IRDiRC Training **2014**

Gentic Tests and Human Variome Project

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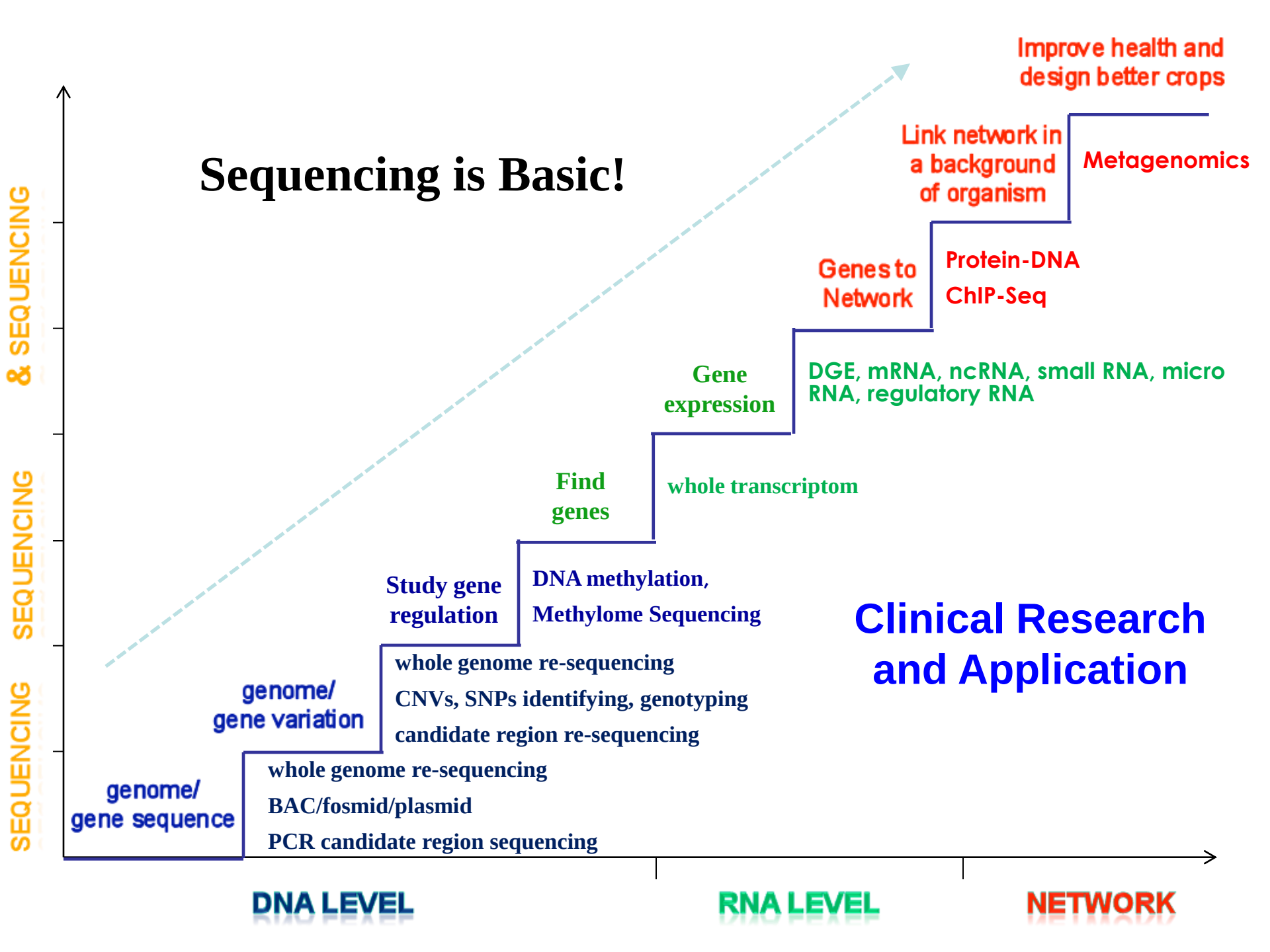
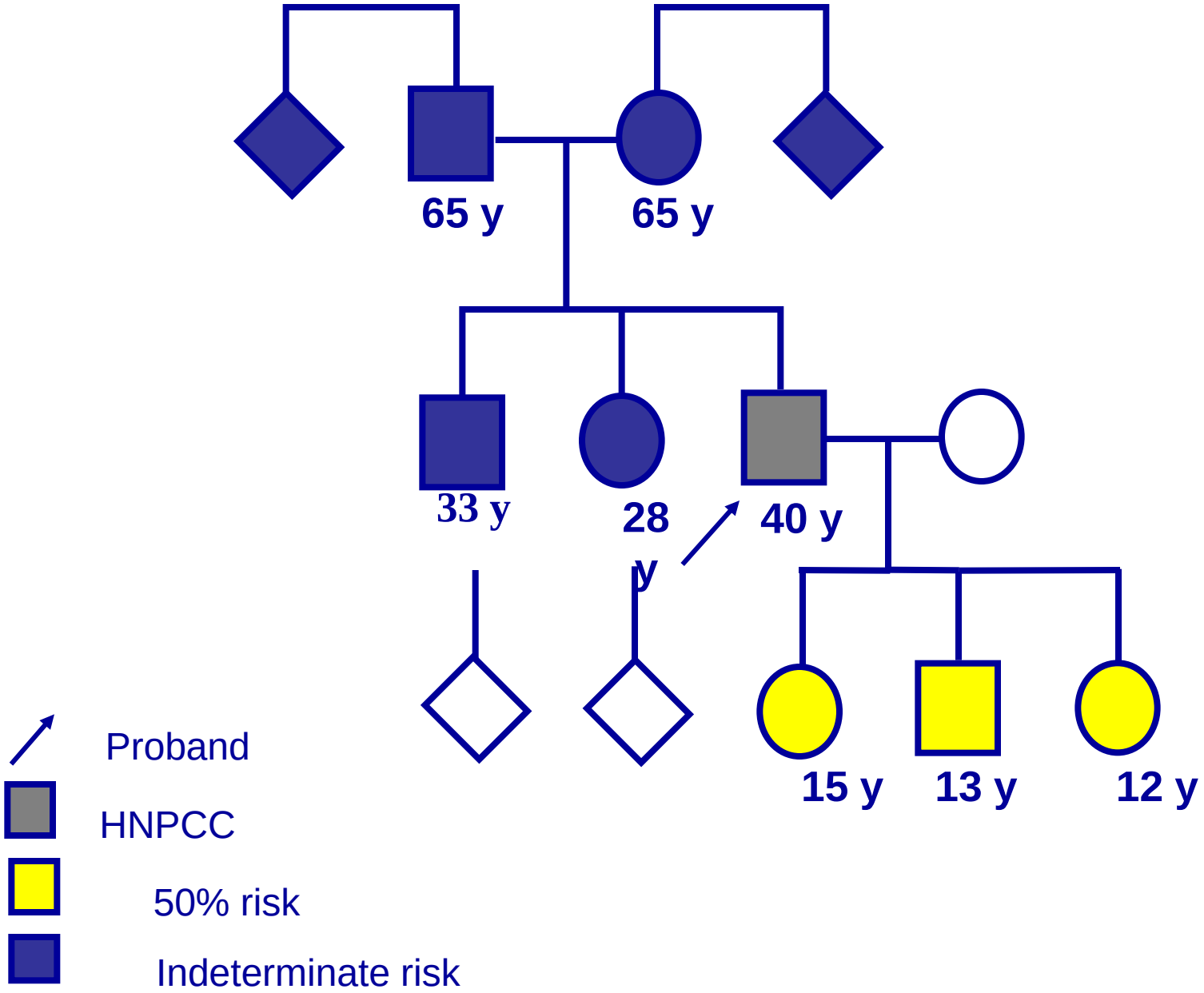

