rs11756091	*KCNK16*

DM related genes in Caucasian

信頼度順	人種	rs番号	ゲノム上の位置
1	共通	rs7903146	*TCF7L2*
2	共通	rs10811661	*near_CDKN2A/B*
3	共通	rs2237892	*KCNQ1*
4	共通	rs8050136	*FTO*
5	共通	rs7754840	*CDKAL1*
6	共通	rs13266634	*SLC30A8*
7	共通	rs4402960	*IGF2BP2*
8	共通	rs5219	*KCNJ11*
9	共通	rs1111875	*near_HHEX*
10	欧米	rs2970847	*PPARGC1A*
11	欧米	rs7578326	*near__IRS1*
12	欧米	rs4457053	*near_ ZBED3*
13	共通	rs231362	*KCNQ1*
14	共通	rs1552224	*ARAP1*
15	共通	rs864745	*JAZF1*
16	欧米	rs1020731	*RBMS1*
17	欧米	rs9300039	*RPL9P23-API5*
18	欧米	rs10010131	*WFS1*
19	欧米	rs1617640	*EPO*
20	共通	rs896854	*TP53INP1*
21	共通	rs5945326	*near_ DUSP9*
22	欧米	rs12779790	*CDC123-CAMK1D*
23	欧米	rs1153188	*near_ DCD*
24	欧米	rs7578597	*THADA*
25	欧米	rs4607103	*near_ ADAMTS9*
26	共通	rs17036101 [rs1801282]	*SYN2-PPARG*
27	欧米	rs10830963	*MTNR1B*
28	共通	rs4430796 [rs7501939]	*HNF1B*

Top 30 ranking for credibility

Receiver Operating Characteristic (ROC) analysis



GRS29 : AUC=0.686

GRS29+HT+BMI: 0.707

age,sex,BMI,HT,smoking,
& family history: 0.719

The predictive power of the gene test is equivalent to family history

Gene test to empower patient's self-care

Why use gene test which is much more expensive than family history taking?

Because, prevention of DM is about education.

Family history of the patient is about the family member, not the patient themselves.

Gene test is about the patient him/her self.

Gene test provides a good tool to educate patients how yourself may relate to diseases.

P4 medicine, a future style?

- Predictive :
- Preventive:
- Personalized:
- Participatory:

GGTTCCAAAAGTTTATTGGATGCCGTT
TCAGTACATTTATCGTTTGCTTTGGAT
GCCCTAATTAAAAGTGACCCTTTCAAA
CTGAAATTCATGATACACCAATGGATA
TCCTTAGTCGATAAAATTTGCGAGTAC
TTTCAAAGCCAAATGAAATTATCTATG
GTAGACAAAACATTGACCAATTTCATA
TCGATCCTCCTGAATTTATTGGCGT
GACACAGTTGGTATATTTA….

Former President Obama was pushing
“Precision Medicine”

P4 medicine is not a far future

- Personal
  - Family history, Actress, Lifestyle
- Predictive
  - Genetic test reveals 87% lifetime risk for breast cancer
- Preventive
  - Preventive mastectomy. Risk reduced to 5%
- Participatory
  - “I want to have all women learn from my experience”

Prenatal testing

Case study 2: Sofia is pregnant with her first child. Wanting to do everything to ensure a healthy newborn, she opts for whole-exome sequencing. The sequencing results identify pathogenic variants in *PKU*, which have been associated with phenylketonuria. Armed with this information, Sofia immediately begins a low-phenylalanine diet during pregnancy and arranges for the availability of a special dietary infant formula to avoid neonatal exposure to phenylalanine. With this treatment plan, the baby is expected to develop normally and lead a healthy adult life.

Preconception testing

Case study 1: Bob and Julie are considering having a child and seek preconception genetic testing. Julie is found to carry seven pathogenic variants for recessive diseases and Bob is found to carry five. There is one gene, *SMN1*, for which both are carriers. This result puts the couple at a 25% risk of having a child with spinal muscular atrophy, a progressive muscle-wasting disease. Julie and Bob decide to pursue preimplantation genetic diagnosis to avoid a pregnancy with an affected fetus by selecting embryos that do not inherit both pathogenic variants.

