

ولقد عرفت ان غشاها بقدر ما باليونانية ايقين بقوتها في الملتصق من اربها
 غشاها في حول الطبقة القرنيه ولا يغشها كما يغشها بالاطراف الطبقات بعضها
 بعضها بعضا لانه لو غشاه كله لمنع البصر من ان يتفقد ه ه
 وهي على هذا المثال



والامبتدى بالاختبار عن منافع كل واحد من الرطوبات والطبقات التي وصفنا مع
 ابتدا اثباتها وكونها ومنتهاتها ومواضعها وقد كتبت تقدمت في اخبارك
 ان الرطوبة الجليديه في وسط العين وان خلفها رطوبة واحده وثلاث طبقات
 وقدمها رطوبة واحده وثلاث طبقات ه فنبتدى بعون الله بالاختبار
عن منفعه الرطوبة التي خلف الجليديه وهي الزجاجيه وعن الثلث
 طبقات التي ذكرنا خلفها فنقول ان كل عضو من اعضاء البدن لا بد له من عند

Towards implementing personalized genomic medicine in the Gulf States



Fahd Al-Mulla B.Sc., M.B.Ch.B., Ph.D. PCTM, FRCP

Professor of Molecular Pathology at Kuwait University

Director of Genomic Medicine Center “GENATAK”

“جيناتاك” Global Med Clinic

My talk



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- Introduce Kuwait and health service
- Kuwait-specific public sector challenges
- Brief History of our work and capabilities
- The private sector model
- Why Genome Arabia?

Kuwait



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Area:
Total: 17,820 sq km
Population:
Total: 3,442,945
Kuwaiti nationals: 1,102,485
Non-nationals : 2,340,460
(Public Authority of Civil Information, 2009)

6-Governorates

Public and Private Hospitals

Centralized specialized Free Health Service:

- Kuwait Cancer Control Center
- Kuwait Medical Genetics Center/maternity

One public many private Universities

Research and funding



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Kuwait University
Office of the Vice President for Research
Research Sector

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Research Sector
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Research Sector

The Research Sector (RS), one of the integral components of Office of the Vice President for Research (OVPR), was established in the year 1979 to promote Kuwait University's scientific and technological concerns, and lay the foundation for developing scientific research as a fundamental institutional obligation, alongside academics. The purpose is to empower future generations with higher education and scientific knowledge, to meet national needs and priorities.

RS promotes, supports and sustains faculty initiatives in basic, applied and humanities research. The office encourages creativity, renders support, and provides a congenial climate for the pursuit of projects through scientific innovation that transpire discovery and lead to distinction. These elements are central to RS's mission of promoting R & D activity at KU, and spearheading faculties initiatives towards ventures of global dimensions, generating new knowledge of profound scientific, social and human value. Embedded within this brief is the broad vision of RS, critical elements of which are outlined here.

Research Rewards Winners

- Research Winners

Video

- How to use Intellectual Property to be a successful Innovator
- Nuclear Energy Seminar
- Science Faculty Research General Facilities (GF)

Scientific Publications

- KU Publications in Refereed Journals

Research Database Links

- ISI Web of Knowledge

Events
<< January 2014 >>

- Research Administration office
 - Funding
 - Sets priorities
 - Outside Peer Reviews
 - Research records
 - Research Core Facilities
 - Patent and IP office
 - Focused on clinical research

Research and External funding



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<http://kfas.org/index.html>



8:32:12
Sunday 5 January, 2014
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Research Directorate
Accepting
**RESEARCH
PROPOSALS**
NOW

November, 2013
KFAS announces its FIRST CALL
FOR RESEARCH PROPOSALS for
Cycle I (November 12th 2013 -
1st review 14th 2014)



- Kuwait Foundation for the Advancement of Sciences. Directed Dr. Adnan Shihab Eldin
 - 1% of profit from local businesses
 - Research, programs and educational-based funding
- Kuwait institute for Scientific research another source of research Funding

Research funding a priority?



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nature International weekly journal of science

Journal home > Archive > Table of contents

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- News and Views
- Brief Communications
- Brief Communications Arising
- Letters
- Naturejobs
- Futures

Also this week

- Nature 2006 issue on Islam and Science
- Most Gulf states spend 0.1-1% of GDP towards research and development
- Better trends now with Qatar 5% and Saudi Arabia matching this and more
- Kuwait-Bahrain-UAE-Oman remain on low spending side

OIL RICH, SCIENCE POOR

The wealthy Arab states offer scant support for science and technology.

Jim Giles finds out whether this indifference to research is likely to change.

When *Nature* surveyed the prospects for science in the Arab world in 2002, our reporter picked out three subjects in which the region excelled¹. One was, and still is, important: desalination technologies to combat water shortages. But the other two highlight the region's threadbare research record. Camel reproduction and falconry research might excite Arab sports enthusiasts, but they are unlikely to set the scientific world on fire.

The monarchies of the Gulf are the richest of all Muslim nations, but little of that wealth is spent on research. Saudi Arabia, Qatar and Kuwait spend about 0.2% of their gross domestic product (GDP) on science — less than one-tenth of the developed-country average of 2.3% and about a third of that spent by less wealthy Iran. The oil monarchs have the



Research barriers



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TheScientist
MAGAZINE OF THE LIFE SCIENCES

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March 2011 » Critic At Large

Another Revolution Needed?

Counting the many plagues that threaten research in the Middle East and North Africa region

By Fahd Al-Mulla | March 1, 2011

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NASA

Scientists around the world face obstacles during their research—a rejected manuscript, a failed funding application, an illegible electrophoresis gel. But these annoyances are simply par for the course when doing science. In the Middle East, however, scientists are up against much steeper challenges—a lesson I learned all too well when I finished my PhD and postdoc at the University of Glasgow in the United Kingdom and returned to my native Kuwait.

In Glasgow, research was facilitated and encouraged. We had several well-trained technicians, up-to-

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4. Suspected Effects of Vitamin D
5. Immune Role in Brain Disorder?

Current Issue



- Very difficult research environment
- Delayed tenders/ethical approvals....
- Please read our cry for help in theScientist

<http://www.the-scientist.com/?articles.view/articleNo/29545/title/Another-Revolution-Needed-/>

Convincing the Policymakers



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- Since 2008-2012
- Demonstrate the effectiveness of GM for theranostics
- Focus on Cost effectiveness?

Cost effective?