Sequencing is Basic!
Improve health and design better crops
Link network in a background of organism
Metagenomics
Genes to Network
Protein-DNA
ChIP-Seq
Gene expression
DGE, mRNA, ncRNA, small RNA, micro RNA, regulatory RNA
Find genes
whole transcriptom
Study gene regulation
DNA methylation,
Methylome Sequencing
whole genome re-sequencing
CNVs, SNPs identifying, genotyping
candidate region re-sequencing
genome/ gene variation
whole genome re-sequencing
BAC/fosmid/plasmid
PCR candidate region sequencing
genome/ gene sequence
SEQUENCING
SEQUENCING
& SEQUENCING
Clinical Research and Application
DNA LEVEL
RNA LEVEL
NETWORK

Gene Tests (1)

- Symptomatic patients
  - Conformational diagnosis of a symptomatic individual;
  - Differential diagnosis of disease with multiple sub-types
  - Pharmacogenetic testing
- Carrier screening, which involves identifying unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed;
- Prenatal diagnostic testing;
- Newborn screening;

Gene Tests (2)

- Presymptomatic testing for predicting adult-onset disorders such as Huntington's disease;
- Genomic profiling
  - Forensic/identity testing/transplantation
  - Cancer monitoring/prognosis
- Infection testing (SARS, HIV, HPV, etc)
- Potential capability testing
- **Health testing**
  - **Presymptomatic testing for estimating the risk of developing late-onset cancers and disorders (Alzheimer's disease, heart disease, etc)**
  - **Life style, nutrition advise**


65 y
65 y
33 y
28 y
40 y
15 y
13 y
12 y
Proband
HNPCC
50% risk
Indeterminate risk

Methods in Genet Dx: cytogenetic, biochemical, DNA-based tests

- Chromosome banding
- FISH
- CGH
- PCR
- RFLP
- SSCP
- RT-PCR
- Quantitative PCR
- Real-time PCR
- CFLP
- HA
- *DHPLC*
- CGGE
- TGGE
- DGGE
- Protein truncating test (PTT)
- Chemical mismatch cleavage (CMC)
- RNase A cleavage
- dideoxy fingerprinting (ddF)
- SAGE
- Mass spectrometry (MS)
- LOH
- DNA sequencing
- DNA chip
- SELDI
- MALDI
- ...

