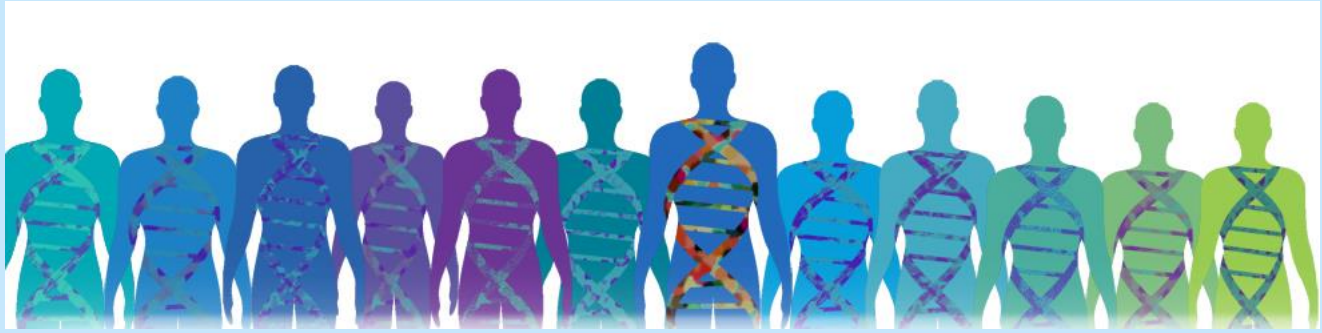
AMERICAN DIABETES ASSOCIATION

DIABETES AND PERSONALIZED HEALTHCARE: WHY GENES MATTER



Katherine Chadwell, DNP, MBMSc, ARNP. GNP-BC, GCNS, CPHQ

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

https://www.nih.gov/precision-medicine-initiative-cohort-program

PARADIGM SHIFT

CURRENT MODEL

- Patient becomes sick
- History and exam
- Differential diagnosis
- Test selection/applicatior
- Refine differential or d
- Treat

