Public Biobanks: Involvement of Children

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ESF-UB Conference in Biomedicine:
"*Biobanks: Introduction and Next Steps*"
Sant Feliu de Guixols, Spain
1-6 November 2008

Nature. 2003 (April 24);422:835-847

feature

A vision for the future of genomics research

- "a large longitudinal population-based cohort study, with collection of extensive clinical information and ongoing follow-up, would be profoundly valuable to the study of all common diseases"

- GWAS require participation of thousands of study participants.
- Control DNA samples are often acquired from public biobanks
- Biomedical research in the post-genomic area has become increasingly dependent on biobanks
- Should public biobanks collect and distribute DNA from children for studies on childhood diseases?
- Under what conditions / provisions?

NEWS OF THE WEEK

Science June 16, 2006

GENETICS

U.S. Hospital Launches Large Biobank of Children's DNA

The core population will be drawn "relatively randomly" from the hospital's 1 million patient base, says Hakonarson, a former CHOP staffer who recently returned from working at deCODE Genetics Inc., the Icelandic company that has paved the way for population biobanks

CHOP will spend $40 million over the next 3 years to analyze DNA from 100,000 CHILDREN and begin searching for links to childhood diseases such as asthma, diabetes, and obesity

…Ethical questions already swirl around existing biobanks, and the storage of children's DNA could raise new issues.

For example, whether to permit DNA to be used for unspecified future projects is "always more ethically sensitive" when decided by parents for their children.

10 Largest Children Biobanks

Name – start year	Current # participants	Target #
Norwegian Mother and Child Cohort (MoBa) -1999	200K	260K
Danish National Birth Cohort – 2005	160K	200K
National Children's Study (NIH, CDC, EPA; USA)	---	100K
Avon Study of Parents and Children (UK) - 1991	23K	23K
Northern Finland Birth Cohorts – 1966	22K	22K
All Babies in Southeast Sweden (ABIS) – 1997	16K	22K
Etude Longitudinale Française depuis l'Enfance (ELFE)	---	20K
Guangzhou Twin Project (China) – 1987	19K	19K
National Child Development Study (UK) -1958	17K	17K
Child and Adolescent Twin Study in Sweden	1K	15K

Children Biobanks

Example: Heart Centre Biobank - Canada

http://canwest.a.mms.mavenapps.net/mms/rt/1/site/canwest-globalontario-pub01-live/current/launch.html?maven_playerId=globalonallvideo&maven_referralObject=1074982

(show only the first two minutes)

Can we assure donors' privacy?

- Until recently the consensus was:
  "Anonymization assures donors' privacy"

- This consensus has been questioned for some time, and infringements of privacy have been documented..

- A recent NRG review claims that privacy of DNA donors cannot be truly assured – and presents the 'open consent' concept utilized by the Personal Genome Project

Lunshof JE, Chadwick R, Vorhaus DB, Church GM.
From genetic privacy to open consent.
Nat Rev Genet. 2008 May;9:406-411.

