Genetics of Hypertension

Anna Dominiczak

Barcelona, 16 December, 2011
HYPERTENSION

• Estimated by the WHO to contribute to 7.1 million deaths annually
• It is a major risk factor for CAD and stroke
• Globally, in 2008 the prevalence of hypertension was ~40% in adults aged 25 and over
Complex Causation of Hypertension

- Race
- Sodium
- Sex
- Physical Activity
- Caffeine
- Stress
- Drugs
- Diet

100% environment

Essential Hypertension

- Insulin resistance
- Oxidative stress
- Sympathetic nervous system
- Endothelial Function
- Renin angiotensin aldosterone
- Renal electrolyte transport
- Monogenic syndromes

100% genetics

Padmanabhan S et al. J Hypertens 2008;26:1275
Monogenic Hypertension & Hypotension

Modified from Lifton at al, Cell 2001
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. We describe a joint GWA study (using the Affymetrix GeneChip 500K Mapping Array Set) undertaken in the British population, which has examined ~2,000 individuals for each of 7 major diseases and a shared set of ~3,000 controls. Case-control comparisons identified 24 independent association signals at $P < 5 \times 10^{-7}$: 1 in bipolar disorder, 1 in coronary artery disease, 9 in Crohn’s disease, 3 in rheumatoid arthritis, 7 in type 1 diabetes and 3 in type 2 diabetes. On the basis of prior findings and replication studies thus-far completed, almost all of these signals reflect genuine susceptibility effects. We observed association at many previously identified loci, and found compelling evidence that some loci confer risk for more than one of the diseases studied. Across all diseases, we identified a large number of further signals (including 58 loci with single-point $P$ values between $10^{-5}$ and $5 \times 10^{-7}$) likely to yield
Genome-wide scan for seven diseases

P < 1 x 10^{-5}

Green

WTCCC,
Nature 7 June 2007
Eight blood pressure loci identified by genome-wide study of 34,433 people of European ancestry

*Christopher Newton Chen et al* (+158 co-authors)

*Nature Genetics* 2009;41:666

Genome-wide association study of blood pressure and hypertension

*Daniel Levy et al* (+43 co-authors)

n=29,136

*Nature Genetics* 2009;41:677
Global BPgen

GBPG - GWAS from 34,433 individuals (17 cohorts)

Discovery cohorts - BLSA, B58C, CoLaus, EPIC-Norfolk, Fenland, InCHIANTI, KORA, SardiNIA, SHIP, SUVIMAX, TwinsUK, DGI controls, FUSION NGT controls, MIGen controls, PROCARDIS controls
• **Meta-analysis of 13 population-based and 4 control cohorts of European ancestry**
  • 34,433 individuals

• **Primary phenotypes**
  • systolic and diastolic BP

• **Methods**
  • Excluded individuals >70 years
  • Imputed BP measures for anti-HT medication + 15/10mmHg
  • adjusted for age, \( \text{age}^2 \), sex, body mass index
  • Imputation and additive model

*Nature Genetics, 2009; 41: 666-676*
**Stage 2a**
Genotyping in population or case-control series
N ≤ 71,225 Europeans, N ≤ 12,889 Indian Asians

- ARYA (n=736)
- BRIGHT-HTN (n=2445)
- BRIGHT-NT (n=673)
- EPIC-Italy (n=3909)
- EPIC-Norfolk-REP (n=15858)
- Finrisk97 (n=7023)
- FUSION2 (n=1162)
- Lolipop-Europeans (n=6006)
- Lolipop Indian Asian (n=12823)
- MDC-CC (n=5330)
- METSIM (n=5934)
- MPP (n=14249)
- PREVEND (n=7272)
- Prospect-EPIC (n=1680)
- Utrecht Health Project (n=2829)

**Stage 2b**
In silico replication samples
n=29,136 European ancestry
CHARGE consortium

- ARIC (n=3219)
- CHS (n=3277)
- FH5 (8096)
- RS (n=4737)
- RES (n=1760)