Newborn screening and paediatric care

Case study 3: Mei has just given birth to a healthy baby girl. She decides to have her daughter's genome assessed using exome sequencing. This test reveals two pathogenic variants in *GJB2*, putting the newborn at risk of hearing loss that can be progressive. Although the child passed a newborn baby hearing screening test, a diagnostic audiological test reveals mild hearing loss, often missed in newborn screening. The baby is fitted with hearing aids to facilitate normal auditory development. The baby's hearing is monitored yearly, and if it progresses to profound deafness, the option for cochlear implantation surgery can be offered to the family.

Adult medicine

Case study 4: Joseph was interested in pursuing genomic sequencing to learn about his own health risks. He ordered a whole-genome sequencing test through a medical geneticist offering concierge services and discovered that he harbours a pathogenic variant for hypertrophic cardiomyopathy. This finding prompted a cardiac evaluation, which revealed normal cardiac morphology and conduction systems; however, a detailed family history assessment identified suspicion for hereditary sudden cardiac death on his mother's side based on unexplained drowning of a sibling and two maternal uncles who died of heart attacks at 55 and 60 years of age. Given the incomplete penetrance of hypertrophic cardiomyopathy, Joseph's actual risk of disease is unclear, but with a positive at-risk genotype, he will pursue regular cardiac evaluations and inform family members of their possible risk.

Elderly health

Case study 6: John had watched his father suffer a long end-of-life battle with Alzheimer disease. Curious about his own risks, he elected to obtain genetic testing through a direct-to-consumer testing company and learned that he harbours two copies of the *APOE* ε4 variant, putting him at heightened risk of Alzheimer disease. He also learned that his ancestral origins were more diverse than he had previously realized and was able to connect with several distant relatives though an online ancestry portal.

Adult medicine

Case study 5: Jessica is seeing a genetic counsellor (GC) to discuss her risk of breast cancer after her grandmother and aunt died of breast cancer and her mother was recently diagnosed. She brings a copy of her aunt's laboratory report from 2008 that notes a pathogenic variant identified and cites a publication to support the variant interpretation. Jessica's GC quickly looks up the variant in ClinVar and discovers that five clinical laboratories now interpret the variant as benign, citing more recent evidence accumulated from clinical testing. The GC suggests that her aunt's testing probably did not identify the correct cause of disease in her family and suggests that Jessica's mother undergo testing to identify another potential cause of hereditary breast cancer that may not have been examined in 2008. If a cause of breast cancer is found in her mother, Jessica would be able to pursue testing to inform her own risk.

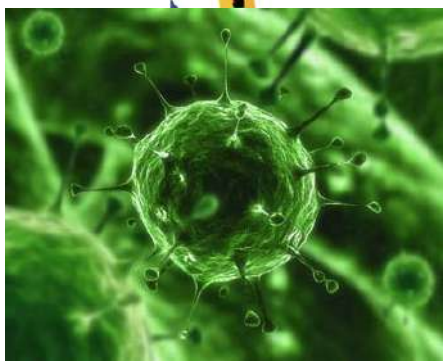
Personal genome will be widely implemented in medicine and healthcare

Nat.Rev.Genet (2017)

… I would like to think that if somebody does a test on me or my genes, that's mine.