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From genetic privacy to open consent.
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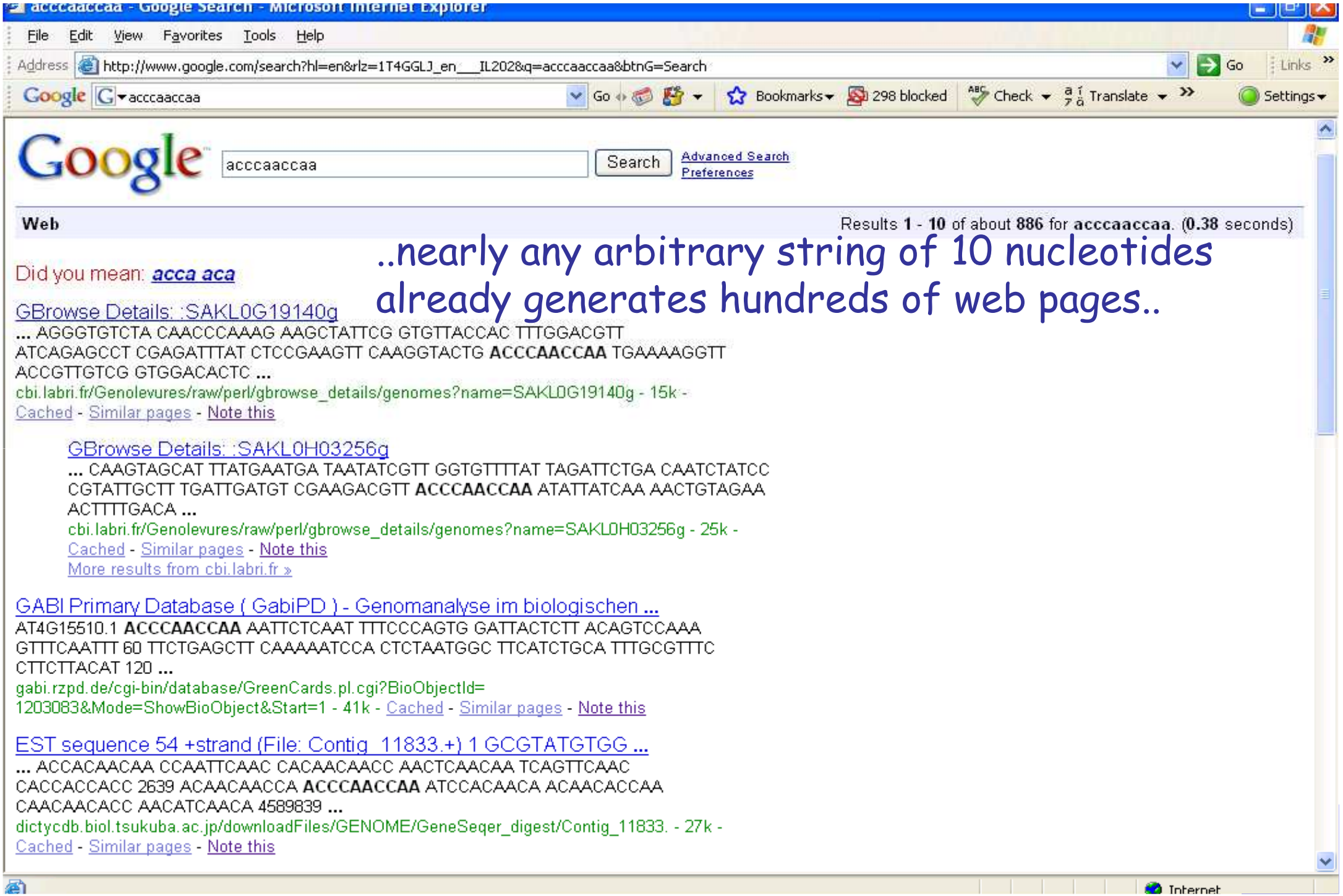
Threats to privacy and confidentiality:

- Re-identification after de-identification using publicly available data
- Combination of surnames, genotype and geographical information
- Any amount of DNA data in the public domain with a name allows for identification within any anonymized data set
- Identification by phenotype using imaging techniques for reconstruction of facial features
- Hacking into computer systems
- Theft or loss of laptop or data storage devices

Lunshof JE, Chadwick R, Vorhaus DB, Church GM.
From genetic privacy to open consent.
Nat Rev Genet. 2008 May;9:406-411.

Causes of disclosure of information content:

- Increased availability of aggregate data in public, private, and state controlled databases:
  - clinical biobanks and databases
  - population biobanks and databases
  - forensic biobanks and databases
  - biometric databases (e.g. US Immigration; on-going legislation in Israel)
- Data sharing and secondary use of data
- Developments in technology and medical informatics
- Information technology accidents
- Increased ease of finding data with web-based search engines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OPEN ACCESS Freely available online August 2008 PLoS GENETICS

Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays

Nils Homer[1,2], Szabolcs Szelinger[1], Margot Redman[1], David Duggan[1], Waibhav Tembe[1], Jill Muehling[1], John V. Pearson[1], Dietrich A. Stephan[1], Stanley F. Nelson[2], David W. Craig[1]*

1 Translational Genomics Research Institute (TGen), Phoenix, Arizona, United States of America, **2** University of California Los Angeles, Los Angeles, California, United States of America