Sequence variation

Single nucleotide
- Base change – substitution – point mutation
- → Insertion-deletions ("indels")
- SNPs – tagSNPs

2 bp to 1,000 bp
- Microsatellites, minisatellites
- → Indels
- Inversions
- Di-, tri-, tetranucleotide repeats
- VNTRs

1 kb to submicroscopic
- → Copy number variants (CNVs)
- → Segmental duplications
- Inversions, translocations
- → CNV regions (CNVRs)
- Microdeletions, microduplications

Microscopic to subchromosomal
- → Segmental aneusomy
- Chromosomal deletions – losses
- Chromosomal insertions – gains
- Chromosomal inversions
- Intrachromosomal translocations
- Chromosomal abnormality
- → Heteromorphisms
- Fragile sites

Whole chromosomal to whole genome
- Interchromosomal translocations
- Ring chromosomes, isochromosomes
- Marker chromosomes
- → Aneuploidy
- → Aneusomy

Structural variation

→ Term defined or discussed in **Box 1**

Molecular genetic detection

Array CGH

Cytogenetic detection

- **Technical innovations have opened the door to a fundamental aspect of human genomic variation and a new window into the genetic basis of disease.**
- **The structure of the human genome is not static and CNVs require special consideration in large-scale genetic studies of disease.**

Sebat: Nat Genet 39 (suppl), 2007.

Scheerer et al: Nat Genet 39 (suppl), 2007

Pros and Cons of Genetic Testing

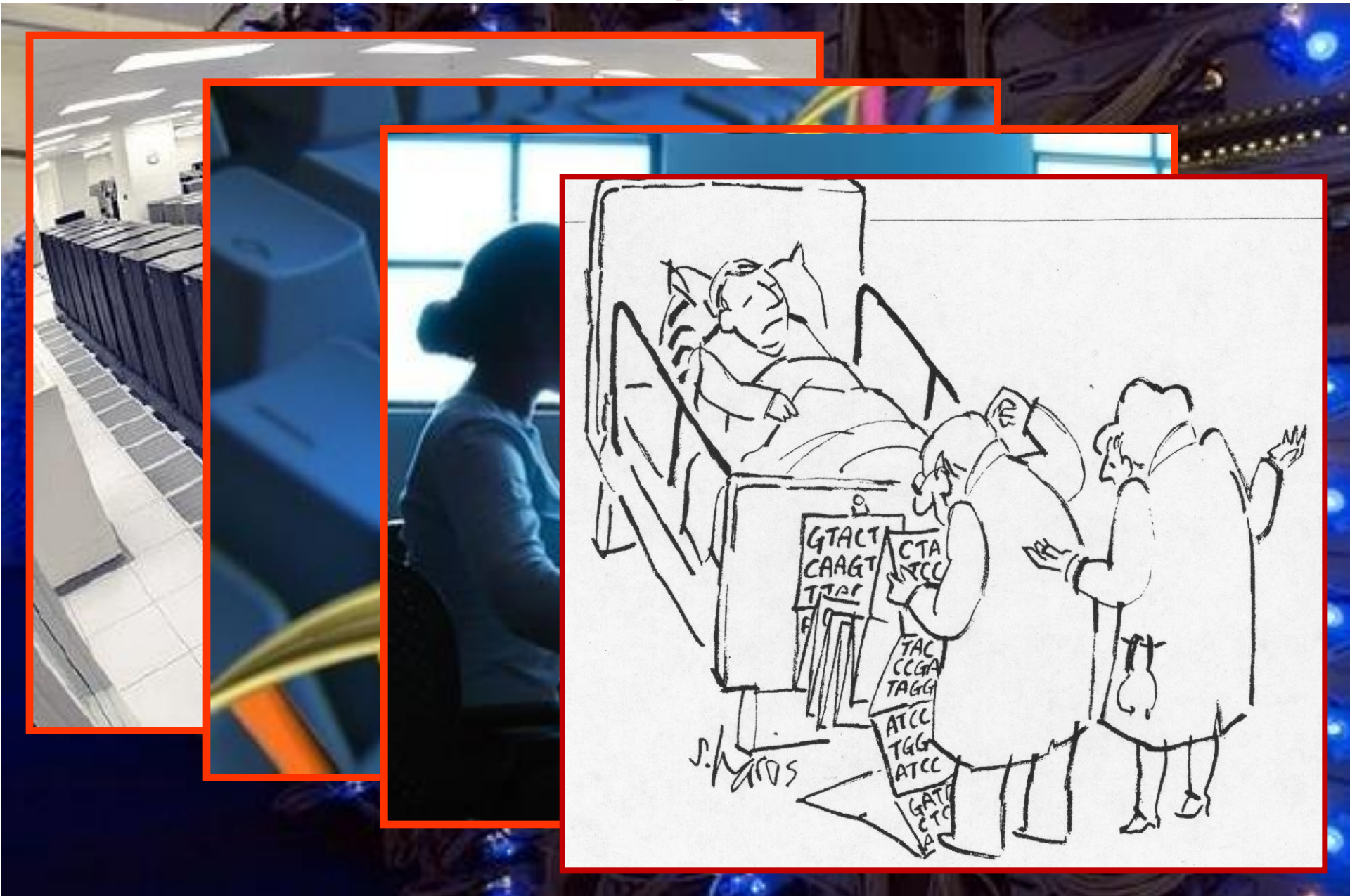
- **Dramatically improved lives**
  - clarify a diagnosis and direct a physician toward appropriate treatments
  - avoid having children with devastating diseases
  - identify people at high risk for conditions that may be preventable
- **Limitations**
  - difficulty in interpreting a positive result of presymptomatic test
  - possibility for laboratory errors
  - potential for provoking anxiety, and risks for discrimination and social stigmatization