- President Obama, February 25, 2016

Genome and Medicine, Healthcare



"By knowing your genes, you can improve your health and save your life"

Milunsky, A

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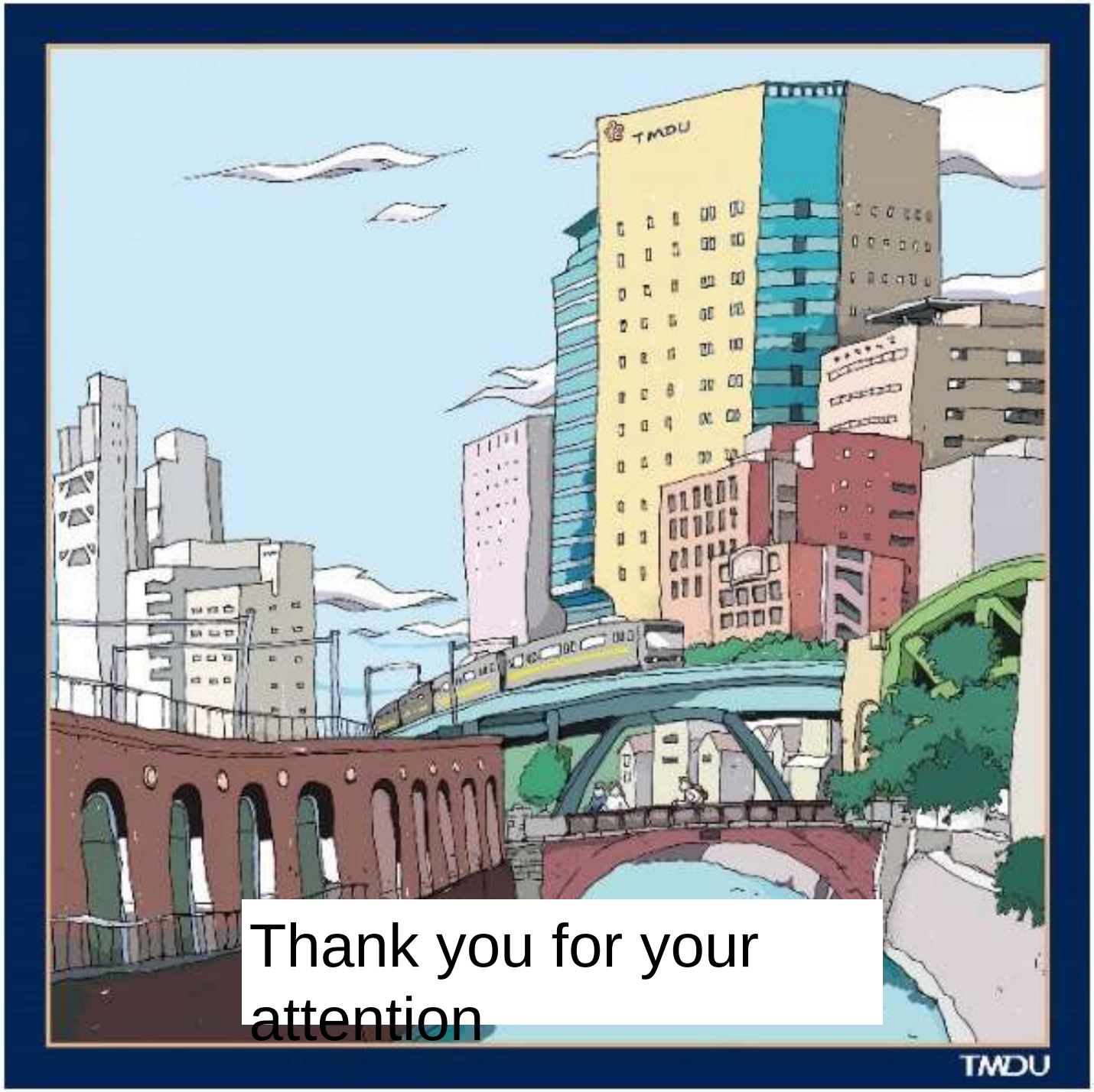
Nay Chi Htun
Kaung Si Thu
Khin Thet Thet Zaw
Tay Zar Kyaw
Aye Ko Ko Min