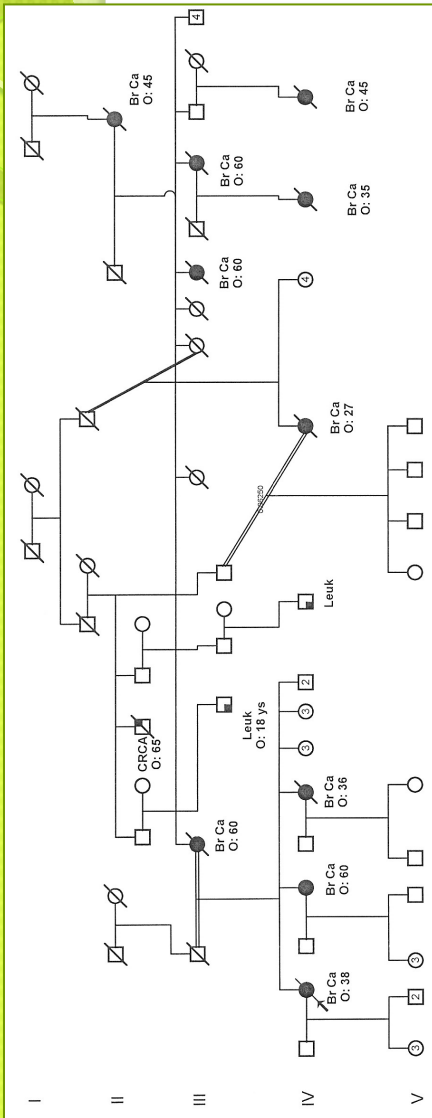


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- Unknown
- Current business model is flawed
 - Benefit can be Lifelong
 - Involves additional modalities
- **James M Crawford** *Personalized Medicine*
(2012) 9(3), 265–286

Cost effective?



- Makes sense at individual/family level
- Current cost to treat generation IV (M-USD)
- Personalized medicine potentially reduces cost (K-USD)

Cost effective? Priceless!



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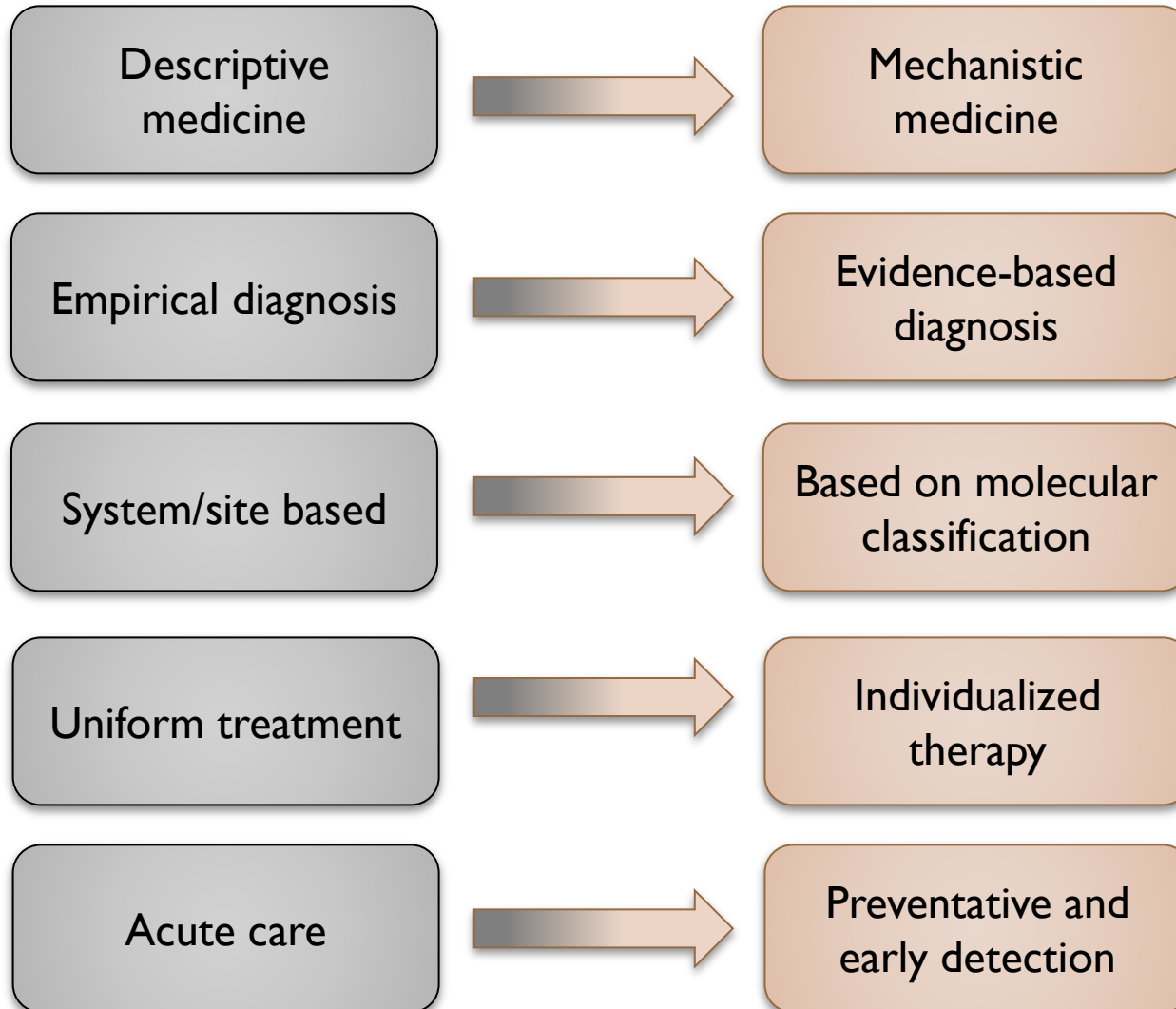


- Ashlyn Blocker
- Channelopathy-associated Insensitivity to Pain (CIP)
- Voltage-gated sodium channel $Na_v1.7$ (*SCN9A*) gene truncating mutation
- IP value of blocking pain through $Na_v1.7$

GM: shifting the paradigm



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Nat Genet. 2010 January ; 42(1): 30–35. doi:10.1038/ng.499.

Exome sequencing identifies the cause of a Mendelian disorder

Sarah B. Ng^{1,*}, Kati J. Buckingham^{2,*}, Choli Lee¹, Abigail W. Bigham², Holly K. Tabor², Karin M. Dent³, Chad D. Huff⁴, Paul T. Shannon⁵, Ethylin Wang Jabs^{6,7}, Deborah A. Nickerson¹, Jay Shendure^{1,†}, and Michael J. Bamshad^{1,2,8,†}

¹Department of Genome Sciences, University of Washington, Seattle, Washington, USA

²Department of Pediatrics, University of Washington, Seattle, Washington, USA ³Department of Pediatrics, University of Utah, Salt Lake City, Utah, USA ⁴Department of Human Genetics, University of Utah, Salt Lake City, Utah, USA ⁵Institute of Systems Biology, Seattle WA, USA

⁶Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, New York, USA ⁷Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland ⁸Seattle Children's Hospital, Seattle, Washington, USA

Abstract

We demonstrate the first successful application of exome sequencing to discover the gene for a rare, Mendelian disorder of unknown cause, Miller syndrome (OMIM #263750). For four affected individuals in three independent kindreds, we captured and sequenced coding regions to a mean coverage of 40X, and sufficient depth to call variants at ~97% of each targeted exome. Filtering against public SNP databases and a small number of HapMap exomes for genes with two novel variants in each of the four cases identified a single candidate gene, *DHODH*, which encodes a key

- Exome sequencing does not require a priori knowledge of gene(s) responsible for a disorder
- Sikkema-Raddatz et al., demonstrated that targeted **NGS** of a disease **specific subset of genes is equal to the quality of Sanger sequencing** and it can therefore be reliably implemented as a stand-alone diagnostic test.