Uses of Molecular Genetic Testing in the United States

- To help physicians provide the best **medical care** for a patient with an inherited disorder

- To help a person with an inherited disorder make informed **personal decisions**

Bottleneck: Big Data collection, sharing, analysis and interpretation




THE
HUMAN VARIOME
PROJECT
Planning Meeting 2008

What is the Human Variome Project?
(www.humanvariomeproject.org)

- Variome – Variation in a genome
- Human Variome Project – Collection & Distribution of Human Variation & its phenotype
- Initiated 20-23 June 2006 in Melbourne, Australia co-sponsored by WHO
- A community activity to collect for databasing
- UNESCO official partner, 2010
- WHO official partner, in progress

References

Nat Genet, 2007. **39**(4): p. 433-6.

Science, 2008. **322**(5903): p. 861-2.

THE HUMAN VARIOME PROJECT

Why is complete data needed?

- Genetic clinicians and diagnostic lab heads consult mutation databases daily (and for hours per patient)
- Data needed to refine pathogenicity predictions
- Cohorts needed for mutation specific therapeutics trials

- Individuals with fully sequenced DNA need lists of mutations to inform themselves of risk
- Pre-marital counselling can be extended genome wide from Thalassemia when we all have our genomes sequenced

HVP Working Groups

- Ethics
- Education
- Data Collection from Clinics
- Data Collection from Laboratories
- Data Transfer, Databasing & Curation (Gene Specific/LSDB)
- Overall Data Integration and Access
- Assessment of Pathogenicity
- Publication, Credit & Incentives
- Country Specific Collection
- Funding Mechanisms and Sustainability
- Nomenclature and Standards
- Translation to Healthcare

Huge Population in China

Fifty-six Ethnic Groups in China

Hailar
Qiqihar
Kashgar
KOREA
INDIA
BURMA
Taibei
Nanning
Guangzhou
Macau
Hong Kong
Dongsha Qundao
Haikou
Xisha Qundao
PHILIPPINES
East China Sea

