PERSONALIZED HEALTHCARE

- Predictive genomic medicine, predictive Medicine, personalized medicine, individualized medicine
- Precisely applying prevention and treatment
- Highest risks of disease, complications, particular prognosis
- Maximize efficacy, minimize side effects

WHAT IS IT?

Precision medicine is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative will generate the scientific evidence needed to move the concept of precision medicine into clinical practice.

WHY NOW?

The time is right because of:

- Sequencing of the human genome
- Improved technologies for biomedical analysis
- New tools for using large datasets

PARADIGM SHIFT

CURRENT MODEL
Patient becomes sick
- History and exam
  - Differential diagnosis
    - Test selection/application
      - Refine differential or diagnosis
        - Treat

ALTERNATIVE MODEL
Test selection/application
- History and exam
  - Differential diagnosis
    - Refine differential or diagnose
      - Treat or prevent
ALTERNATIVE MODEL

- Risk Reduction
- Early Detection
- Diagnosis/Prognosis
- Therapeutic Decision-Making
- Tailored Therapy
Use G2C2 to search for Genetics & Genomics Resources for use in Your Classroom or Practice

Find websites, books, articles and more - enhance your class content with peer-reviewed resources.

http://g-2-c-2.org//
PERFORMANCE INDICATORS

Professional Practice

- Risk Assessment and Interpretation
- Genetic Education, Counseling, Testing, and Results Interpretation
- Clinical Management
- Ethical, Legal, and Social Implications (ELSI)

Professional Responsibilities

- Professional Role
- Leadership
- Research


http://www.aacn.nche.edu/education-resources/Genetics__Genomics_Nursing_Competencies_09-22-06.pdf
THE HUMAN GENOME PROJECT: THE BASICS AND BEYOND
GENE: SLC2A4 (GLUT4)

Cytogenetic Location: 17p13, which is the short (p) arm of chromosome 17 at position 13
Molecular Location: base pairs 7,281,735 to 7,288,048 on chromosome 17 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)

Credit: Genome Decoration Page/NCBI

81 million base pairs

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<td>Chondrosarcoma, extraskeletal myxoid</td>
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<td>Wilms tumor, type 4</td>
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<td>Parkinsonism-dementia</td>
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<td>Pseudohypopaldosteronism type II</td>
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<td>Osteogenesis imperfecta</td>
<td>Hemolytic anemia</td>
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<td>Ehlers-Danlos syndrome, types I and V1IA</td>
<td>Renal tubular acidosis, distal</td>
<td>Renal tubular acidosis, distal</td>
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<td>Osteoporosis, idiopathic</td>
<td>T-cell leukemia virus (I and II) receptor</td>
<td>T-cell leukemia virus (I and II) receptor</td>
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<td>Ovarian carcinoma antigen</td>
<td>Dementia, frontotemporal, with Parkinsonism</td>
<td>Dementia, frontotemporal, with Parkinsonism</td>
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<td>Neuroblastoma</td>
<td>Trichodentosseous syndrome</td>
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<td>Glanzmann thrombasthenia, type A</td>
<td>Glanzmann thrombasthenia, type B</td>
<td>Glanzmann thrombasthenia, type B</td>
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<td>Thrombocytopenia, neonatal alloimmune</td>
<td>Symphalangism, proximal</td>
<td>Symphalangism, proximal</td>
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<td>CLL/lymphoma, B-cell</td>
<td>Synostoses syndrome, multiple</td>
<td>Synostoses syndrome, multiple</td>
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<td>Retinitis pigmentosa</td>
<td>Muli breynanism</td>
<td>Muli breynanism</td>
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<td>Pituatory tumor, invasive</td>
<td>Growth hormone deficiency</td>
<td>Growth hormone deficiency</td>
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<td>Myocardial infarction, susceptibility to</td>
<td>Myeloperoxidase deficiency</td>
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<td>Alzheimer disease, susceptibility to</td>
<td>Cataracts</td>
<td>Cataracts</td>
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<td>Myotonia congenita, atypical</td>
<td>Tylosis with esophageal cancer</td>
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<td>Cramps, familial</td>
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<td>Adrenoleukodystrophy, pseudoneonatal</td>
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<td>Lung cancer, small-cell</td>
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<td>Leukemia, acute myeloid, therapy-related</td>
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<td>Campomelic dysplasia with autosomal sex reversal</td>
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<td>Apoptosis inhibitor</td>
<td>Sanfilippo syndrome, types A and B</td>
<td>Sanfilippo syndrome, types A and B</td>
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<tr>
<td>Diabetes mellitus, type II</td>
<td>Radical fringe</td>
<td>Radical fringe</td>
</tr>
</tbody>
</table>
TRIPLET REPEATS