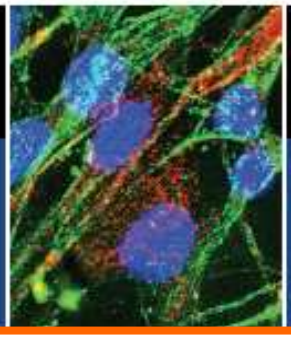
Abstract

We use high-density single nucleotide polymorphism (SNP) genotyping microarrays to demonstrate the ability to accurately and robustly determine whether individuals are in a complex genomic DNA mixture. We first develop a theoretical framework for detecting an individual's presence within a mixture, then show, through simulations, the limits associated with our method, and finally demonstrate experimentally the identification of the presence of genomic DNA of specific individuals within a series of highly complex genomic mixtures, including mixtures where an individual contributes less than 0.1% of the total genomic DNA. These findings shift the perceived utility of SNPs for identifying individual trace contributors within a forensics mixture, and suggest future research efforts into assessing the viability of previously sub-optimal DNA sources due to sample contamination. These findings also suggest that composite statistics across cohorts, such as allele frequency or genotype counts, do not mask identity within genome-wide association studies. The implications of these findings are discussed.

Jennifer Couzin J, *Science*, September 7, 2008

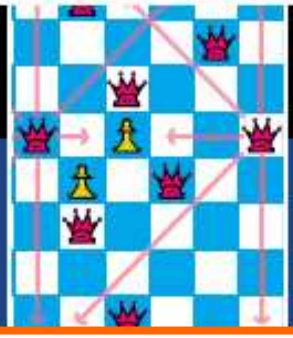
NEWS>>

THIS WEEK



The genetics of two aggressive cancers

1280



MathFest: By the numbers

1282

Last week, scientists learned that a type of genetic data that is widely shared and often posted online can be traced back to individuals who proffered up their DNA for research.

The revelation, in a paper published in *PLoS Genetics*, prompted the NIH in Bethesda, Maryland, and the Wellcome Trust in the United Kingdom to strip some genetic data from their publicly accessible Web sites, and NIH to recommend that other institutions do the same.

researchers pool genetic data from hundreds of people to look for broad patterns of genetic inheritance. Because the pool

biggest chance of error comes from false posi-

about 1000 people all told, says James Ostell, who oversees that and other NIH databases.

NIH officials are informing geneticists

What about forensic DNA collections?

..This is beyond the scope of the current discussion, but note this:

GSP online Genomics, Society and Policy
2006, Vol.2, No.1, pp.41–56.

Bar-coded children: an exploration of issues around the inclusion of children on the England and Wales National DNA database

MAIRI LEVITT & FLORIS TOMASINI

The National Police DNA database in England and Wales has been steadily growing and is the biggest in Europe with over 3 million samples.

There are at least 750,000 juveniles age 10-17 included (230,000 were added in 2004-05)

Under the current law in England and Wales, DNA samples can be taken from anyone arrested in connection with a recordable offence, without their consent.

These samples are kept permanently and the DNA profiles and some personal data are entered on the National DNA database even if the person is never charged or is subsequently acquitted of the offence.

OECD Draft Guidelines for Human Biobanks and Genetic Research Databases (April 2008)

The OECD is inviting comments on the draft *Guidelines for Human Biobanks and Genetic Research Databases*. The deadline for submitting comments is **16th May 2008**.

Comments may be provided via email at: hbgrd.guidelines@oecd.org Comments may also be provided directly through our Web Site at: www.oecd.org/sti/biotechnology/hbgrd

This version of the draft Guidelines is being released to elicit public comments. This is not a final version of the draft Guidelines.

CONSENT: In the event that the OECD will publish the responses received, please indicate clearly whether or not you wish to have your comments rendered public, including associated with your name or your organisation's name. In the event that consent is not clearly expressed, it will be presumed to not have been given.

OECD

OECD Draft Guidelines for Human Biobanks and Genetic Research Databases

4.6 HBGRDs involving child participants should have a clear policy on whether, when and how a child's assent will be obtained.

4.7 HBGRDs involving child participants should have a clear policy on what steps, if any, will be taken once the child becomes legally competent to consent.

38. Particular care will need to be given to respecting the individual privacy of each participant where children have been recruited into family studies.

Inclusion of children in biobanks?

- Adults may elect to be "*health altruists*" and consent to donating tissues or DNA to biobanks, taking the privacy risk

Kohane IS, Altman RB. Health-information altruists--a potentially critical resource. *NEJM* 2005;353:2074-2077.