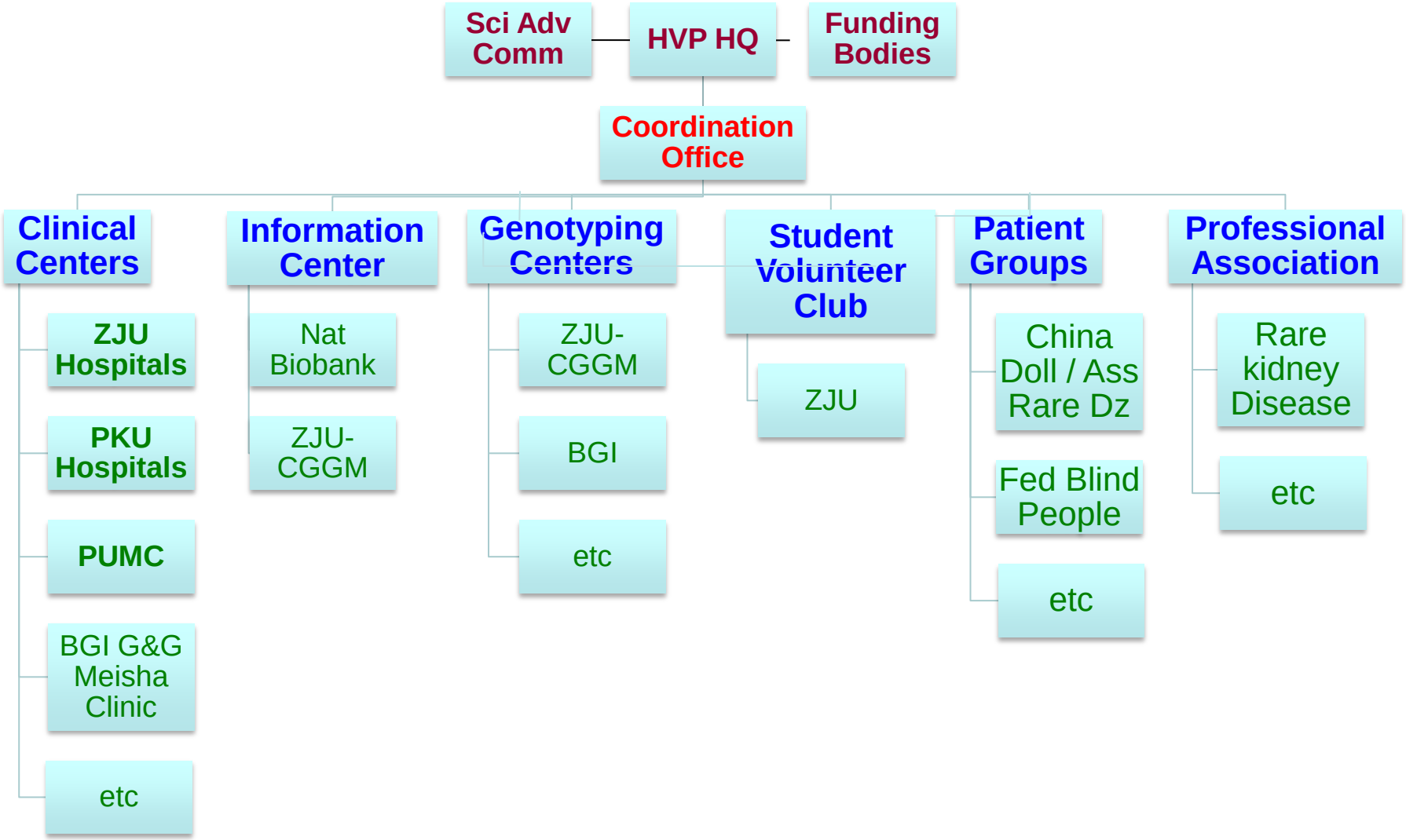
Initiation of HVP (China Consortium)

www.china-HVP.org/

- **ZJU-led National Network of 11 institutions from 6 provinces, Nov 1, 2008 Beijing China**