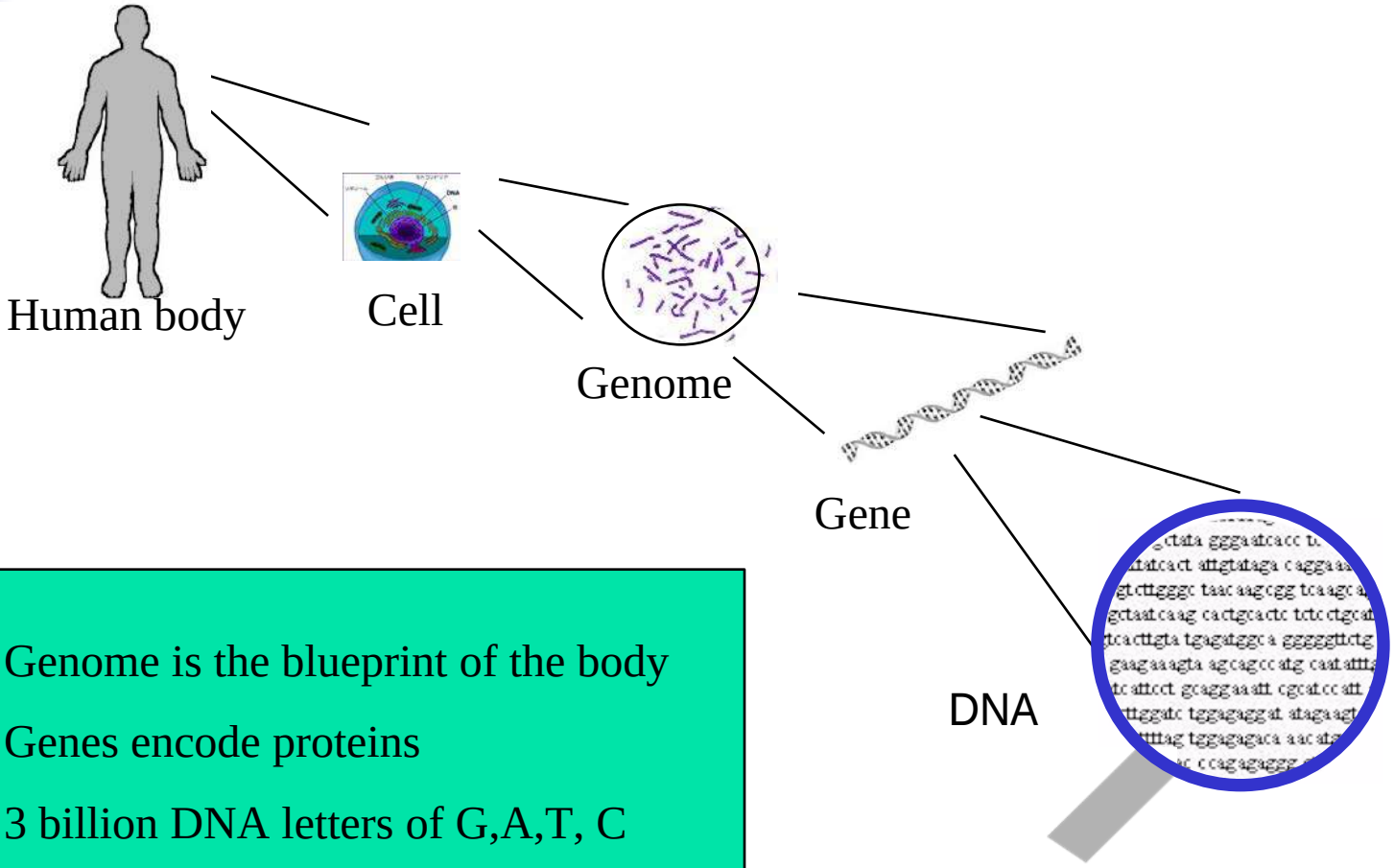
Mar 2017


TMDU
Thank you for your attention
TMDU

What is personal genome？

- Further development in sequencing ability
  - DNA-chip → Millions of SNPs
  - Next generation Sequencer→ 3 billion DNA letters
- Extremely powerful in monogenic diseases
  - Diagnose half of the ~7000 monogenic diseases
- How about multifactorial diseases？
  - Cohort study of 10,000~100,000 participants are underway to detect rare variants affecting common diseases.