= 8 new BP loci
13 new BP loci in total

- **FGF5**
  - **PLCD3**
  - **MTHFR/NPPA/NPPB**
  - **ZNF652**
  - **c10orf107**
- **CYP17A1**
- **CSK/CYP1A2/ULK3**
- **SH2B3**
  - **ULT4**
  - **TBX3-TBX5**
  - **CACNB2**
  - **ATP2B1**

**Global BPgen scan for continuous traits**

**CHARGE case/control scan for hypertension**
BP and Hypertension – consistent effects
The International Consortium for BP Genome-wide studies ICBP GWAS

ICBP-GWAS (SBP/DBP)

GWAS from up to 70K individuals (29 cohorts)

Validation in up to 130K European, 24K South Asian, 20K African and 30K East Asian ancestries
- **27 SNPs targeted for validation** using a staged design
- **Genotyping/look ups performed in** 130k individuals of European ancestry
- **16 novel** genome-wide significant loci for SBP and/or DBP
- **12/13 previously published** loci confirmed

29 independent SNPs in total
GWAS in 200,000 individuals

Studying Extremes

n=2000 Hypercontrols

- Malmö Diet and Cancer Study (MDC)
- BP< 120/80mmHg
- at least 50 years of age
- free from cardiovascular events during 10yr follow-up
- not on hypertensive medication

n=2000 Cases

- Nordic Diltiazem Study (NORDIL)
- 2 consecutive BPs ≥ 160/100mmHg
- diagnosis < 60 years of age

<table>
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<tr>
<th>Age at enrolment, years</th>
<th>Controls (n=1699)</th>
<th>Cases (n=1621)</th>
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<tr>
<td>BMI, kg/m²</td>
<td>24.2 (3.5)</td>
<td>27.1 (7.8)</td>
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<tr>
<td>SBP, mmHg</td>
<td>115.8 (6.8)</td>
<td>175.8 (22.5)</td>
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<tr>
<td>DBP, mmHg</td>
<td>73.7 (5.7)</td>
<td>104.7 (12.0)</td>
</tr>
</tbody>
</table>

Padmanabhan et al, PLoS Genetics 2010
Overview of Association Results in the Discovery Sample

Padmanabhan et al, PLoS Genetics 2010
Replication: association of rs13333226 and hypertension

Adjusted Analysis; n=39,706 subjects

Swedish
BRIGHT/ASCOT
MPP
MDC
PREVEND
CoLaus
KORA
SHIP
B58C
TwinsUK
MIGen
DGI
Fenland
MONICA/PAMELA
NESDA

Overall 0.85 [0.81; 0.89]
P = 1.5x10^{-13}

Odds Ratio

0.91 1.1
Genomic region with typed and imputed SNPs

Chromosome 16 position (kb)

Observed (-log_{10}P)

Recombination rate (cM/Mb)

rs13333226
p=1.14x10^{-7}

Meta-analysis p=1.5x10^{-13}

GP2
UMOD
PDILT
FLJ20581
LOC123876
The uromodulin (UMOD) gene encodes the Tamm Horsfall protein/uromodulin

It is a glycosylphosphatidylinositol (GPI) anchored glycoprotein

It is the most abundant tubular protein in the urine, which is expressed primarily in the thick ascending limb of the loop of Henle (TAL)
UMOD – functional studies

• we found a direct relationship between urinary uromodulin & sodium excretion

• this was shown in hypertensive patients (BRIGHT study) and in general population (HERCULES study)

• minor G allele of the SNP rs13333226 is associated with a lower risk of hypertension & lower urinary uromodulin excretion
Urinary Uromodulin and Sodium excretion according to rs13333226 Genotype in the HERCULES study.
Unifying hypothesis