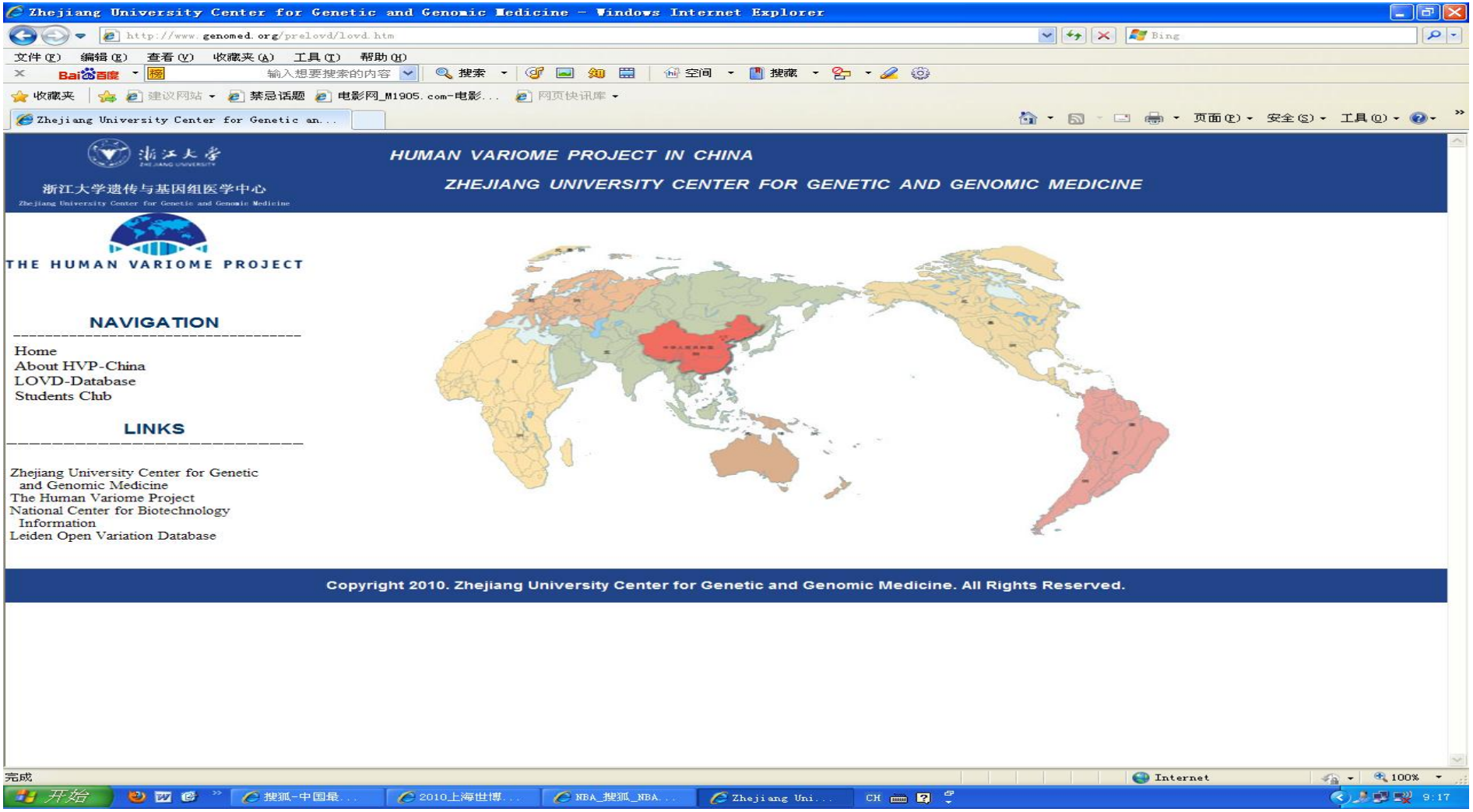
THE HUMAN VARIOME PROJECT

HVP-China Node



Database of HVP China Node

http://www.genomed.org



HVP LOVD-CHINA Current Status

Zhejiang University Center for Genetic and Genomic Medicine

LOVD v.2.0 Build 12 [Current LOVD status]
Register as submitter | Log in

Home | Variants | Submitters | Submit | Documentation

LOVD - China Current system status

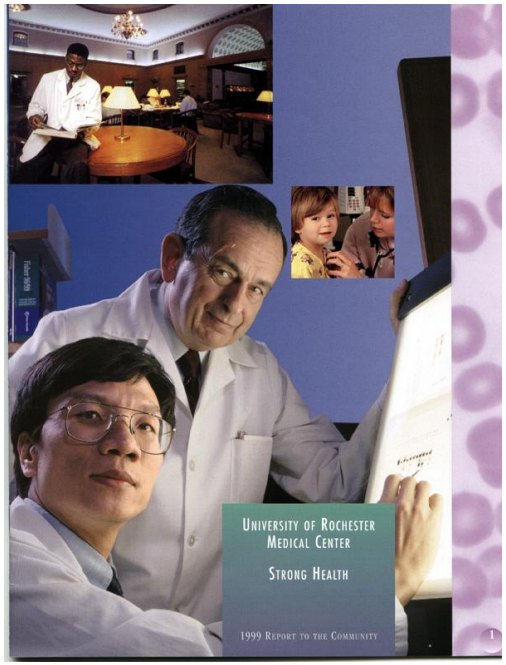
2010/05/12 23:01:52 UTC - Wednesday, May 12th 2010

Gene symbol	Gene name	Total variants	Unique variants
AKAP9	A kinase (PRKA) anchor protein (yotiao) 9	48	47
ANK2	ankyrin 2, neuronal	71	56
APC	adenomatous polyposis coli	273	194
BRCA1	breast cancer 1, early onset	223	134
BRCA2	Breast cancer 2, early onset	112	62
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	7	5
KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1	944	471
KRT9	keratin 9	0	0
LMBRD1	LMBR1 domain containing 1	0	0
MCEE	methylmalonyl CoA epimerase	0	0
MLH1	mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)	146	89
MLH3	mutL homolog 3 (E. coli)	55	49
MMAA	Methylmalonic Aciduria (cobalamin deficiency) cblA type	0	0
MMAB	methylmalonic aciduria (cobalamin deficiency) cblB type	0	0
MMACHA	methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuri	2	2
MMADHC	methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuri	0	0
MSH2	mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)	123	79
MSH6	mutS homolog 6 (E. coli)	7	7
MTR	5-methyltetrahydrofolate-homocysteine methyltransferase	0	0
MTRR	5-methyltetrahydrofolate-homocysteine methyltransferase reductase	0	0
MUT	methylmalonyl Coenzyme A mutase	0	0
PMS1	postmeiotic segregation increased 1 (S. cerevisiae)	18	18
PMS2	postmeiotic segregation increased 2 (S. cerevisiae)	14	14
SCN4B	sodium channel, voltage-gated, type IV, beta	7	6
SCN5A	sodium channel, voltage-gated, type V, alpha subunit	666	403
SNTA1	syntrophin, alpha 1 (dystrophin-associated protein A1, 59kDa, acidic compon	9	9
	Total of 32 gene entries	**4424**	**2762**

International LQTS Registry and LQTS Molecular Genetics Laboratory at Rochester

International LQTS Registry

- Established by Dr. Moss in 1979.
- To date, 1206 proband-identified families have been enrolled.
- Global collaboration.