Human body, Genome, Gene, DNA



- Genome is the blueprint of the body
- Genes encode proteins
- 3 billion DNA letters of G,A,T, C

How does Insulin gene work?

8101 gaaaggagat gaaatataaa gaacatagaa tatagagagg gggtatggag aatggaatat
8161 agcttggact atagcaaata gagaataaaa tataaagtat ggagtatgga gaaaaaaatg
8221 tggagcatgg aaaatgaaga atgaggaata gagtatgaag aataaagaat ggaatggggt
8281 ctagattatg gagaatgata cctggagcat ggaaaatgga gaatggaatg gaatatggaa
8341 aatggacaat agagagtgga atatggacga tggtaggtgt atgaagtatg aaactttgga
8401 ggatggagaa tggacaaaaa ctacagaata tggagactga gtatggataa tgaagtatgg
8461 agtatacagt atcgacaatg gagtaccaag tatgataaat attgtgcaaa gtgtgtactg
8521 catgtgtgca cagagaacct gaagcaatat atggtccaag aggaaggcct agtgcaaggc
8581 ctgatatatg gtagatgttc ccagaaacta aggtaaggca ggtagcactg gatctgcaca
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10381 atgggtgggg atggaggggg cccttctaaa gaggactggc tcccacgggc cctcaggcca
10441 gagtgcactg cccgcattca aggcaaccct tgaagggttg ggaggcccac caccacgcca

Insulin gene

1 gctgcatcag aagaggccat caagcacatc actgtccttc tgccatggcc ctgtggatgc
61 gcctcctgcc cctgctggcg ctgctggccc tctggggacc tgacccagcc gcagcctttg
121 tgaaccaaca cctgtc[illegible]gtg tgcggggaac
181 gaggcttctt ctacacc[illegible]tgcag gtggggcagg
241 tggagctggg cgggg[illegible]cctg gaggggtccc
301 tgcagaagcg tggcatggg gaacaatgct gtaccagcat ctgtcccctc taccagctgg
361 agaactactg caactagacg cagcccgcag gcagcccccc acccgccgcc tcctgcaccg
421 agagagatgg aataaagccc ttgaaccagc

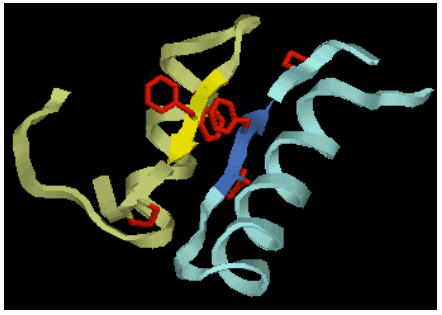
Insulin mRNA

Transcription
Splicing

Translation

Insulin protein

1 malwmrllpl lallalwgpd paaafvnqhl
31 cgshlvealy lvcgergffy tpktrreaed
61 lqvgqvelgg gpgagslqpl alegslqkrg
91 iveqcctsic slyqlenycn



Controls blood sugar level

Application of Insulin gene to medicine

- Recombinant DNA technology

Dr. Paul Berg
Prof of Stanford University. Nobel-Prize Laureateof Chemistry in 1980 due to this Discovery.

Cloning of Insulin gene and production of Insulin protein in E.coli

→Treatment for Insulin Dependent Diabetics

Human Genome Decoded (2003, 4)

International project： USA、UK、Fr、De、Japan, etc

Size：3 billion letters（G,A,T,C ）

Gene No. 25000~30000 (Functions known for ~1/3）

Gene region：2~3 % (Others are Junk?)