UMOD ↓

↓ Na reabsorption in TAL

↓ ECV & ↓ BP

Padmanabhan et al, PLoS Genetics 2010
Luciferase promoter activity

786-0 2Kb
G   T   T   G   A   T

TK-10 2Kb
A   A   T   C   A   T

ACHN 2Kb
G   T   C   G   G   C

rs13333226

HeLa cells

NRK 52E cells

1 Kb Achn
1 Kb 786-0
1 Kb TK10
2Kb Achn
2Kb 786-0
2Kb TK10

*** p<0.0001

*** ***

Luciferase activity (Ratio)

Construct
Transcription factor analysis of rs4997081

TK-10 Umod promoter

rs4997081 C allele
transcription binding sites
rs4997081 G allele
transcription binding sites

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<tr>
<th>rs4997081 C allele</th>
<th>rs4997081 G allele</th>
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<td>GAGA</td>
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<tr>
<td>GAL4</td>
<td>GAL4</td>
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Cardiovascular phenotyping of the mouse THP (umod) Knock-out

Radiotelemetry

Tail-cuff plethysmography

- Baseline Week 1 NaCl
- Baseline Week 2 NaCl

SBP (mmHg)

Recovery Baseline
New Pathway for HTN from GWAS of Extremes

**ASSOCIATIONS**

- Low urinary uromodulin
- Low BP
- High GFR
- Low FENa

**HYPOTHESIS**

- Increased sensitivity to luminal Na
- ↓ GFR
- Renin ↓ - by Ca+2, high BP
- Na excretion ↓

- Decreased sensitivity to luminal Na
- ↑ GFR
- Renin ↑ - by Ca+2, low BP
- Na excretion ↑

**G rs13333226**
Rare functional variants under purifying selection protect against hypertension

Ji et al, Nat Genet, 2008
Ehret et al. Nature 2011
Johnson et al. AJHG (2011)
The Genetic Architecture of BP

- each SNP explains a very small proportion of the total variation in SBP & DBP, 0.05-0.10% or 1mmHg/allele systolic and 0.5mmHg/allele diastolic BP

- but the aggregate effects of several variants do produce meaningful population changes in risk

- 2mmHg ↓ SBP → 6% reduction of stroke & 5% reduction of CAD

- there are many more common variants associated with BP that remain to be discovered
Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect

Effect size
50.0
3.0
Intermediate
1.5
Modest
1.1
Low

Allele frequency
Very rare
Rare
Low frequency
Common

Rare alleles causing Mendelian disease
Low-frequency variants with intermediate effect
Common variants implicated in common disease by GWA

Few examples of high-effect common variants influencing common disease

Manolio et al, Nature 2009
GWAS – the biggest gains

- whilst risk stratification is important, the greatest impact will be on our understanding of biology & pathophysiology of human disease

- in most cases genes & regions identified are novel & fill critical gaps in our current knowledge

- the argument here is that a common non-coding SNP might have a small effect but the underlying gene/protein/mechanism might be very important as a drug target – example of the HMG-CoA reductase
“As for the future, your task is not to foresee, but to enable it”

Antoine de Saint – Exupéry

The Wisdom of the Sands
22nd European Meeting on Hypertension and Cardiovascular Protection
LONDON, April 26-29, 2012 ICC London
www.esh2012.org
<table>
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<th>SNP</th>
<th>Position</th>
<th>Nearest gene</th>
<th>Effect allele freq</th>
<th>Beta (s.e.)</th>
<th>P</th>
<th>BP response</th>
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<td>3p24</td>
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<td>SNTG1</td>
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<td>FAM110B</td>
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<td>2.45 (0.5)</td>
<td>3 x10^{-07}</td>
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<td>SNP</td>
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<tr>
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<td>2.13 (0.5)</td>
<td>3.9 x10^{-06}</td>
<td>DBP</td>
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In Silico Replication

NORDIL

PEAR

p_SBP: 0.12
P_DBP: 0.044

Combined P-value $1.3 \times 10^{-7}$

PEAR Study, Dr Julie Johnson, Univ of Florida
Cardiovascular phenotyping of the mouse THP (umod) Knock-out