Repeated sequence of CAG (polyglutamine tract)

Normal replication

Template slippage introduces insertion of extra CAG

Abnormal protein with extra Gln residue

Figure 12-4

Molecular Biology: Principles and Practice
© 2012 W. H. Freeman and Company

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Normal</th>
<th>Disease</th>
<th>Gene</th>
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<td>37-100</td>
<td>Huntingtin</td>
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<td>Kennedy disease</td>
<td>CAG 17-24</td>
<td>40-55</td>
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<td>Spino-cerebellar Ataxia</td>
<td>CAG 19-36</td>
<td>43-81</td>
<td>Ataxin 1</td>
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<td>Machado Joseph D</td>
<td>CAG 12-36</td>
<td>67-75</td>
<td>SCA</td>
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<td>Myotonic dystrophy</td>
<td>CTG 5-35</td>
<td>50-400</td>
<td>DM</td>
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<tr>
<td>Fragile X</td>
<td>CGG CCG GCC 6-50</td>
<td>200-1000</td>
<td>FMR1</td>
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</tbody>
</table>
SINGLE NUCLEOTIDE POLYMORPHISMS

Linked SNPs outside of gene
- no effect on protein production or function

Causative SNPs in gene
- Non-coding SNP: changes amount of protein produced
- Coding SNP: changes amino acid sequence

DNA molecule

Version 1: C T A A G T A
Version 2: C T A C G T A
Version 3: C T A G G T A
Version 4: C T A T G T A

SNP

http://learn.genetics.utah.edu/
EPIGENOME

Nature (genome)  Inherited

Nurture (epigenome)  Acquired
Factors Influencing Epigenetic Modifications

- Developmental program (includes aging)
- Genetic variation
- Nutrition
- Environment
- Drugs
- Others
Published Genome-Wide Associations through 12/2013
Published GWA at \( p \leq 5 \times 10^{-8} \) for 17 trait categories

NHGRI GWA Catalog
www.genome.gov/GWASTudies
www.ebi.ac.uk/fgpt/gwas/
Tissues and cell types profiled in the Roadmap Epigenomics Consortium.

## THE REST OF THE STORY

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Examples of Techniques Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcriptomics</td>
<td>“The quantitative study of all genes expressed in a given biological state”(^{25})</td>
<td>Gene expression microarrays; RNA sequencing(^{25})</td>
</tr>
<tr>
<td>Proteomics</td>
<td>Large-scale analysis of all the proteins in an organism, tissue type, or cell (called the proteome). Proteomics can be used to reveal specific, abnormal proteins that lead to diseases</td>
<td>Matrix-assisted laser desorption/ionization(^{28}); mass spectroscopy; electrospray ionization(^{29})</td>
</tr>
<tr>
<td>Metabolomics (metabolic profiling)</td>
<td>“Measurements of the metabolome, which represents the entire collection of all small-molecule metabolites present in any biological organism”(^{36})</td>
<td>Nuclear magnetic resonance; mass spectrometry(^{36})</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>“Pharmacogenomics is the study of an individual’s interaction with a specific drug based upon the genetic make-up of the individual”(^{39})</td>
<td>“Pharmacogenomics studies the influence of genetic variations on the patient’s response to specific drugs, such as the correlation between the efficacy or toxicity of a certain drug and a specific gene expression or a single-nucleotide polymorphism”(^{39})</td>
</tr>
<tr>
<td>Bioinformatics</td>
<td>“Information technology as applied to the life sciences, especially the technology used for the collection and analysis of genomic data”(^{118})</td>
<td></td>
</tr>
</tbody>
</table>

DIABETES AND PERSONALIZED HEALTHCARE PERSPECTIVES
10 LEADING CAUSES OF DEATH, U.S.

