Predictive Genetic Tests: What Do We Know?

Peter Ray, PhD
The Hospital for Sick Children

April 16, 2010
The Era of Genomic Medicine
What you are. Who you are.

Your genome is the ultimate form of information (past-present-future),

“NGS is erasing the barriers of entry and the boundaries to creativity in genomics”
The Human Genome Project

Has created:

• Major advances in technology for analyzing DNA

• An explosion in knowledge of genetics and genetic disease
Molecular Genetic Testing

- Disease Genes Identified
- Molecular Tests Offered in North America
- Molecular Tests Offered In Ontario

www.genetests.org
9 of the 10 Leading Causes of Mortality Have Genetic Components

Heart disease (31.0% of deaths in ‘98)
Cancer (23.2%)
Stroke (6.8%)
COPD (4.8%)
Injury (4.2%)
Pneumonia/Influenza (3.9%)
Diabetes (2.8%)
Suicide (1.3%)
Kidney disease (1.1%)
Chronic liver disease (1.1%)
The Value of Presymptomatic Diagnosis

“In about 20 percent of patients, sudden death is the first sign of heart disease.”

Roger Blumenthal, M.D,
Johns Hopkins
Complex Disorders

Environmental factors

Multiple gene effects
Complex Disease
Polygenic Inheritance

Gene A
Gene B
Gene C
Gene D

Disease

Small number of common variants with small effect
Complex Disease
Heterogenetic Inheritance

Gene A
Gene B
Gene C
Gene D

Disease

Large number of rare variants with large effect
Heterogenetic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number of Genes</th>
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<tbody>
<tr>
<td>Breast Cancer</td>
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<tr>
<td>Colorectal Cancer (HNPCC)</td>
<td>5</td>
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<tr>
<td>Ahrrythmogenic Right Ventricular Cardiomyopathy</td>
<td>5</td>
</tr>
<tr>
<td>Congenital Muscular Dystrophy</td>
<td>5</td>
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<tr>
<td>Neuronal Ceroid Lipofusinosisis (Batten Disease)</td>
<td>8</td>
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<tr>
<td>Focal Segmental Glomerulosclerosis</td>
<td>4</td>
</tr>
<tr>
<td>Hereditary Spastic Paraplegia (recessive)</td>
<td>9</td>
</tr>
<tr>
<td>Fanconi Anemia</td>
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</table>
Complex Disease
Polygenic Inheritance

Small number of common variants with small effect
A gene for heart disease

Researchers this week have pinpointed a gene that may help predict whether someone is at risk from early onset coronary artery disease long before they know there might be a problem.

For years scientists have known that this devastating form of heart disease is passed on from generation to generation, but the culprit gene causing the disease has until now remained relatively unknown.

Earlier studies identified a link between the disease and a region of chromosome 7, a particular neuropeptide Y gene or NPY.

Now this latest study published this week in the open-access journal PLoS Genetics by a huge team of people led by Sviati Shah and Elizabeth Hauser from Duke University Medical Center in the United States, has revealed six variations in this NPY gene that are inherited between generations and are strongly associated with disease.

Coronary artery disease occurs when the arteries bringing blood to the heart become lined by a build-up of cholesterol, fat and other substances, a process known as atherosclerosis. This narrowing of the arteries can restrict blood flow to the heart and ultimately lead to a blockage and a heart attack. It's a disease that gets more likely as you get older but it does affect younger people, for example affecting around 10 to 15% of Americans.

What the Duke University researchers did to find out more about the genetics of early onset coronary artery disease was to identify which version of the gene is carried by members of nearly a thousand families with a history of the disease, and by a group of unrelated people who have had an angiogram at the Duke University Medical Centre since 2001.

They discovered a strong link between six versions of the gene and people who have had actual heart disease or a history of the disease in the family.
Direct to Consumer Genetic Testing
Direct to Consumer Genetic Testing

What Health Compass tests for

What Health Compass tests for

A look at the health conditions included in our most extensive genetic testing service

- Abdominal aneurysm
- Alzheimer's disease
- Atrial fibrillation
- Brain aneurysm
- Breast cancer
- Celiac disease
- Colon cancer
- Crohn's disease
- Diabetes, type 2
- Glaucoma
- Graves' disease
- Heart attack
- Lung cancer
- Lupus
- Macular degeneration
- Multiple sclerosis
- Obesity
- Osteoarthritis
- Prostate cancer
- Psoriasis
- Restless legs syndrome
- Rheumatoid arthritis
- Stomach cancer, diffuse

Heart attack

Obesity
Risk Factors for Heart Disease

Smoking
High Blood Pressure
High Cholesterol
Obesity

Lack of Exercise
Unhealthy Diet
Stress
Type A personality
Personalizing Risk Factors

Obesity increases risk of heart disease
A genetic test, like any other laboratory test is a tool that when used by a trained health care provider can improve diagnosis and patient management.

Without informed consultation testing could be over-interpreted or misinterpreted resulting in increased patient risk
Complex Genetic Testing

Clinical Utility

• Incomplete knowledge base to interpret the clinical significance of the results
• Applying population statistics to individual prediction
• Inadequate understanding of genetics by public and physicians
• Genetic data is generally beyond the experience of the public
  • assumed to be “scientific” and thus accurate
Complex Disease
Polygenic Inheritance

Small number of common variants with small effect
Identifying the Genetic Cause of Disease

The Personal Genome Project (www.personalgenomes.org)
- Sequence 100,000 genomes
- Collect extensive medical and physical information
- Identify genetic variants predisposing to disease
- Cost $1B - financed by google
## DNA Sequencing Technology

<table>
<thead>
<tr>
<th>Year</th>
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<tr>
<td>1993</td>
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<td>2009</td>
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<tr>
<td>?</td>
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$1000 genome
$10,000 Interpretation
Issues in Implementation of Genomic Diagnostics

Laboratory Issues:

Genetic Knowledge

- Phenotype /genotype correlations
  - Very large clinical databases
  - Longitudinal studies
  - Many thousands of patients
  - Genetic Interactions
Issues in Implementation of Genomic Diagnostics

Clinical Issues:

- New “clinical” bioinformatics algorithms
- New counseling algorithms
  - Selective information transfer
  - “Need to know” counseling
- Utilization of primary health care providers
- Need to regularly reanalyze genome in light of new knowledge
Future Diagnostics
Genomic Profiling

Sequence each individual's genome and detect all CVNs at birth to determine:

- carrier status of all genetic disorders
- predisposition to all common disease
- all drug sensitivities
- optimal treatments/therapies

- behavioural traits
- personality
- IQ
HEALTH & TECHNOLOGY

Medical science aims to microchip you

The American Medical Association has endorsed the use of implantable microchips to help reduce medical errors and adverse drug reactions.

It said the chips may help to identify patients, "thereby improving the safety and efficiency of patient care," reports the latest issue of the Canadian Medical Association Journal.

But the AMA's policy recommendation was filled with cautions, since the security of the microchips hasn't been established. Some observers fear the potential for loss of privacy.

"The implantable microchip devices are being looked at worldwide by hospitals and other facilities," said an AMA representative.

In the U.S., the Food and Drug Administration has already approved a microchip — with limited storage and a transmission range of a few metres — that contains basic information, such as the owner's identity.

CHIP continued on A11

UNDER YOUR SKIN

Microchips approved in the U.S. get implanted under the skin with a needle, most likely in the arm, and hold identification numbers that can be scanned by a radio frequency reader and then used...
Thank-You