Genomic medicine: What has changed?



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Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Yaping Yang, Ph.D., Donna M. Muzny, M.Sc., Jeffrey G. Reid, Ph.D.,
Matthew N. Bainbridge, Ph.D., Alecia Willis, Ph.D., Patricia A. Ward, M.S.,
Alicia Braxton, M.S., Joke Beuten, Ph.D., Fan Xia, Ph.D., Zhiyv Niu, Ph.D.,
Matthew Hardison, Ph.D., Richard Person, Ph.D., Mir Reza Bekheirnia, M.D.,
Magalie S. Leduc, Ph.D., Amelia Kirby, M.D., Peter Pham, M.Sc., Jennifer Scull, Ph.D.,
Min Wang, Ph.D., Yan Ding, M.D., Sharon E. Plon, M.D., Ph.D.,
James R. Lupski, M.D., Ph.D., Arthur L. Beaudet, M.D.,
Richard A. Gibbs, Ph.D., and Christine M. Eng, M.D.

ABSTRACT

BACKGROUND

Whole-exome sequencing is a diagnostic approach for the identification of molecular defects in patients with suspected genetic disorders.

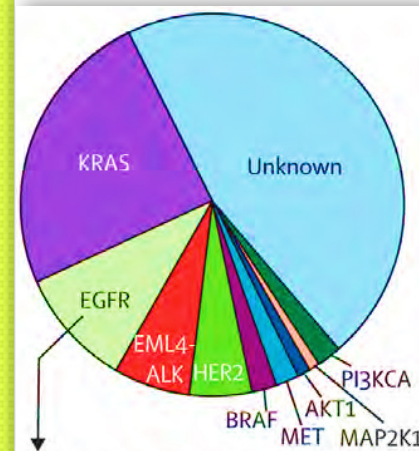
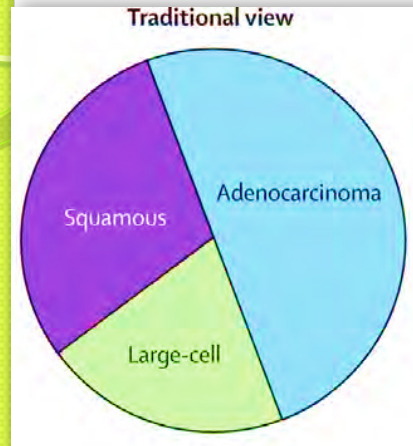
METHODS

We developed technical, bioinformatic, interpretive, and validation pipelines for whole-exome sequencing in a certified clinical laboratory to identify sequence variants underlying disease phenotypes in patients.

RESULTS

We present data on the first 250 probands for whom referring physicians ordered whole-exome sequencing. Patients presented with a range of phenotypes suggesting potential genetic causes. Approximately 80% were children with neurologic phenotypes. Insurance coverage was similar to that for established genetic tests. We

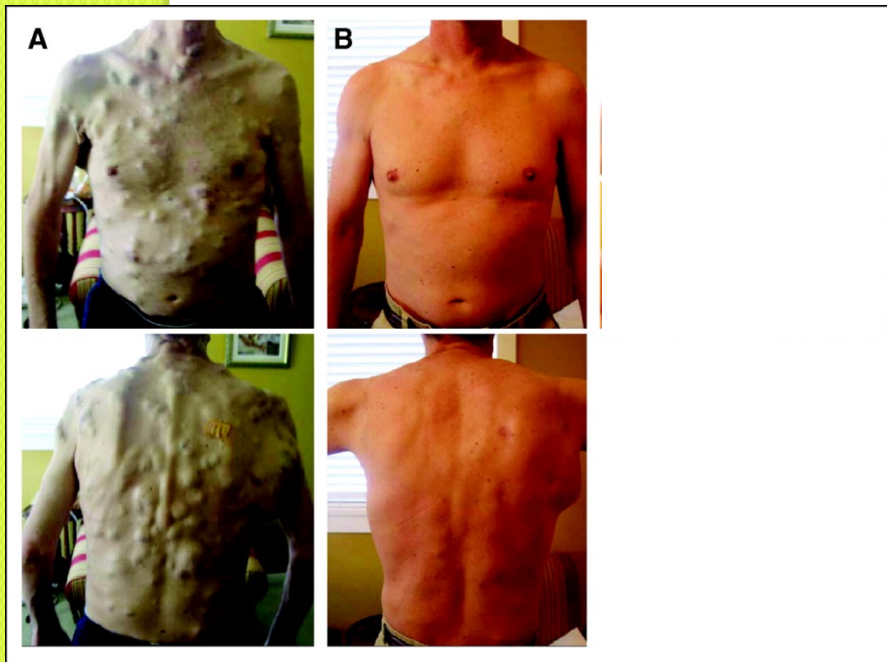
- 62 of the 250 patients (neurological phenotype, unknown syndromes), achieving a **25% molecular diagnostic rate** .
- Much higher than Sanger sequencing and microarrays



HOW HAS THIS CHANGED MEDICAL PRACTICE?

- **Mutations associated with drug sensitivity:**
 - **EGFR Gly719X, exon 19 deletion, Lue858Arg, Leu861Gln**
- **Mutations associated with primary drug resistance:**
 - **EGFR exon 20 insertions**
- **Mutations associated with acquired drug resistance:**
 - **EGFR Thr790Met, Asp761Tyr, Leu747Ser, Thr854Ala**
- **Targeted exome approach**