The following are my personal views – there are no simple solutions, and public consultation is needed:

- We should not allow children to be "health altruists"
- Thus, we should not allow parents to expose their children to future privacy risks

- Guidelines for children's biobanks may need to be modified, while allowing space for extra circumstances (harmonized for the EU, the OECD, and ideally globally)

Inclusion of children in biobanks? (2)

The following are my personal views – there are no simple solutions, and public consultation is needed:

By default, DNA samples from children may be allowed in public biobanks only when there are no alternatives:

- Childhood diseases or other conditions when the child is unlikely to become *a mentally competent, consenting adult*

- Expected societal benefits (e.g. saving lives) are deemed *far larger* than privacy risks for the child
  (to be decided case-by-case by the relevant IRB)

Inclusion of children in biobanks? (3)

For all other situations, one of the following scenarios (or their combinations) may be an option - - depending on the biobank structure and mode of operation:

1. Collecting DNA samples and tissues ONLY from adults

Note: family sets may still be collected – children in such sets may be >18

2. Collecting phenotypic data – while waiting for the child to be 18 for collecting DNA (phenotypic data *e.g.* MRI may not be available later)

3. Collecting children's DNA samples but NOT distributing them until the donor is 18 y – when s/he is re-contacted for consent (minimizing collection costs)

4. Collecting children DNA samples only for specified projects (never with 'blanket consent') and taking extra measures against data sharing (sharing only aggregated data)

Inclusion of children in biobanks is discussed in recent manuscripts:

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 148C:31–39 (2008)

ARTICLE

Ethical Implications of Including Children in a Large Biobank for Genetic-Epidemiologic Research: A Qualitative Study of Public Opinion

DAVID KAUFMAN,* GAIL GELLER, LISA LEROY, JULI MURPHY, JOAN SCOTT, AND KATHY HUDSON

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 148C:40–46 (2008)

ARTICLE

Ethical Issues Raised by Incorporation of Genetics Into the National Birth Defects Prevention Study

MARY M. JENKINS,* SONJA A. RASMUSSEN, CYNTHIA A. MOORE, AND MARGARET A. HONEIN

GenEditorial

GenEdit (2008) 6:3, 1-8

…there is a need to elaborate guidelines specific to biobanks and longitudinal studies involving children

…recommendations regarding parental authorization, the child's assent and consent, and on the return of results in this context.

BIOBANKS AND LONGITUDINAL STUDIES: WHERE ARE THE CHILDREN?

Julie Samuël[1], Nola M. Ries[2], David Malkin[3] and Bartha Maria Knoppers[4]

The inclusion of children in longitudinal research using biobanks raises specific ethical and legal issues. This article analyzes ethical frameworks concerning participation in biobanks and suggests that such frameworks, developed in the context of competent adults as research subjects, are not adapted for research involving children. It concludes that there is a need to elaborate guidelines specific to biobanks and longitudinal studies involving children and provides recommendations regarding parental authorization, the child's assent and consent, and on the return of results in this context.