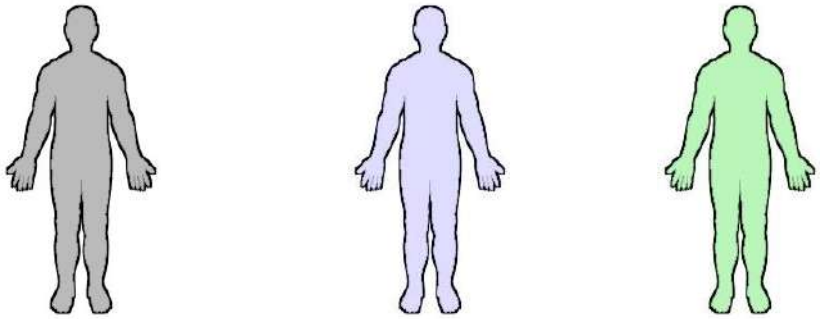
Human genome sequence in 24 CD-ROMs. Now it can be accessed through internet (GenBank)

Single nucleotide variants (SNVs)

Since one person has one pair of genome inherited from mother and father, one SNP comprises three Genotypes.

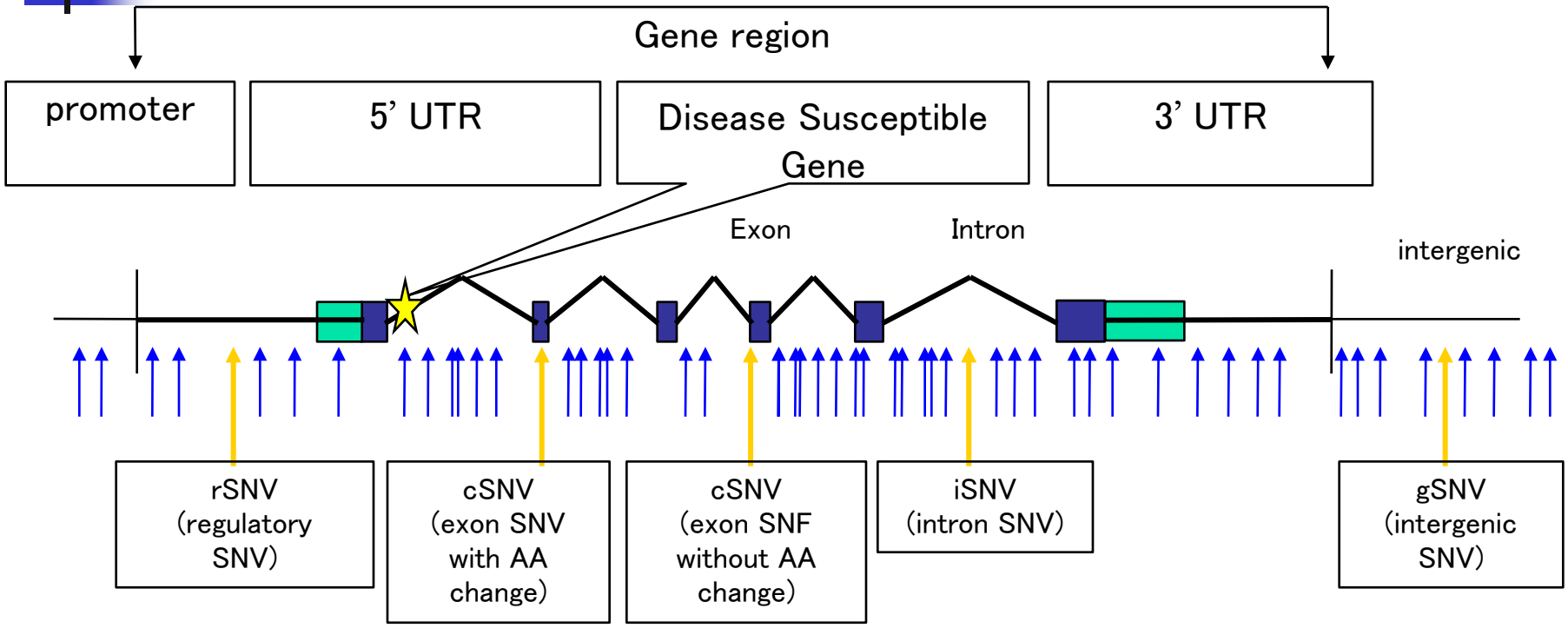
Ex: When the SNP is G/A

G G	G A	A A
homo	hetero	homo



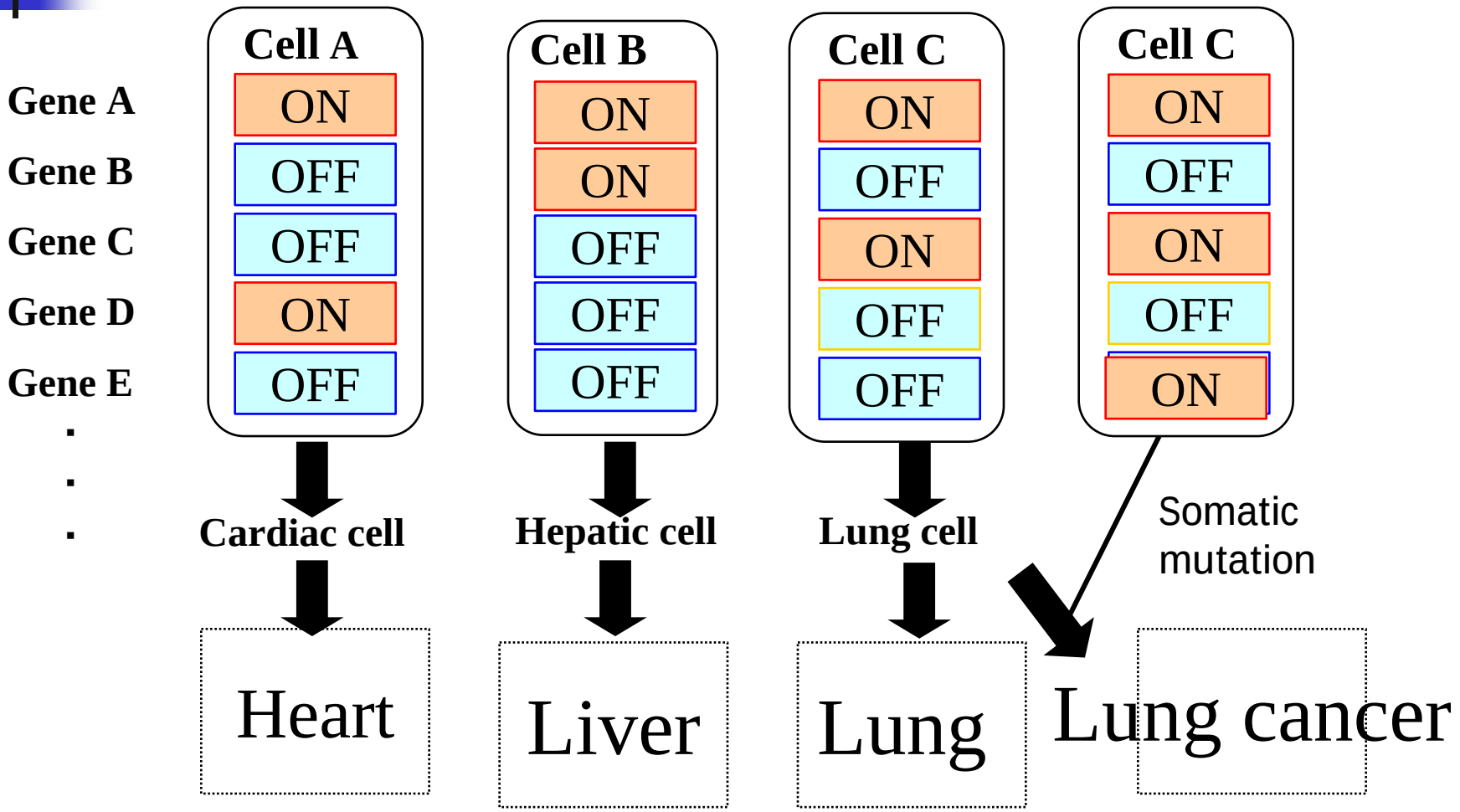
Question: Who is most susceptible to a certain disease?