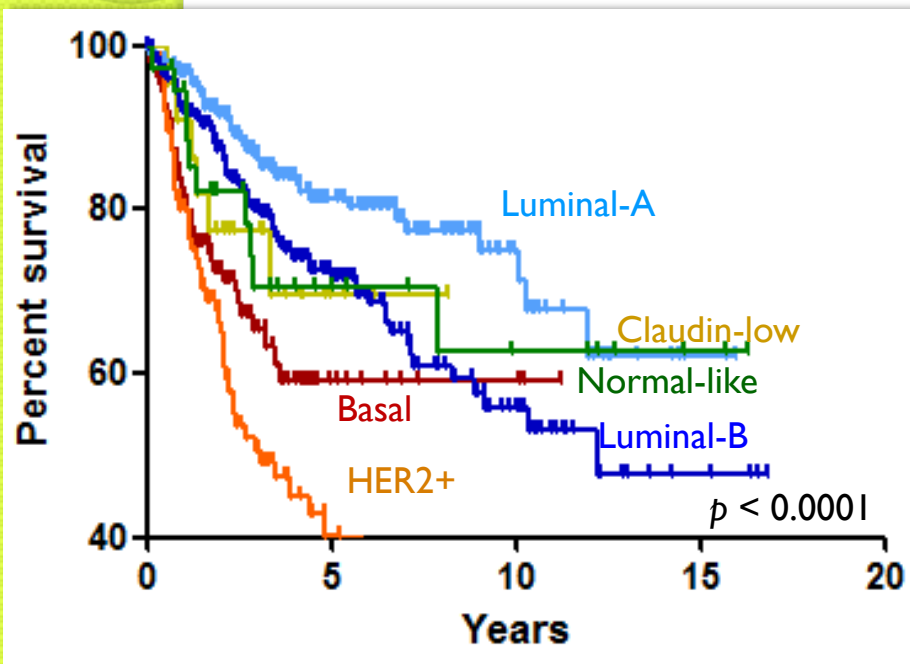
Melanoma



- **38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits.**
- A) before initiation of PLX4032 Vemurafenib
- B) 15 weeks of therapy with PLX4032
-
-