Israel is Ethnically Diverse

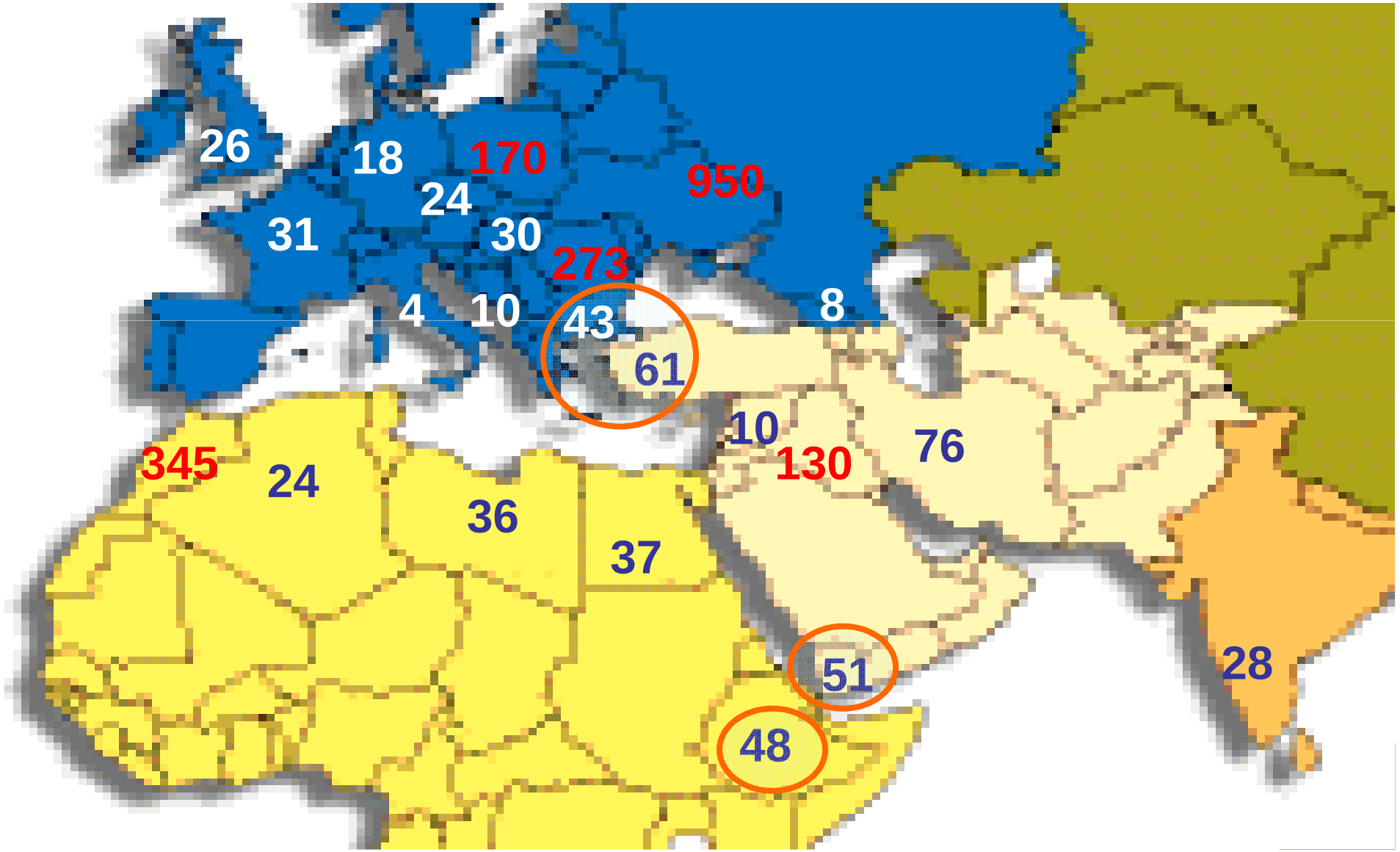
TEL AVIV UNIVERSITY אוניברסיטת תל-אביב

National Laboratory for the Genetics of Israeli Populations

Welcome to the *National Laboratory for the Genetics of Israeli Populations.*

The *National Laboratory for the Genetics of Israeli Populations* was initiated in 1994 by the *Israel Academy of Sciences and Humanities*. It is located at the *Sackler Faculty of Medicine*, on the *Tel-Aviv University* campus. The laboratory is a national repository for human cell lines, representing the unique and large ethnic variation of the Israeli populations. We concentrate on collecting and establishing human cell lines representing the various ethnic groups in *Israel*. We also collect cell lines from individuals and families affected by genetic disorders unique to Israeli populations.

Immigration to Israel: 1948 - 1998 (in thousands; 2008 population: 7.2 M)



http://nlgip.tau.ac.il

"All donors are adult Israeli citizens (over 18 years old) and have given written informed consent for the study of their genetic material (DNA or cells) for biomedical research"

DNA Samples and Cell Line Catalog

(A matching cell line is available for each DNA sample)

Ethnic Group	Number of unrelated donors
Jewish	
· Ashkenazi (Central European ancestry)	466
· Ethiopian	72
· Georgian	24
· Iranian	76
· Iraqi	103
· Kuchin (India)	85
· Libyan	89
· Moroccan	150
· Sephardi (Turkey & Bulgaria)	166
· Tunisian	29
· Yemenite	159
Bedouin	58
Druze	79
Palestinian	117

CYP2D6

- Metabolizes ~25% of current drugs
- One of the most studied human genes (>3600 PubMed studies – since 1967)

- Relatively common "poor metabolizers":

- Europeans 5% – 10%
- Africans 2% – 19%
- East Asians ~1 – 2%

Relatively common "ultra-fast metabolizers" (>2 gene copies):

- Europeans 2% – 8%
- Ethiopians 17%

Table II. Genotype frequencies for the cytochrome P450 genes *CYP2C19* and *CYP2D6* in Israeli ethnic groups[a]