- Heart disease: 599,413
- Cancer: 567,628
- Chronic lower respiratory diseases: 137,353
- Stroke: 128,842
- Accidents: 118,021
- Alzheimer's disease: 79,003
- Diabetes: 68,705
- Influenza and Pneumonia: 53,692
- Kidney diseases: 48,935
- Intentional self-harm: 36,909

An integrated approach, taking into account genetic and epigenetic determinants is required for the effective prevention of T2DM beginning from the start of life

Asia: “diabetes epicenter”

Chen et al., Nat Rev Endocrinol. 2012
Search


diabetes

Filters

- All (162)
- Health Conditions (65)
- Genes (89)
- Help Me Understand Genetics (8)

Submit

**MTHFR gene**

diabetes and deafness (MIDD). People with this condition have diabetes and sometimes hearing loss.

**IRSI gene**
in this gene are associated with type II diabetes and susceptibility to insulin resistance. [provided

**CCGR gene**
glucose levels. Defects in this gene are a cause of non-insulin-dependent diabetes mellitus (NIDDM

**PDX1 gene**
lead to early-onset insulin-dependent diabetes mellitus (NIDDM), as well as maturity onset diabetes of

**HNF1B gene**
the embryonic pancreas. Mutations in this gene result in renal cysts and diabetes syndrome and
# ESTABLISHED TYPE 2 DIABETES SUSCEPTIBILITY LOCI

<table>
<thead>
<tr>
<th>Index SNP</th>
<th>Chromosome</th>
<th>Position</th>
<th>Region/gene</th>
<th>Identification</th>
<th>$\lambda_s^*$</th>
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<td>rs2237892</td>
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</table>

*The sibling recurrence risk ratio calculated in European populations, with the exception of the KCNQ1 locus, which was based on East Asian populations.  
†The primary association for this locus is with body mass index.  
‡The primary association for this locus is with fasting glucose levels.  
GWA—genome-wide association; SNP—single nucleotide polymorphism.

Diabetes Mellitus (2015)

- T1D
  - Type 1a
  - Type 1b
  - LADA
  - IPEX
  - MEA

- T2D
  - Idiopathic hyperglycemia
  - Obese
  - Non-obese (Asian)
  - Ketosis-prone

- Monogenic

- GDM

- Other Disease-Associated
  - Cystic Fibrosis
  - Pancreatitis
  - Hemochromatosis
  - Acromegaly (other endocrinopathies)
  - HCV/HIV
  - Others

- Drug-Associated

- Neonatal
  - Permanent
  - Transient

- MODY
  - HNF4A, GCK, HNF1A, PDX1, HNF1B, ABCC8, KCNJ11, PAX4, KLF11, INS, CEL, NEUROD1, BLK

- Syndromic
  - EIF2AK3
  - WFS1,2
  - Mitochondrial

- Type 1
  - IPEX

- Congenital Lipodystrophies

- Genetic Defects in Insulin Action
  - Type A Insulin Resistance
  - Leprechaunism
  - Rabson-Mendenhall Syndrome

## Optimal Treatments for Monogenic Diabetes by Subtype

<table>
<thead>
<tr>
<th>Monogenic diabetes subtype</th>
<th>Distinguishing clinical features</th>
<th>Examples of causal genes</th>
<th>Optimal treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCK-MODY</td>
<td>Mild fasting hyperglycaemia</td>
<td>GCK</td>
<td>Diet alone</td>
</tr>
<tr>
<td>HNF1A-MODY</td>
<td>Young onset diabetes</td>
<td>HNF1A</td>
<td>Low dose sulphonylurea</td>
</tr>
<tr>
<td>Neonatal diabetes</td>
<td>Diabetes diagnosed before 6 months</td>
<td>KCNJ11, ABCC8, INS</td>
<td>High dose sulphonylurea, insulin</td>
</tr>
<tr>
<td>HNF4A-MODY</td>
<td>Young onset diabetes, increased birth weight and macrosomia</td>
<td>HNF4A</td>
<td>Low dose sulphonylurea</td>
</tr>
</tbody>
</table>