LV mass index

Renal mass index

Control + 4%NaCl

THP+/+ THP-/-
BP loci (June 2011)

- GBPG/CHARGE/KARE – 13
- MTHFR/NPPA/NPPB – 2 (Newton-Cheh et al, 2009; Tomaszewski et al 2010)
- NORDIL/MDC -1
- ICBP-GWAS – 24 (excl. GBPG/CHARGE overlap)
- CVD50 BP consortium – 5 (excl ICBP-GWAS overlap and Johnson et al 2011)
- Takeuchi et al (2010) – 1

TOTAL = 51 distinct BP variants
Future

• ongoing even larger meta-analyses of GWAS = International Consortium for BP-Genome-Wide Association Study (ICBP-GWAS)

• Studies targeting individuals with extreme phenotypes

• careful analysis of CNVs

• data from the 1000 Genomes Project open the possibility of reliable imputation of rare variant genotypes

• resequencing (next-generation) of cases and controls for fine mapping & causal variants
• rather than seeking a new twist on a long-studied pathway or asking whether discoveries in model organisms are relevant to humans, researchers can explore hundreds of genes proven by GWAS to be relevant to human disease

• the challenge is to develop research methods to take us from genetic localisation to medically useful application
H25K designed and manufactured using the complete human genome sequence, allowing users to explore biology across 25,509 annotated human genes and >300,000 transcripts.
• Counselling & testing for monogenic cardiovascular diseases should remain in medical setting

• Pharmacogenomics with more & more gene variants predicting either efficacy or toxicity of drugs will become an important tool of stratified medicine

• Genetic tests for cardiovascular disease risk have minimal predictive ability & benefit
Liddle Syndrome

**Normal**

- **Enac**
- **PPPXY**
- **WW domain interaction**

**Liddle Syndrome**

- **Clathrin-coated pit**
- **Amiloride**
- **Triamterene**

Potassium-sparing diuretics

Amiloride, Triamterene
Glucocorticoid Remediable Aldosteronism

Aldosterone synthase  11β-hydroxylase

5'  3'  5'  3'

Unequal crossing over

5'  3'  5'  3'

Ang-II - Aldosterone - 11β-hydroxylase - Ang-II

Aldosterone synthase

5'  3'

Chimeric Gene

ACTH - Aldosterone - Cortisol - ACTH

5'  3'  5'  3'

Rx - Glucocorticoids
• Double-blind, active-controlled randomized trial of antihypertensive treatment (ALLHAT)

• ACE I/D genotypes in 37,939 participants

• ACE I/D genotype was not a predictor of CHD, nor did it modify the response to antihypertensive treatment

Arnett et al., Circulation 2005;111:3374-83
GWAS of warfarin dose

CYP2C9

rs4917639 (P=3.1x10^{-31})

rs1057910 (P=4.5x10^{-17})

rs1799853 (P=8.8x10^{-13})

VKORC1

*2*3Composite

rs9923231 (P=5.4x10^{-78})

Genome wide significance

Takeuchi et al, Plos Genetics 2009; 5:e11000433
Warfarin dose: clinical and pharmacogenetic algorithm based on race & genotype

The International Warfarin Pharmacogenetic Consortium, NEJM 2009;360:753
Statin Induced Myopathy

85 participants with myopathy and 90 matched controls
80 mg of simvastatin daily

SLCO1B1

• SLCO1B1 encodes the organic anion–transporting polypeptide OATP1B1, which mediates the hepatic uptake of various drugs, including most statins and statin acids.

• Statin blood concentrations are higher in people with the C allele.
• 2009, two large-scale meta-analyses of GWAS for BP and hypertension published (Global BPGen & CHARGE)

• more stringent significance threshold (p < 5x10^{-8})

• genome imputation approaches to combine data across cohorts that used different SNP genotyping chips.