Genotype	Predicted phenotype	Yemenite Jews [% (95% CI)]	Sephardic Jews [% (95% CI)]	Ethiopian Jews [% (95% CI)]	Bedouins [% (95% CI)]
*CYP2D6**4/*4	PM	0	8.5 (0.5, 16.5)	0	2.0 (0, 5.9)
*CYP2D6**1/*2xN[b]	UM	5.3 (0, 13.1)	6.4 (0, 13.4)	10.7 (0, 22.1)	4.0 (0, 9.4)
*CYP2D6**2/*2xN[b]	UM	0	6.4 (0, 13.4)	7.1 (0, 16.6)	0

CYP2D6 "poor metabolizers" (PM) are at greater ADR risk from drugs metabolized by CYP2D6 (higher than normal blood levels)

Examples: risperidone; propranolol

CYP2D6 "ultra-fast metabolizers" (UM; extra gene copies) are at greater ADR risk from pro-drugs metabolized by CYP2D6

Example: Codeine → Morphine

Sephardic Jews are more likely to have ADRs from drugs metabolized by CYP2D6:

8.5% are CYP2D6 PM and 12.8% are UM

http://alert-project.org/

http://alert-project.org/
The ALERT project (2008-2012)

- Data-mining from ~30 million electronic health records (EHR) from Denmark, Italy, Netherlands and the UK
- Aims:
  - discover new adverse drug reactions (ADRs) by EHR data-mining
  - suggest biomarkers for avoiding ADRs

- Children are included in some of the participating databases

- No genetic information is included in the EHR databases

- We believe that in this study the inclusion of personal health records from children is highly justified

2006 CDC Study (two-years survey)

ADRs were directly implicated in **6.7%** of emergency department visits leading to hospitalization
(~1 in 15 hospitalized patients!)

Children below 4 years: ADRs accounted for 14.7% of emergency department visits leading to hospitalization
(~1 in 6 hospitalized children!)

- **Women 8.1% vs. men 5.4%**

- Leading drugs causing ADRs: Warfarin; Acetaminophen; Aspirin; Ibuproen; Clopidogrel; Phenytoin.

Budnitz *et al* (2006) National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 296:1858-1866.

For reprint orders, please contact:
reprints@futuremedicine.com

Pharmacogenomics 2007; 8:311-314

EDITORIAL

Primum non nocere: adverse drug events must be taken seriously

Table 1. Drugs implicated in ADEs in US emergency departments.

Drug	% of all ADEs*	ADE-relevant genes
Warfarin	5.2	*CYP2C9*; *VKORC1*
Acetaminophen‡	5.0	*CYP2E1*; *GST-M1*
Aspirin	2.5	*COX-1*; *GPVI*
Ibuprofen	2.1	*CYP2C8*; *CYP2C9*
Clopidogrel	1.6	*CYP3A5*; *CYP2C19*
Phenytoin	1.1	*CYP2C9*; *CYP2C19*; *MDR1*
Metformin	1	*CYP2C11*; *CYP2D1*
Azathioprine§	<1	*TPMT*; *GST-M1*
Methotrexate§	<1	*MTHFR*; *MRD1*
5-fluorouracil§	<1	*DPD*
Risperidone§	<1	*CYP2D6*

According to the CDC report [1] and relevant polymorphic genes whose testing can potentially lower their ADE rates.

**Each percentage point represents an estimated 7000 annual emergency department visits according to the CDC report.*

‡In various combinations.

§Drugs that contribute <1% each of all ADEs leading to emergency department visits were not listed in the CDC report.

Tel-Aviv University

Gregory Livshits, Head, The Yoran Institute for Human Genome Research
Orit Kimchi, Michal Bar-Chen, Yael Ovadia, Eli Bar, Merav Kaplan,
Lior Ben-Artzi, Nava Levit, Meytal Shahar, Nibal Mahajna
Galit Levi, Tal Barkan, Rinat Rimon-Vardi

USA

Yvone Wan, University of Kansas Medical Center (CYP2D6; CYP2C19)
Howard McLeod, University of North Carolina (PGENI)

ALERT PROJECT

Johan van der Lei, Erasmus University, Netherlands (project coordinator)
and >50 consortium members ☺

Special thanks:

Jeantine Lunshof, Social Sciences, Maastricht University, Netherlands
Isabel Fortier, P3G Observatory, Canada
Ellen Clayton, Center for Biomedical Ethics and Society, Vanderbilt University, TN, USA

Slides & manuscripts:

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