### Examples of rarer subtypes with extrapancreatic features

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical Features</th>
<th>Causal Genes</th>
<th>Optimal treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1B-MODY</td>
<td>Renal cysts, genitourinary abnormalities, exocrine pancreatic insufficiency</td>
<td>HNF1B</td>
<td>Early insulin</td>
</tr>
<tr>
<td>Mitochondrial diabetes</td>
<td>Deafness, short stature, pigmentary retinopathy</td>
<td>MTTL1</td>
<td>Sulphonylurea initially but rapid progression to insulin requirement</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>Optic atrophy, diabetes insipidus, deafness, renal tract abnormalities, neurological abnormalities</td>
<td>WFS1</td>
<td>Insulin</td>
</tr>
<tr>
<td>TRMA syndrome</td>
<td>Megaloblastic anaemia, deafness</td>
<td>SLC19A2</td>
<td>Thiamine ± sulphonylurea ± early insulin</td>
</tr>
</tbody>
</table>

GCK, glucokinase; HNF4A, hepatocyte nuclear factor 4A; MODY, maturity-onset diabetes of the young; TRMA, thiamine responsive megaloblastic anaemia.
The Revised Diabetes Pie (2013)

ANDIS project (Sweden): Reclassification based on genetic markers and biomarkers

Groop et al., Mol Cell Endocrinol. 2013
PRECISION MEDICINE DIABETES CLINIC

- Prevention
- Diagnosis
- Treatment
- Monitoring

GREATEST RISK CONSIDERATIONS

- Fasting plasma glucose 100-125 mg/dl (impaired fasting)
- Plasma Glucose 2 hours after 75g. oral glucose challenge of 140-199 mg/dl (impaired glucose tolerance)
- Hemoglobin A1c

Not All persons at the Same RISK for microvascular and macrovascular complications

THE GENETIC EYE
FAMILY HISTORY:
IN GENETICS, THE FAMILY IS THE PATIENT

- A comprehensive family history is an important first step in the analysis of any disorder, whether or not the disorder is known to be genetic
- It can be critical in diagnosis
- May show that a disorder is hereditary
- Can provide information about the natural history of a disease and variation in its expression
- Clarify the pattern of inheritance
- The diagnosis of a hereditary condition allows the risk in other family members to be estimated, so that proper management, prevention and counseling can be offered to the patient AND the family
Look for these Red Flags

- Family history of multiple affected members
- Onset of disease at age earlier than expected
- Condition in the less-often affected sex
- Disease in the absence of known risk factors
- Ethnic predisposition of genetic disorders
- Close biological relationship between parents
- Developmental delays
- Unexplained mental retardation
- One or more major malformations
- Recurrent pregnancy losses (>2)
- Unexpected drug reactions/responses

http://www.nchpeg.org/index.php?option=com_content&view=article&id=59&Itemid=75
QUESTIONS: MONOGENIC DIABETES

1. Diabetes diagnosed before one year of age; or
2. Type 1 diabetes and a parent or child with type 1 diabetes; or
3. Diabetes other than Type 1 diagnosed at 30 years of age or less; or
4. Type 2 diabetes diagnosed by 45 years of age, not extremely overweight at diagnosis, and 2 or more relatives diagnosed with diabetes by 50 years of age; or
5. Diabetes along with other features, such as birth defects, intellectual disability, deafness or blindness; or
6. Lean and have or have had gestational diabetes; or
7. Diabetes suspected by your physician to be monogenic or unusual in some way

Think Genomics and Drugs!

Pharmacogenomics is how a person’s genomic makeup influences their response to drugs

ANY OF THESE MEDICATION RESPONSES at RECOMMENDED DOSES

★ Unexpected reactions
★ Toxicity
★ No Response
★ Limited response
★ Some decreased efficacy
★ Decreased efficacy

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
https://www.pharmgkb.org/

http://healthyblackmen.org/2012/03/11/physicians-patients-pills-part-i/
Case Study

Genetics and Complex Disease

Case Study

Although almost every disease has a genetic component, most diseases are not inherited in predictable, single-gene patterns (dominant, recessive, x-linked). That is why most of the conditions that burden us from a public health perspective – caries, diabetes, heart disease – are called "complex."