• SBP & DBP in both consortia plus genome scan for hypertensive genes in CHARGE

• both consortia identified genome-wide significant associations at 8 loci with 3 discovered by both consortia
Future

- ongoing even larger meta-analyses of GWAS = International Consortium for BP-Genome-Wide Association Study (ICBP-GWAS)

- Studies targeting individuals with extreme phenotypes

- careful analysis of CNVs

- data from the 1000 Genomes Project open the possibility of reliable imputation of rare variant genotypes

- resequencing (next-generation) of cases and controls for fine mapping & causal variants
Genetic testing for cardiovascular disease: are we there yet?

- expectations are high that increasing knowledge on the genetic basis of cardiovascular disease will lead to personalised (or stratified) medicine

- with preventative & therapeutic interventions targeted at high risk individuals based on their genetic profiles

but

- most cardiovascular diseases are caused by complex interactions of many genetic variants and non-genetic risk factors
BP and genes (May 2011)

- GBPG/CHARGE/KARE – 13
- MTHFR/NPPA/NPPB – 2
- NORDIL/MDC - 1
- ICBP-GWAS – 23 (excl. GBPG/CHARGE overlap)
- CVD50 BP consortium – 6 (excl ICBP-GWAS overlap)

- TOTAL = 46 distinct BP variants
Future Plans

Common Variant Analysis

- Published – PLoS Gen - 2010
  1700 Cases/
  1700 Controls

- Ongoing – Collaboration with M Caulfield
  GWAS Meta-Analysis
  10,000 Cases/
  10,000 Controls

Rare Variant Analysis

- Collaboration with Rick Lifton

- Two ongoing projects - 2011
- NIH Exome Project
GWAS – the biggest gains

• whilst risk stratification is important, the greatest impact will be on our understanding of biology & pathophysiology of human disease

• in most cases genes & regions identified are novel & fill critical gaps in our current knowledge

• the argument here is that a common non-coding SNP might have a small effect but the underlying gene/protein/mechanism might be very important as a drug target – example of the HMG-CoA reductase
Summary

• Analysis of CVD50 Bead Chip discovered 9 bona fide BP loci
  • 6 novel associations
    4 replicated here and 2 replicated by parallel work (ICBP-GWAS)
  • Concurrent discovery of AGT (Johnson et al, 2011)
  • 2 associations previously reported using GWAS
    ATP2B1 and MTHFR/NPPA/NPPB
  • Effect size per SNP ~ 0.5mmHg
Future

- Studies targeting individuals with extreme phenotypes
- Careful analysis of CNVs
- Data from the 1000 Genomes Project open the possibility of reliable imputation of rare variant genotypes
- Resequencing (next-generation) of cases and controls for fine mapping & causal variants
• Meta-GWAS - 13 new blood pressure loci

• Each variant only explains a very small proportion of total variation in either SBP or DBP (0.05-0.1%; 1mmHg/allele SBP or 0.5mmHg DBP)

  Continuous and graded relationship of BP to risk of stroke and coronary heart disease
  
  *2mmHg change in SBP over a range of values is estimated to translate to 6% less stroke and 5% less coronary heart disease

• ? new drug targets

Ref: *Stamler et al, Hypertension. 1989
• **Gene-centric array**
  • 2150 candidate genes - selected for cardiovascular phenotypes/ incorporated data from early GWAS studies
  • Cosmopolitan tagging
  • Class 1 - genes (n=430) - $r^2=0.8$, MAF of 2%
  • Class 2 - genes (1430) - $r^2=0.5$, MAF of 5% and MAF of 10% for 240 class genes
  • Additional SNP content
    Seattle SNPs