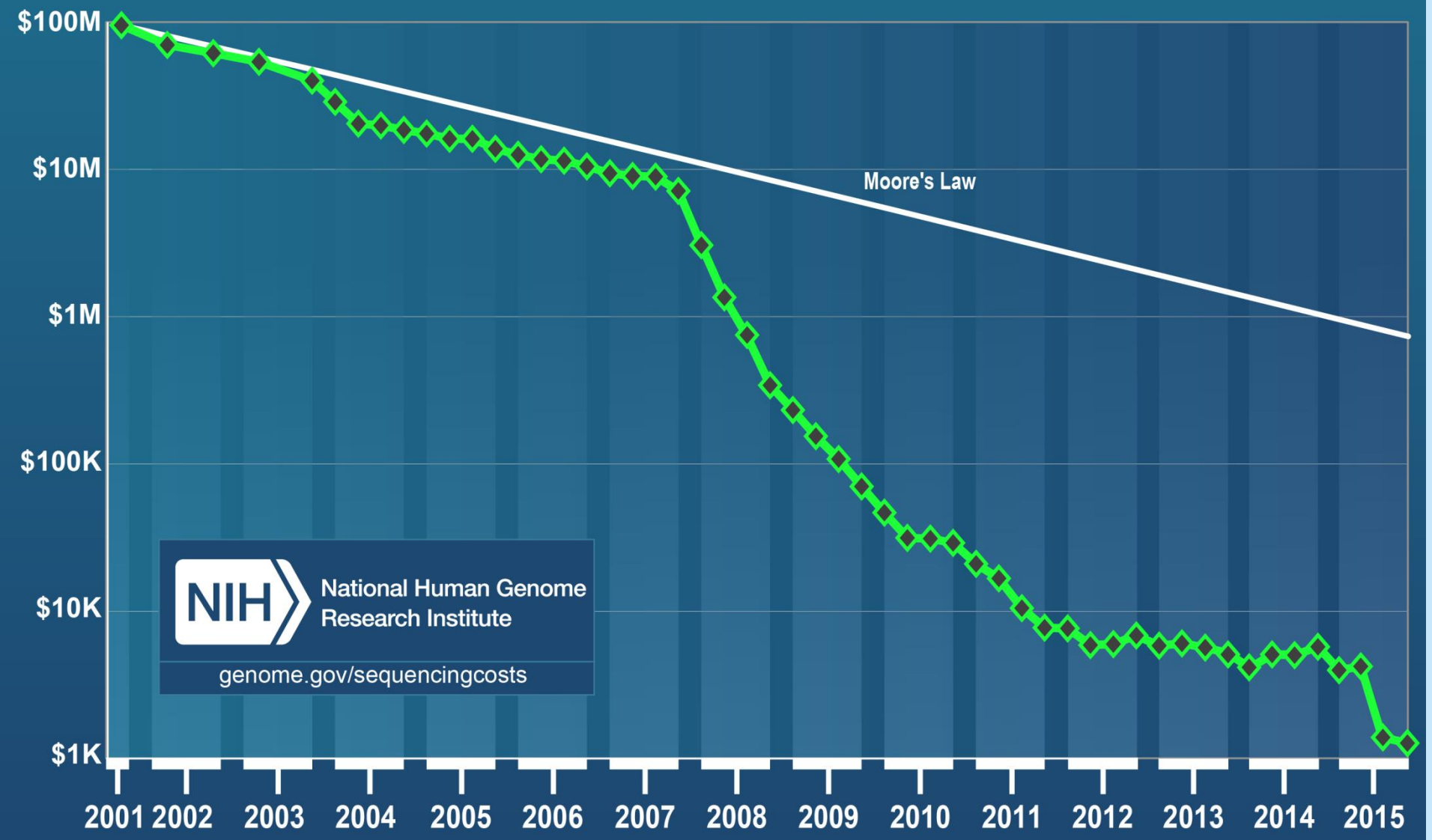
ALTERNATIVE MODEL

- 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

Cost per Genome



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PERFORMANCE INDICATORS

Professional Practice

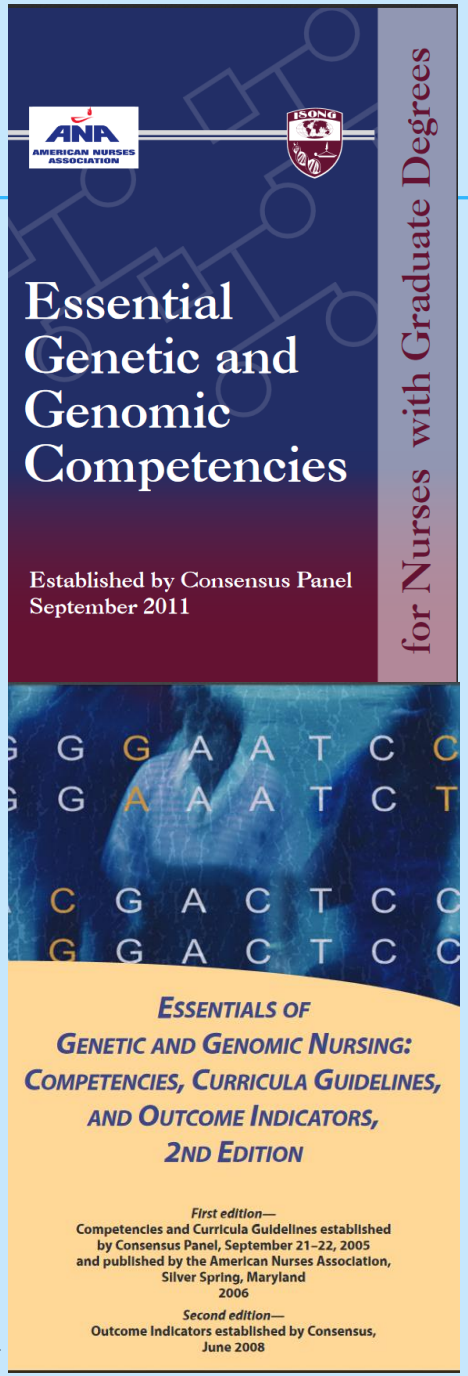
- Risk Assessment and Interpretation
- Genetic Education, Counseling, Testing, and Results Interpretation
- Clinical Management
- Ethical, Legal, and Social Implications (ELSI)