Breast Cancer in Kuwait: Subtyping of breast cancer

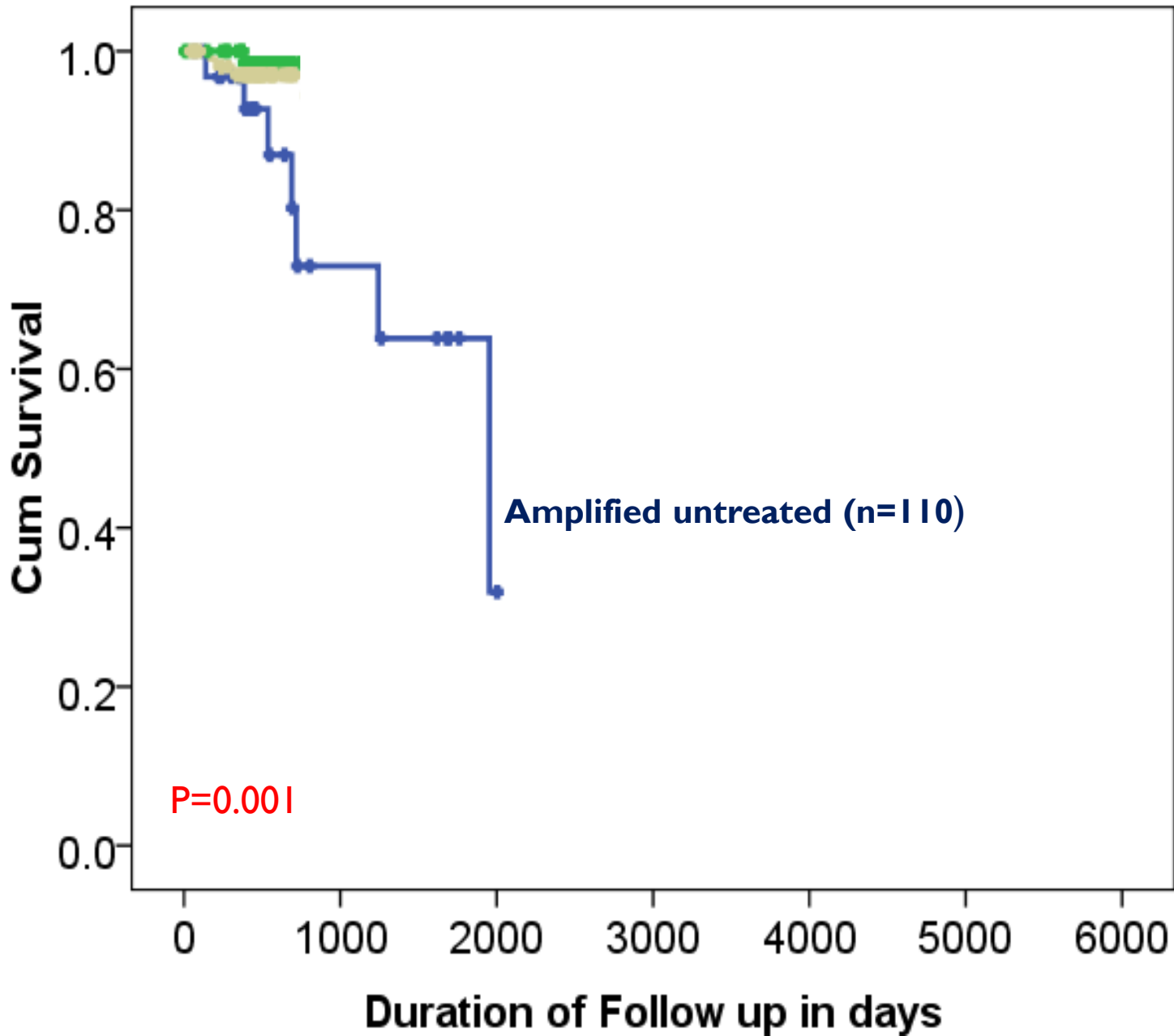


Prognostic breast cancer indices

Subtyping of Breast cancer

- MamaPrint
- Oncotype
- PAM50
- Nottingham index pro

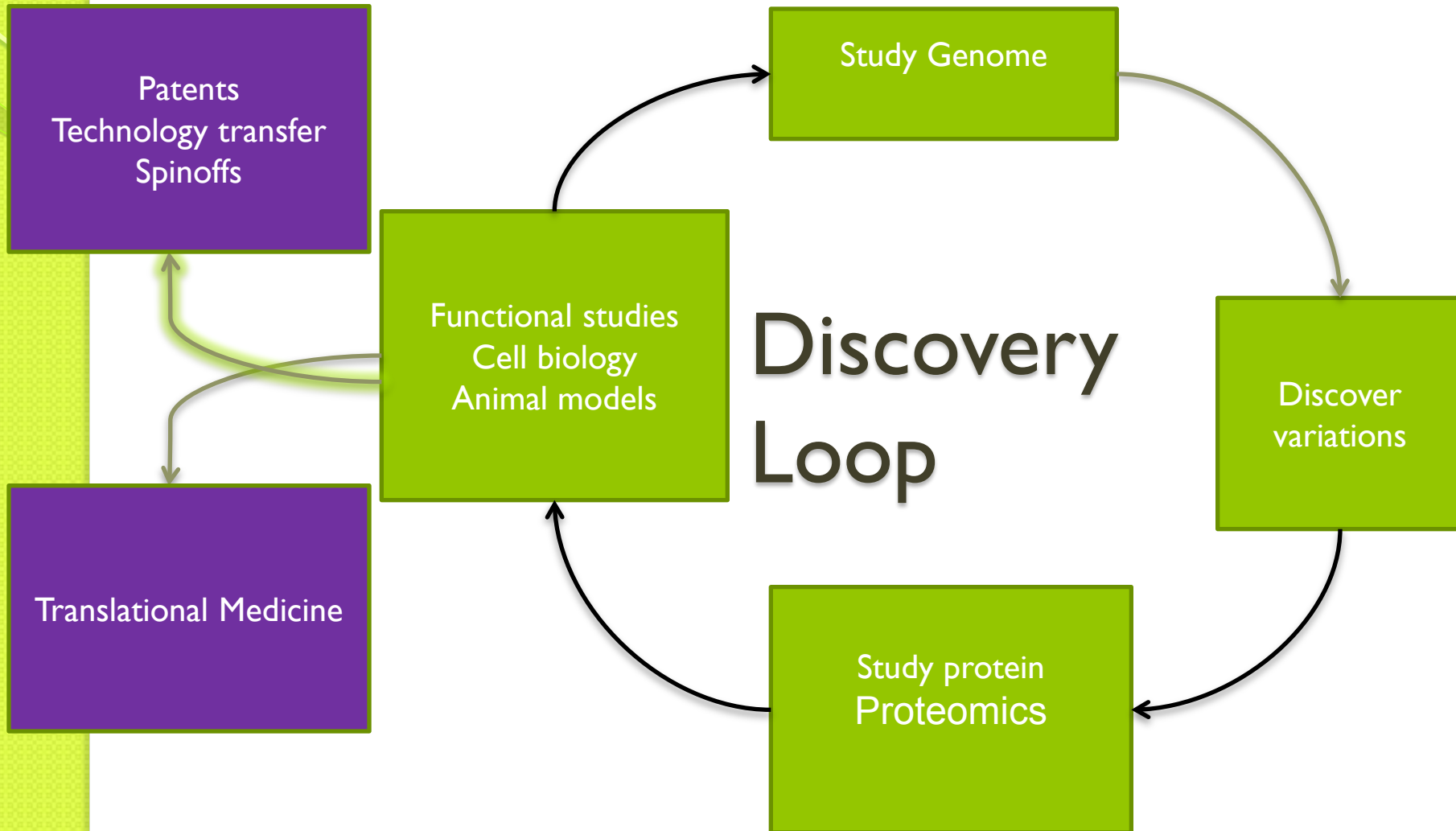
- Kuwait RKIP-based index
2333 cases



Molecular Pathology (al-mulla.org)



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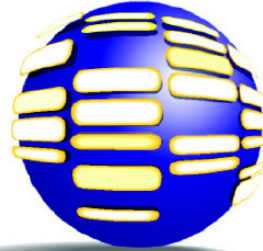


Molecular Pathology (al-mulla.org)



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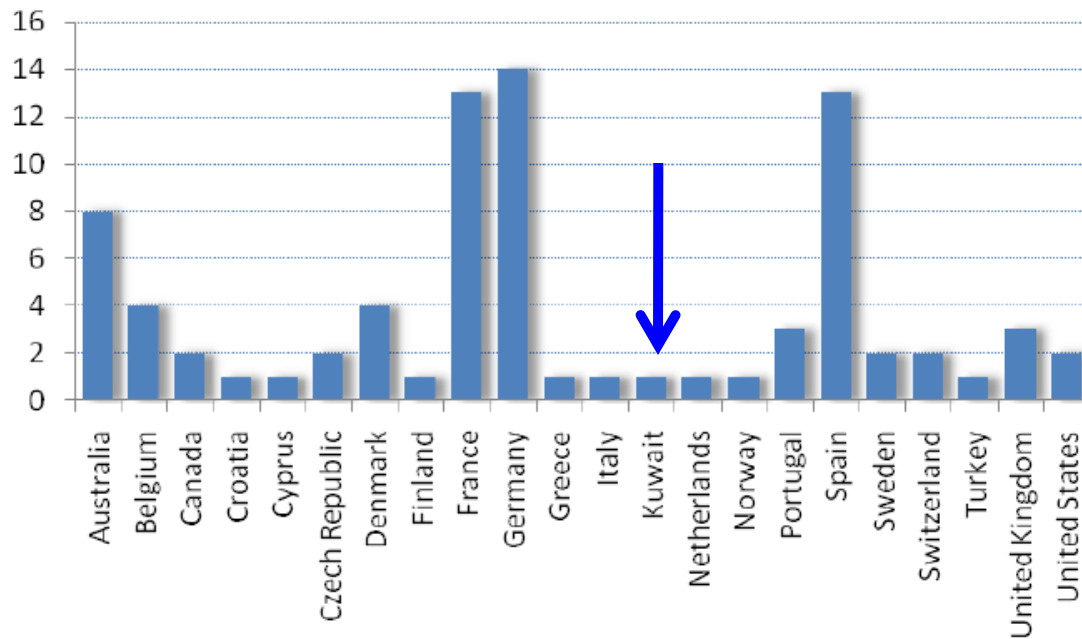
EMQN



The European Molecular Genetics Quality Network



United Kingdom National External Quality Assessment Service



Top-to-bottom model



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- No major reaction from policymakers
- Not reaching-out to the people/families
- Few doctors/specialists understood our GM initiative
- No mechanism payment between hospitals and University
- Health equity

GM and the private sector



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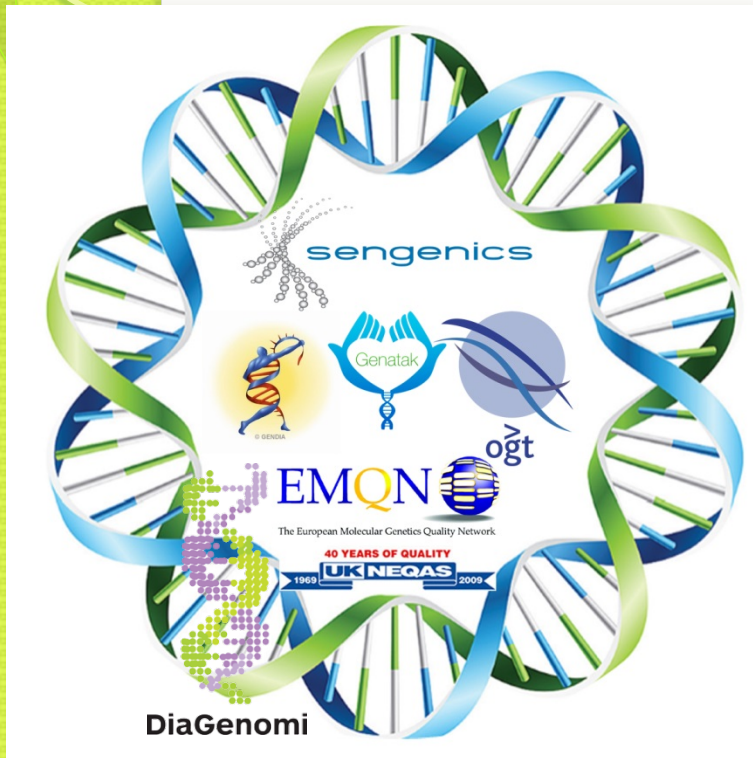


- Bottom-to-top
- Reach the people who need it directly
- Limited bureaucracy
- Genatak (Arabic for your genes)
- Global Med Clinic houses major specialties: Primary care, cardiology, pediatrics,....under the license of Dr. Jamal Al-Ghanim...and now personalized genomic medicine to serve all

Genatak Laboratory Network



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- Genatak is part of a large world-wide network of laboratories that collectively offer highly specialized 2000 genetic tests
- Access to 11 NGS instruments
- The network laboratories are accredited by various agencies like CPA, CAP and CLIA and follow stringent quality assurance programs.
- The laboratory network offers genetic counseling services

What do we do?