LQTS Molecular Genetics Laboratory

- Established in the Fall of 1999.
- > 3000 samples are collected and mutational analysis is performed.
- Many novel mutations have been identified.
- Platform for genotype-phenotype co-relationship studies, identification of new LQT genes and modifier genes.

HUMAN MUTATION Database in BRIEF 31: E1801-E1810 (2010) Online

DATABASE IN BRIEF

HUMAN MUTATION

OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY
www.hgvs.org

LQTS Gene LOVD Database

Tao Zhang[1,2*], Arthur Moss[3].*, Peikuan Cong[2],*, Min Pan [2].*, Bingxi Chang[4], Liangrong Zheng[5], Quan Fang[4], Wojciech Zareba[3], Jennifer Robinson[3], Changsong Lin[2], Zhongxiang Li[6], Junfang Wei[7], Qiang Zeng[8], Long QT International Registry Investigators, HVP-China Investigators, and Ming Qi[1,2,9**]

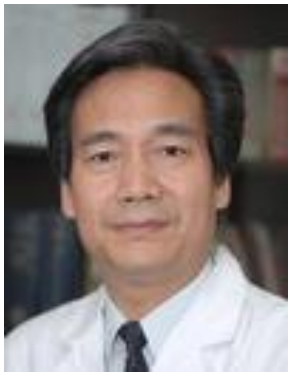
Novel LOVD Databases for Hereditary Breast Cancer and Colorectal Cancer Genes in the Chinese Population

Pan, et al, 2011 Human Mutation

InSiGHT-CHINA, Clinical Group

- Zhejiang University Med

Dr. M Chen



Dr. Youming Li

Dr. Shu Zheng

University Med
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Dr. Jian Dong

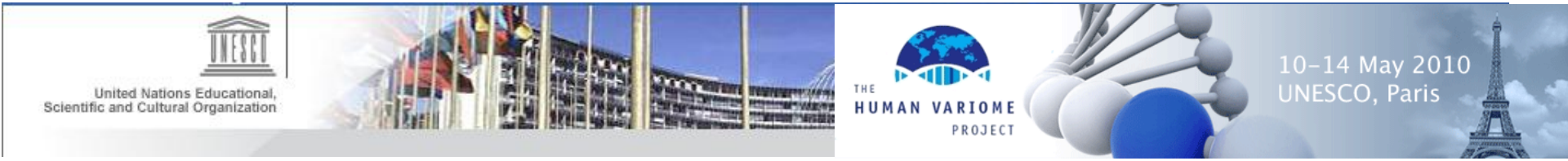
Drs. YL He and SR Cai

HVP – China Student Volunteer Club

Peikuan Cong

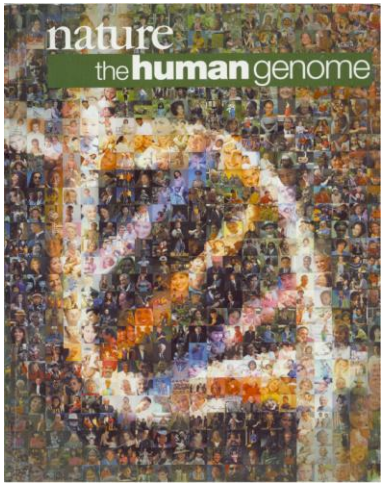
THE HUMAN VARIOME PROJECT

（HVP）2010-巴黎会议



HGP to HapMap to HVP

25-33%



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GENETICS

China Bets on the Variome to Uncover Hereditary Diseases

BEIJING—One in five people on the planet live in China, yet the prevalence of genetic diseases here is an enigma. Known cases of cystic fibrosis are rare, for example, but geneticists are unsure whether that's because Chinese are less susceptible or because the disease is underdiagnosed. Genetic testing services are woeful, with "no quality control and no standards," says Qi Ming, director of the Zhejiang University Center for Genetic & Genomic Medicine in Hangzhou.

China aims to change that with a 3 billion yuan ($470 million) contribution to the Human Variome Project, an international effort to catalog gene variations affecting human health (*Science*, 7 November 2008, p. 861). The commitment—the largest from any country and over a quarter of the target budget—was made official at a ceremony here last week set to the *Star Wars* theme song. The windfall is intended to jump-start China's genetic services as much as fund global health work.

Under the agreement, China plans to set up a domestic research network, or "node," overseen by Qi at Zhejiang University to gather data from hospitals and clinics. Internationally, China will provide support for 5000 to 8000 disease-specific databases. Sequencing of numerous samples will be done at Zhejiang University and BGI in Shenzhen, along with BGI branches in Copenhagen and Cambridge, Massachusetts.