Professional Responsibilities

- Professional Role
- Leadership
- Research

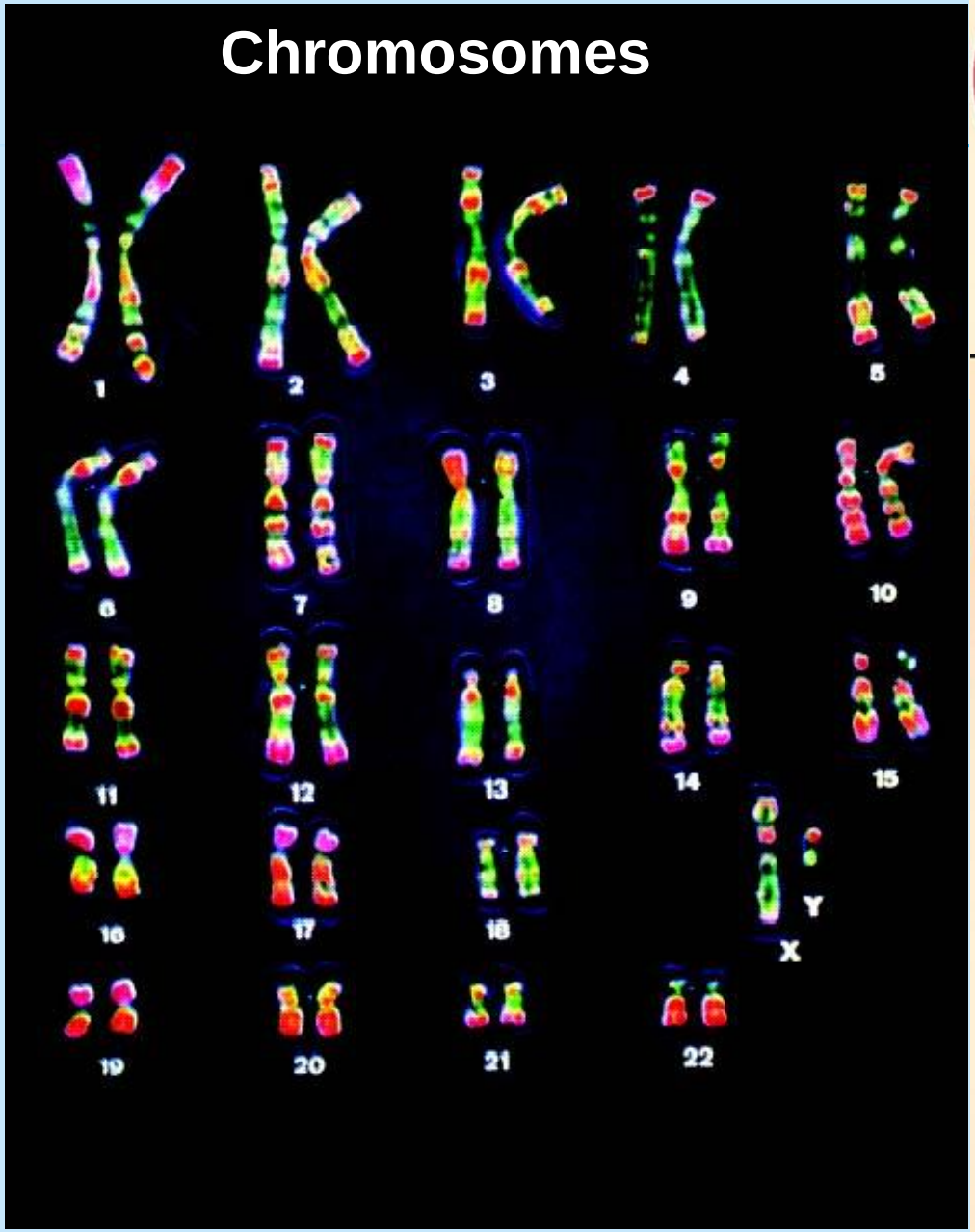
http://www.nursingworld.org/MainMenuCategories/EthicsStandards/Genetics-1/Essential-Genetic-and-Genomic-Competencies-for-Nurses-With-Graduate-Degrees.pdf

http://www.aacn.nche.edu/education-resources/Genetics__Genomics_Nursing_Competencies_09-22-06.pdf



THE HUMAN GENOME PROJECT: THE BASICS AND BEYOND

Chromosomes



Change of chromosome number

Changes number in autosome chromosomes

Example: Down's syndrome

Changes number in sex chromosomes

Examples: Turner syndrome, Klinefelter syndrome, XYY condition.

Change of chromosome structure

Duplication

Genes sequences are **repeated** several to many hundreds or thousands of times.