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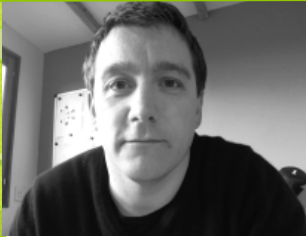


1. **Genetic Disorders and Counseling**
 - a) Postnatal Diagnose of more than 2000 genetic diseases
 - b) Premarietal test for 108 recessive disorders
 - c) Prenatal diagnosis from maternal blood
 - d) Preimplantation genetic screen (PGS)
 - e) Preimplantation genetic diagnosis (PGD)
2. **Personalized Genomic Health**
 - a) Personalized cancer treatment
 - b) Pharmacogenomics
 - c) Nutrigenomics
3. **Predictive Genomic (Families)**
 - a) Detect and prevent susceptibility to heart diseases
 - b) Diabetes and obesity
 - c) Detect susceptibility to cancer and initiate preventative measures
4. **Genetic and molecular Consultation services**

Bioinformatics



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Dr. Darrol Baker

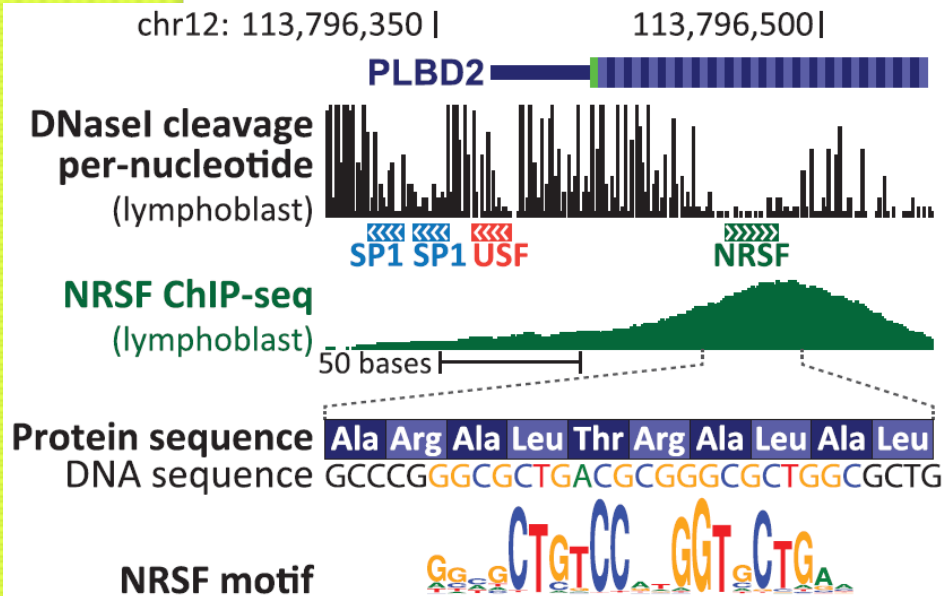
1. Reports should serve clinicians and patients
2. Reports should be dynamic serve you for life
3. Reports should look attractive

The screenshot displays a comprehensive bioinformatics software interface with several key components:

- Patient View:** Includes patient identification forms and a small patient icon.
- Body View:** Shows a 3D anatomical model of a human torso with highlighted internal organs.
- Genome Report:** A central panel with a color-coded legend for different genomic features and a table of suspect variants.

| Chromosome | Position | Normal | Alt Allele | Frequency | Class | Predicted Effect | Protein | Gene | Primary Site |
|------------|----------|--------|------------|-----------|---------------|-------------------|---------|--------|------------------------|
| 1 | 3889056 | L | 1 | | Missense | TOXNATED | F | OSFP1 | Heartbeat |
| 1 | 26420915 | L | 1 | | | | F | ETNK2 | CNS |
| 2 | 5211991 | L | 1 | | | | F | PAGS | Skin |
| 4 | 127679 | L | 1 | | | | F | PIRFB | CNS |
| 4 | 1820793 | L | 1 | 0.835 | Synonymous | TOXNATED | F | FGF10 | Skin |
| 6 | 25424054 | L | 2 | 0.266 | Synonymous | TOXNATED | F | PIRFB | CNS |
| 5 | 2897024 | L | 1 | 0.397 | Synonymous | TOXNATED | F | CHNAD2 | Skin |
| 5 | 12227289 | L | 0 | 0.228 | Synonymous | TOXNATED | F | JAK1 | Large Intestine |
| 6 | 12586200 | L | 2 | 0.833 | Missense | TOXNATED | F | SYN1 | CNS |
| 7 | 10488883 | L | 1 | | | | F | PRK11 | Cherry |
| 7 | 20460284 | L | 1 | | Missense | TOXNATED | F | ZNF796 | Ovary |
| 9 | 22962183 | L | 0 | | Missense | FUNCTION CHANGING | F | CEBNA3 | Central Nervous System |
| 9 | 21963118 | L | 2 | 0.823 | | | F | CEBNA3 | Central Nervous System |
| 9 | 12796144 | L | 0 | 1 | | | F | PCYO | Lung |
| 9 | 12618398 | L | 1 | 0.851 | | | F | SNY1 | CNS |
| 9 | 14877912 | L | 0 | | Splice Region | FUNCTION CHANGING | F | CATN3B | Breast |
| 10 | 15762917 | L | 1 | | | | F | MYT1L | CNS |
| 10 | 8772298 | L | 1 | | | | F | PSY1 | Uterus |
- Gene Overview:** A detailed view of a specific gene, including its sequence, exons, introns, and associated data like drug sensitivity and mutation frequency.
- Personal Genomics:** A section for individual genetic data, represented by a DNA double helix icon.
- Body View (Mobile):** A smartphone displaying a 'My Genome' app interface.