• **Aim (BHF funding)**
  • To find BP/HTN genes
• Ascertained studies
  • BRIGHT \((N=3641)\)
    Cases \(\geq 150/100\text{mmHg}\) single reading or \(\geq 145/95\text{mmHg}\) on 3 readings, siblings affected.
    Controls \(\leq 140/85\text{mmHg}\)
  • NORDIL/MDC \((N=3765)\)
    Cases defined \(BP \geq 160/100\text{mmHg}\) and diagnosis \(<60\text{ years}\)
    Controls \(BP \leq 120/80\text{mmHg}\) and \(\geq 50\text{ years}\)
  • ASCOT \((N=1239)\)
    Untreated \(160/100\text{mmHg}\) or treated \(>140/90\text{mmHg}\), \(>40\text{ years}\) + other risk factors
  • AIBIII/NBS controls \((N=2810)\)

• Population studies
  • Whitehall II \((N=4578)\)
  • PROCARDIS \((N=3198)\)
  • BWHHS \((N=3413)\)
  • GRAPHIC \((N=2024)\)

Total sample size \((N = 25,061)\)
QQ Plots for DBP and PP

DBP

MAP

\[-\log_{10}(\text{expected } P\text{-value})\]

\[-\log_{10}(\text{observed } P\text{-value})\]

- MAF > 5%
- MAF ≤ 5%
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Best discovery association P-value, phenotype</th>
<th>Replication association P-value for independent one-tailed test</th>
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<td>P=2.8x10^{-6} DBP</td>
<td>P=9.5x10^{-6} ***</td>
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<td>P=7.0x10^{-10} MAP</td>
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<td>P=4.2x10^{-9} HTN DBP^2</td>
<td>P=5.0x10^{-3} * 2</td>
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<td>P=4.77x10^{-6} SBP</td>
<td>P=7.4x10^{-6} ***</td>
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<td>P=7.5x10^{-6} DBP</td>
<td>P=3.9x10^{-7} ***</td>
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<tr>
<td>chr12</td>
<td>P=1.5x10^{-7} HTN MAP^2</td>
<td>P=1.6x10^{-8} *** 2</td>
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CVD50 BP Consortium

BRIGHT
- T Johnson, S Newhouse, C Wallace, P Howard, A Onipinla, S Shaw-Hawkins, Y Zhang, M Brown, N Samani, M Farrall, J Connell, M Lathrop, A Dominiczak, M Caulfield, P Munroe

ASCOT
- A Stanton, M Caulfield, D Shields, P Sever

AIBIII
- A Stanton

NORDIL/MDC
- S Padmanabhan, O Mellander, C Delles, WK Lee, A Dominiczak

NBS
- W Ouwehard, N Samani

WHII
- M Kumari, M Marmot

BWHHS
- T Gaunt, D Lawlor, I Day

PROCARDIS
- www.procardis.org

GRAPHIC
- M Tomaszewski, P S Braund, CP Nelson, S Rafelt, MD Tobin, PR Burton, NJ Samani

• NPHSII
  - J Cooper, J Palmen, PJ Talmud, SE Humphries

• ELSA
  - M Kumari, A Taylor, M Marmot

• INTERGENE
  - F Nyberg, A Levinsson, J Gustavsson, A Rosengren, DS Thelle, Å Torinsson Naluai

• HYPEST
  - S Sober, E Org, M Laan

• MRC NSHD
  - R Hardy, G Davy Smith, D Kuh, A Wong

• BRHS
  - RW Morris, P Whincup, A Hingorani

• EAS
  - I Tzoulaki, G Fowkes

• OHGS
  - L Chen, A Stewart, B Roberts

• HYPERGENES
  - E Salvi, F Macciardi, D Cusi, X Jeunemaitre, N Devos

• CARe
  - X Zhu, E Fox, S Ganesh, Y Li, D Levy
SYSTEMS MEDICINE STRATEGIES

Integrate & evaluate

Ontologies:
Communicate between data

Classification
- biological process
- molecular function
- cellular component

Modelling:

Refinement and validation

Tools

Publicly available information

Dissemination
Cardiovascular Continuum 2010

- Risk factors
  - Oxidative and mechanical stress
  - Inflammation

- Tissue injury (MI, stroke, renal insufficiency, peripheral arterial insufficiency)

- Atherothrombosis and progressive CV disease

- Early tissue dysfunction

- Network

- Physiology

- Pathological remodeling

- Target organ damage

- End-organ failure (CHF, ESRD)

- Death

- Modified from Schadt EE. Nature 2009
Rival genetic tests leave buyers confused

Firms that offer to predict your risk of disease give worryingly varied results, discovers Nic Fleming

LEADING genetic testing companies are providing clients with widely divergent and inaccurate predictions of their chances of developing serious diseases. That is the finding from tests conducted by different firms on the same person.