SNV in the context of genome



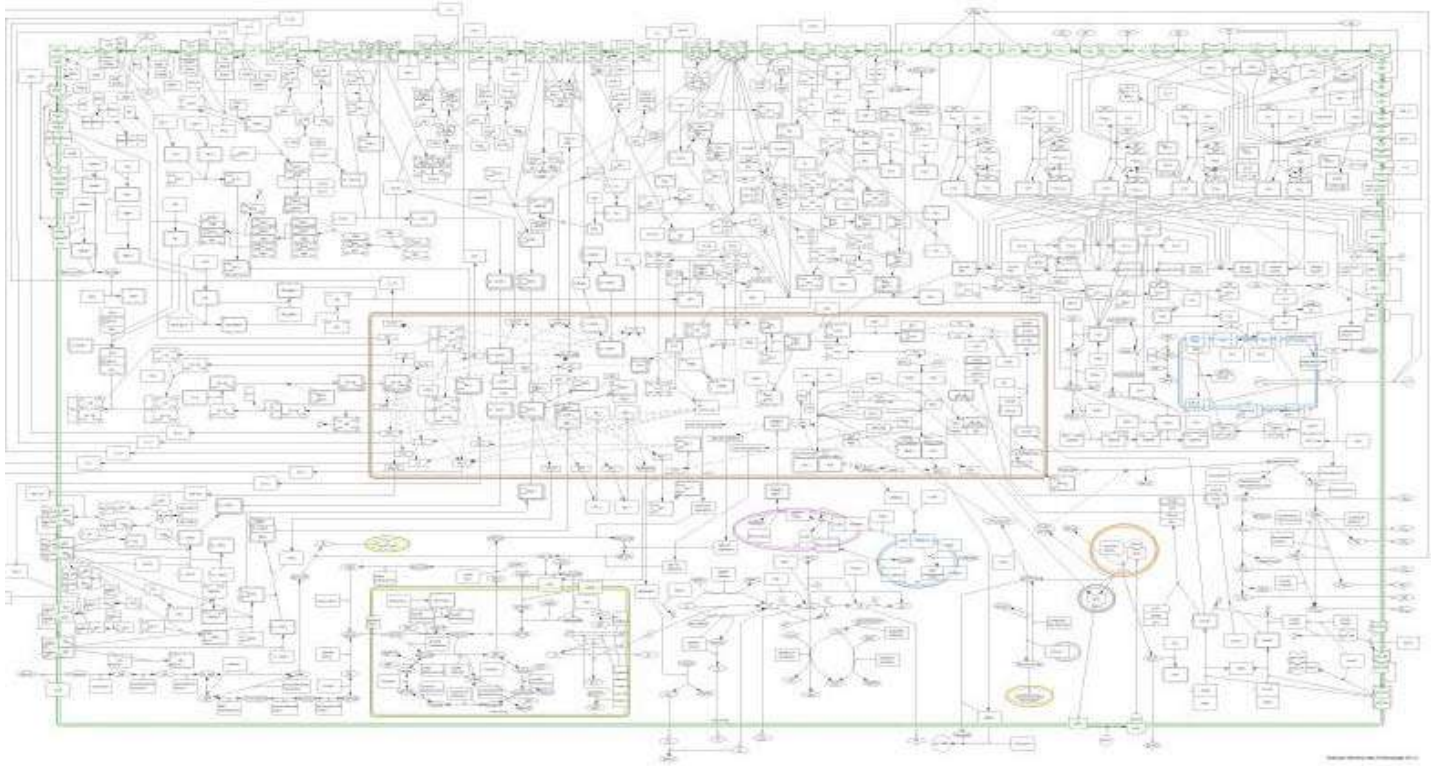
1. Most SNVs may not be related to any phenotypic changes
2. Some of them lead to changes in gene function (Qualitative, Quantitative)

Gene Expression Pattern determines the fate of cells



Pathways of Gene products (proteins)

- Genes function within a pathway



Gene function is one of the major theme in Medical Science.