“Exomes on the go”
We need funding and help



Exonic Transcription Factor Binding Directs Codon Choice and Affects Protein Evolution

Andrew B. Stergachis,¹ Eric Haugen,¹ Anthony Shafer,¹ Wenqing Fu,¹ Benjamin Vernot,¹ Alex Reynolds,¹ Anthony Raubitschek,^{2,3} Steven Ziegler,³ Emily M. LeProust,^{4*} Joshua M. Akey,¹ John A. Stamatoyannopoulos^{1,5†}

Genomes contain both a genetic code specifying amino acids and a regulatory code specifying transcription factor (TF) recognition sequences. We used genomic deoxyribonuclease I footprinting to map nucleotide resolution TF occupancy across the human exome in 81 diverse cell types. We found that ~15% of human codons are dual-use codons (“duons”) that simultaneously specify both amino acids and TF recognition sites. Duons are highly conserved and have shaped protein evolution, and TF-imposed constraint appears to be a major driver of codon usage bias. Conversely, the regulatory code has been selectively depleted of TFs that recognize stop codons. More than 17% of single-nucleotide variants within duons directly alter TF binding. Pervasive dual encoding of amino acid and regulatory information appears to be a fundamental feature of genome evolution.

Data generation and databases



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| Path | Exon | Codon | DNA change | DNA reported | RNA change | Protein |
|------|------|-------|---------------------|--------------|------------|------------------|
| +7 | 13 | 554 | c.1660C>T | - | - | p.Arg564 |
| +7 | 15E | 1112 | c.3336_3340delAAATC | - | - | p.Asn1135SerfsX4 |

- Crime against genomics! Extract one info from NGS and discard or hide the rest!!
- Where do you place the 'one pathogenic data'
 - ✓ **International** Curated databases : do not reinvent the wheel
 - "Insight-group" Lynch syndrome
 - BIC
- Where do you place the 'one pathogenic data'
 - ✓ Genomic Medicine Alliance database

Data generation and databases



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nature
genetics

Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database

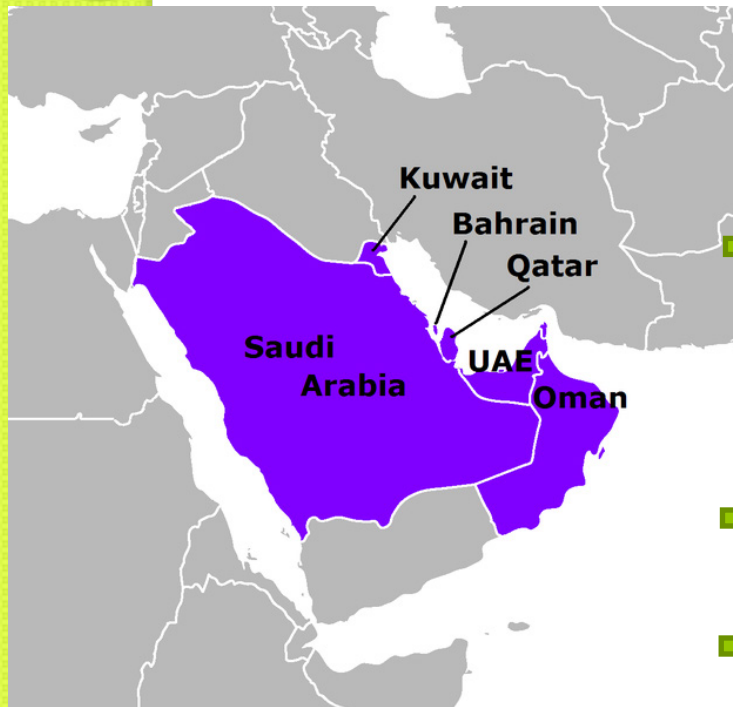
Bryony A Thompson^{1,2,46}, Amanda B Spurdle^{1,46}, John-Paul Plazzer³, Marc S Greenblatt⁴, Kiwamu Akagi⁵, Fahd Al-Mulla⁶, Bharati Bapat⁷, Inge Bernstein^{8,9}, Gabriel Capella¹⁰, Johan T den Dunnen¹¹, Desiree du Sart¹², Aurelie Fabre¹³, Michael P Farrell¹⁴, Susan M Farrington¹⁵, Ian M Frayling¹⁶, Thierry Frebourg^{17,18}, David E Goldgar^{19,20}, Christopher D Heinen^{21,22}, Elke Holinski-Feder^{23,24}, Maija Kohonen-Corish²⁵⁻²⁷, Kristina Lagerstedt Robinson²⁸, Suet Yi Leung²⁹, Alexandra Martins¹⁷, Pal Moller³⁰, Monika Morak^{23,24}, Minna Nystrom³¹, Paivi Peltomaki³², Marta Pineda¹⁰, Ming Qi^{33,34}, Rajkumar Ramesar³⁵, Lene Juel Rasmussen³⁶, Brigitte Royer-Pokora³⁷, Rodney J Scott^{38,39}, Rolf Sijmons⁴⁰, Sean V Tavtigian²⁰, Carli M Tops¹¹, Thomas Weber⁴¹, Juul Wijnen¹¹, Michael O Woods⁴², Finlay Macrae³ & Maurizio Genuardi^{43,44} on behalf of InSiGHT⁴⁵

- Even in Curated databases:
- Errors are high
- Assessment using validated criteria altered classifications for **66%** of 12,006 database entries.
- Phenotypes largely lacking
- Large number of SNP in our population NOVEL

Gulf states: Genome Arabia at last



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- Enormous time depth of human habitation (second only to sub-Saharan Africa)
- This nodal geography means that countless peoples have arrived, settled and passed through, creating a very complex palimpsest of **Genetic diversity/heterogeneity**

➔ **50% of all marriages are contracted between first cousins**

- **Genetic homogeneity/useful autozygosity mapping (Dr. Sultan's team >50 genes)**

➔ **Arabs are not represented in the Human genome project, HapMap, 1000 Genome project**

➔ **Rarer variants found only in Arab populations have yet to be discovered**

- **Greatest blunder against identifying rare variants, important in Diseases (25-30% T2D, PCO, Mendelian inheritance)**

Genome Arabia: Rare variants



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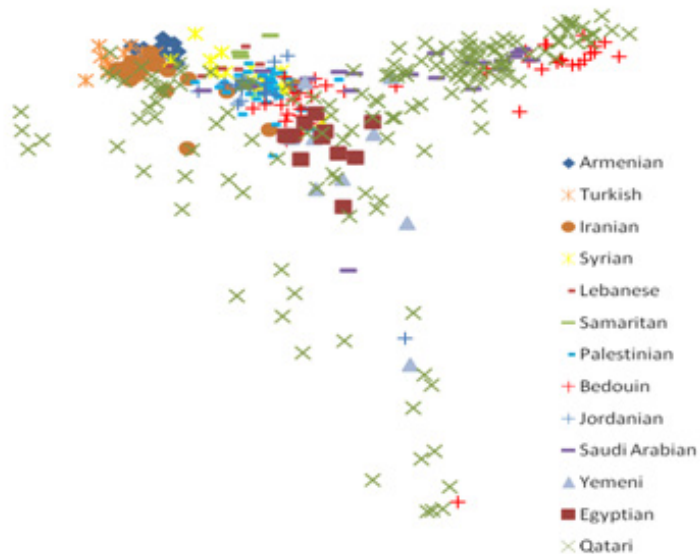
Qatar National Research Fund

- **A** survey by Bodmer et al., found that:
45% of known rare variants conferred more than a 3-fold risk of disease, whilst 45% of common alleles had odds ratios below 1.2.
- **P**ivate mutations in PCSK9 (<0.5% frequency) can change LDL-C by over **100 mg/dl**; ~20% **f**requency allele found by GWAS only changed LDL-C by **3 mg/dl**.
- Low frequency and rare variants tend to have larger effect sizes, are extremely important mediators of complex disease risk.