Using my own DNA, I approached three firms who between them provide the majority of genetic tests for

Dr Paul Jenkins of GeneticHealth
LOW TO MODERATE
The firm rated the reporter’s risk of cardiovascular disease as ‘low to moderate’

Kari Stefansson of deCODEme
ABOVE AVERAGE
The company assessed the reporter’s risk of heart attack, angina and sudden cardiac death as above average

Ama Wojcicki of 23andMe
BELOW AVERAGE
The firm described the reporter’s risk of heart attack between the ages of 16 and 84 as below average

The Sunday Times, 7th Sept 08
• Several companies offer to assay individual's genome at 500,000 - 1 million SNPs and provide estimates of disease risk based on known genetic risk factors

• Such services should be reliable and of high scientific standard

• Customers must be given help to interpret results and health professionals need improved education about genetics
• 2,000 individuals for each of the 7 major diseases

• 3000 shared controls

• 24 independent association signals identified at $p<5\times10^{-7}$

• Across all diseases-58 loci with $p$ values between $10^{-5}$ and $5 \times 10^{-7}$

WTCCC, Nature 2007;447:661
Global BPgen scan for continuous traits

CHARGE scan for continuous traits

CHARGE case/control scan for Hypertension

Gene Sets:
- FGF5, PLCD3, MTHFR/NPPA/NPPB, ZNF652, c10orf107
- PLEKHA7, ULK4, CSK/CYP1A2/ULK3, SH2B3
- CYP17A1, CACNB2, ATP2B1, TBX3-TBX5, TBX3-TBX5
Global Disease Mortality 2002

Cardiovascular disease
Malignant neoplasms
Injuries
Respiratory infections
COPD and asthma
HIV/AIDS
Perinatal conditions
Digestive diseases
Diarrhoeal diseases
Tuberculosis
Childhood diseases
Malaria
Diabetes

Mortality (millions)

0 5 10 15 20

Contribution of Risk Factors to Burden of Disease Mortality*


Developing countries

- Blood pressure
- Tobacco
- Underweight
- Alcohol
- Cholesterol
- Unsafe sex
- Overweight
- Unsafe water, sanitation, hygiene
- Low fruit and vegetable intake
- Indoor smoke from solid fuels
- Physical inactivity

Developed countries

Percentage of Mortality Attributable to Risk Factors
Proven targets of antihypertensive medications

- > 29,000 individuals from the CHARGE consortium
- Validation in Global BPGen (>34,000 individuals)
- Women’s Genome Health Study (>86,000 individuals)

Associations at 3 loci (out of 30) including \textit{ADRB1, AGT & ACE}

\texttt{rs1801253, rs2004776, rs4305}

\textit{Johnson et al, Hypertension 2011;57:903}
• Identification of association between SBP or DBP and common variants in 8 regions near:
  - **CYP17A1**, **CYP1A2**, **FGF5**, **SH2B3**, **MTHFR**, **c10orf107**, **ZNf652**, **PLCD3**
  - *P* values range from $7 \times 10^{-24}$ to $1 \times 10^{-8}$

• Variants associated with continuous blood pressure were also associated with dichotomous hypertension.
• there were 2000 cases for each disease and 3000 common controls

• phenotyping was not available for the shared control group

• we estimated that if 5% of controls meet the definition of cases, loss of power is approx. the same as reduction of sample size by 10%

• however, hypertension might have had 30% not 5% misclassification bias.....

• thus “hypercontrols” would have been more suitable than common controls