The cash infusion is a boon for the Human Variome Project, which has been on shaky footing ever since it began in 2006. Progress "has been at a suboptimal rate," concedes the project's scientific director, Richard Cotton, a geneticist at the University of Melbourne. "The contribution of China will accelerate this activity considerably," he says. Since China signed on in January, the number of countries with established nodes has risen from five to 12.

Genomic duo. Qi Ming (*right*) heads up China's research on the Human Variome Project, launched in 2006 by scientific director Richard Cotton.

CREDITS: HUMAN VARIOME PROJECT (2)

Behind China's investment is a desire to become a powerhouse in genetic research. In the 1990s, the country supplied 1% of the Human Genome Project budget. It later chipped in 10% of funding for the International HapMap Project, an effort to log common genetic variations. The jump to 25% for the more extensive variome project better matches China's portion of the world population, officials say—and shows that it has become a "powerful country in science and technology," boasts Li Xitao, director of the Chinese node.

China's largesse also has a practical purpose: to build up genetic services and train professionals in an emerging field. "A major goal is translational medicine," Qi says. Global funding for cataloging genetic variations lags because many of the corresponding diseases are rare. In China, Qi says, geneticists face an additional barrier: Three ministries must approve new medical training programs. By signing on to the Human Variome Project, scientists will sidestep that bureaucratic obstacle.

Using that end run, China plans to establish genetic counseling programs at leading universities. Full master's degree programs will be bolstered by short-term training courses for specialists. Ultimately, Qi hopes that an army of trained clinicians will help geneticists unravel the cystic fibrosis mystery—as well as uncover novel variations in China's 56 ethnic groups.

That could be good news for doctors worldwide tasked with diagnosing—and eventually preventing via prenatal screening—genetic disorders in people of Chinese descent. With few clues to genetic variations common in certain ethnic groups, clinicians don't know where in the genome to start looking for culprits. "You're searching for a needle in a haystack," Cotton says. With China coming on board, the search should get easier.

–MARA HVISTENDAHL

nature genetics

NATURE GENETICS | ANALYSIS

Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene

EDITORIAL

nature genetics

Standards for clinical use of genetic variants

The price of DNA sequencing has never been lower. However, there is little consensus as to when the identification of a genetic variant is clinically useful. Clinical geneticists carrying out systematic community reviews of evidence for the pathogenicity of variants collected in locus-specific and disease-specific databases are beginning to bridge the gap between research evidence and rules used to make clinical decisions.

HVP GLOBAL HAEMOGLOBINOPATHIES INITIATIVE

Rapid Targeted Deep Sequencing for Molecular Screening and Clinical Genotyping in Subjects with Hemoglobinopathies

ICCAC Aug 5, 2014

Xiangming Xu Zhiyu Peng Ming Qi

Southern Medical University Shenzhen BGI Medical co., LTD.

Zhejiang University Zunyi Medical College

Hainan Medical University 303 Hospital of People's Liberation Army

Guangdong Women and Children Hospital

People's Hospital of Yunnan Province HVP-China

Look forward to your supports & collaborations!

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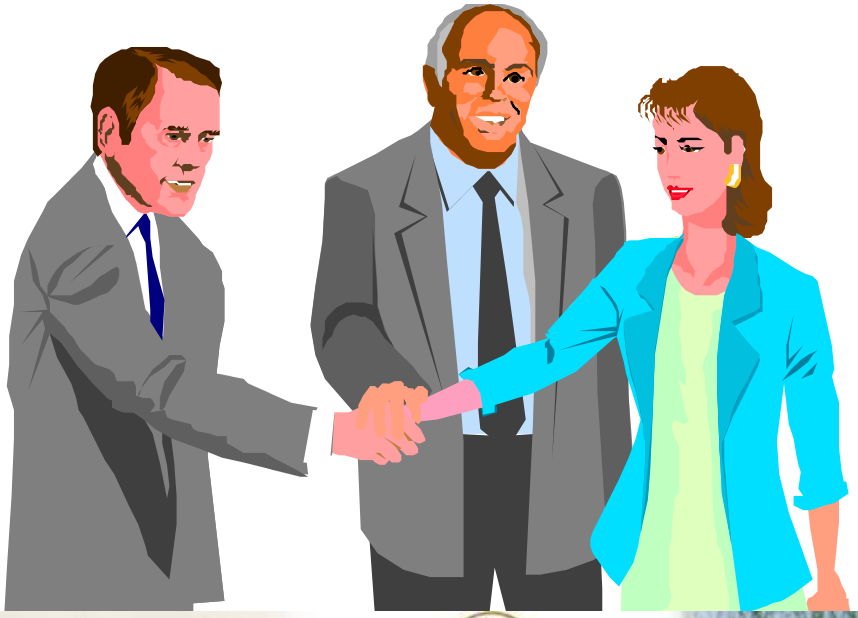
www.genomed.org/en



华大基因
BGI