Genome Arabia: Rare variants



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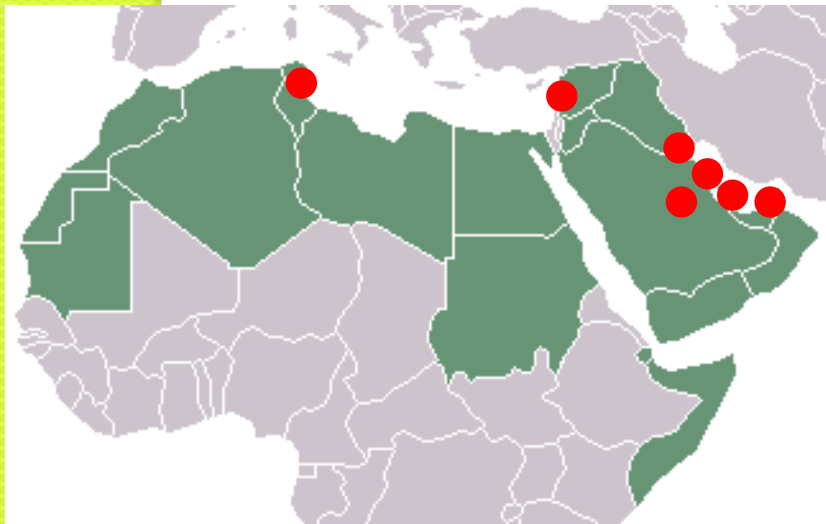


- Data are from Li *et al.*, Behar *et al.*, and Hunter-Zinck *et al.* Used ~20,000 SNPs which overlapped between the Illumina 650Y and Affymetrix 5 arrays and which allowed unambiguous identification of alleles.
- Need to sample the population well

Genome Arabia



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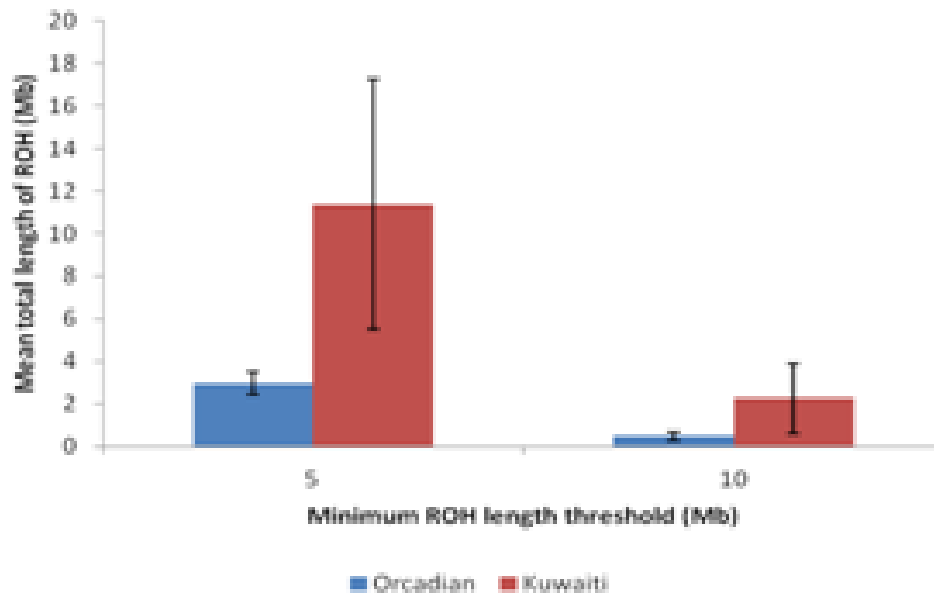
- In 2012:
Set up Genome Arabia working group to whole genome and exome sequence 360 - 1000 normal Arabs.
Grant funded by QNRF.
Prof. Lotfi Chouchane Qatar Weil Cornell
Prof. Jim Wilson University of Edinburgh

Involvement of (Pan Asian population Genomic Initiative) PAPGI

Genome Arabia



Mean Total Length of ROH > 5 and 10 Mb in Kuwait and Orkney



- **Considerable higher proportion of ROH over 5 Mb was observed in the Kuwaiti samples when compared to the Orkney population.**
- **Over **three times** as many Kuwaitis had at least one ROH > 10 Mb in length than Orcadians.**
- **Indicating recent inbreeding loops in their pedigrees.**

Genome Arabia



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| EXomes | Case1 | Case2 | Case3 | Case4 | Case5 | Case6 | Case7 | Case8 |
|-----------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Ethnicity | Bedouin | Bedouin | Bedouin | Mixed | Mixed | Syrian | KU | Mixed |
| Breeding | Inbred | Inbred | Inbred | | | mother | father | child |
| Total variants | 139,128 | 132,863 | 123,653 | 102,542 | 102,337 | 46,083 | 44,458 | 45,253 |
| Novel Variants | 13,255 | 12,540 | 12,169 | 10,137 | 9,969 | 3,127 | 3,081 | 3,084 |
| Novel serious consequences | 747 | 740 | 744 | 743 | 734 | 670 | 647 | 662 |

Saudi Genome



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9 December 2013 Last updated at 01:33 GMT



Hundred thousand genomes to be mapped in Saudi Arabia

By Helen Briggs
BBC News



Saudi Arabia is launching a national research project to study the genetic basis of disease in its population

Up to 100,000 people in Saudi Arabia are to have their genetic codes mapped in a new human genome project.

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Qatar Genome launched

Project is road map for future treatment of personalized medicine

By Habib Toumi, Bureau Chief

Published: 12:08 December 10, 2013

GULF NEWS



Manama: Shaikha Moza Bint Nasser, the Chairperson of the non-profit Qatar Foundation for Education, Science and Community Development has announced the launch of the 'Qatar Genome'.

"In Qatar, when we strived to build our all-inclusive culture of health, we transformed our health centers into research and academic centers, which incorporate hands on experience," Shaikha Moza said.

"As a result of the integration of scientific research and the clinical realities, I am pleased to announce the project 'Qatar Genome', a project that consists of a road map for future treatment of personalized medicine," she said as she opened the World Innovation Summit for Health (WISH) in the Qatari capital Doha on Tuesday.

Thank you



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behind the Veil, is a human
that is 90-99% identical to
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