Complex diseases arise from a combination of factors, including the interaction of multiple genes, lifestyle choices, and environmental exposure.

Although these conditions are more frequent, their patterns of transmission are more elusive because the disease traits don’t segregate neatly from generation to generation, as do single-gene disorders.

Instead, complex traits aggregate or cluster within families, and it is difficult to predict who will be affected and how the disease will express itself.
The most marked oral complications seen in uncontrolled diabetic patients includes:

- periodontal disease (which is more severe and has a higher prevalence than that seen in the non-diabetic),
- xerostomia,
- burning mouth syndrome,
- candidiasis,
- delayed and abnormal wound healing,
- increased propensity to infection,
- diminished salivary flow, and
- salivary gland enlargement.
DEBBIE

A 40-year-old Hispanic woman who comes to you to replace a crown. She has never been to your office before, and during oral examination, you find periodontal disease, several canker sores, and a carious lesion, even though she claims to have excellent home care. She makes an appointment for a restoration the following week. At her next appointment, she also complains of xerostomia, but attributes it to allergies.
TAKING THE FAMILY HISTORY WILL HELP PUT DEBBIE’S INTRAORAL FINDINGS INTO A BROADER PERSPECTIVE. GO THROUGH THE QUESTIONS BELOW TO CONSTRUCT DEBBIE’S GENETIC FAMILY HISTORY.
IS DEBBIE OVERWEIGHT?
IS THIS COMMON IN THE FAMILY?

1/2 sister  Debbie  brother
overweight     40 y.o.  overweight

virtually all, except the uncle, who is a health nut.
HOW LONG HAS DEBBIE HAD THESE SYMPTOMS?

1/2 sister Debbie 40 y.o. symp. ~ 3 yrs.

Your patient

off and on for about three years
HAS DEBBIE OR ANYONE ELSE IN HER FAMILY BEEN DIAGNOSED WITH DIABETES?

brother, uncle, and 1st cousin on mother’s side, 1/2 sister from mother’s second marriage
WHAT TYPE - INSULIN DEPENDENT OR NON-INSULIN DEPENDENT?
HOW OLD WERE THEY WHEN THEY WERE DIAGNOSED?

- Father: NIDDM, Dx 38
- 1/2 sister (Debbie): NIDDM, Dx 38, symp ~3 yrs
- Brother: NIDDM, Dx 34
- Uncle: NIDDM, Dx 47 y.o.
- 1st cousin: NIDDM, Dx 36
1. Diabetes diagnosed before one year of age; or
2. Type 1 diabetes and a parent or child with type 1 diabetes; or
3. Diabetes other than Type 1 diagnosed at 30 years of age or less; or
4. Type 2 diabetes diagnosed by 45 years of age, not extremely overweight at diagnosis, and 2 or more relatives diagnosed with diabetes by 50 years of age; or
5. Diabetes along with other features, such as birth defects, intellectual disability, deafness or blindness; or
6. Lean and have or have had gestational diabetes; or
7. Diabetes suspected by your physician to be monogenic or unusual in some way

ENVIRONMENTAL CONSIDERATIONS:

- City and Country where born
- Culture
- Diet
- Lifestyle
- Occupation
- Stress
- Exposure to chemicals (pesticides, insecticides, paints, solvents, asbestos, hair dyes, etc...)
- Tobacco Use
- Alcohol Use
Does a clear pattern of inheritance emerge

- A. Autosomal Dominant Inheritance
- B. Autosomal Recessive Inheritance
- C. X-Linked Recessive Inheritance
- D. None of the above
Thank-You
REFERENCES


-Grop, L., Pociot, F., Institutionen för kliniska vetenskaper, Malmö, Medicinska fakulteten, Department of Clinical Sciences, Malmö, Faculty of Medicine, . . . Endokrinologi. (2013). Genetics of diabetes - are we missing the genes or the disease? *Molecular and Cellular Endocrinology*, (April,12)