Deletion

Loss of some segment of a chromosome

Inversion

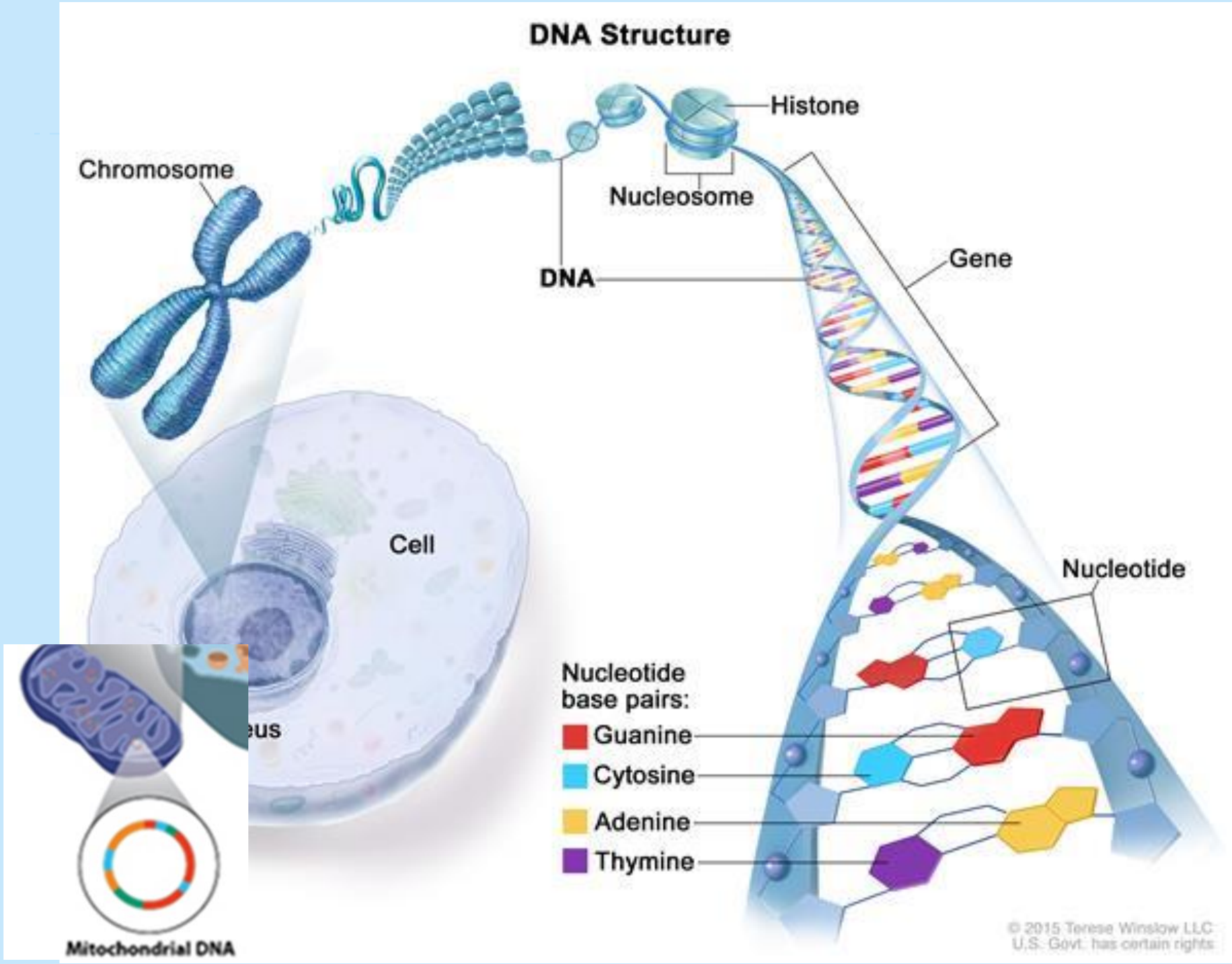
A linear segment of DNA within the chromosome becomes oriented in the **reverse direction**, with no molecular loss.

Translocation

Exchange of segments DNA between **non-homologous chromosomes**

ASK4BIOLOGY.COM

https://ehumanbiofield.wikispaces.com/Chromosomes+CH


DNA Structure
Histone
Chromosome
Nucleosome
Gene
DNA
Cell
Nucleotide
Nucleotide base pairs:
Guanine
Cytosine
Adenine
Thymine
Mitochondrial DNA
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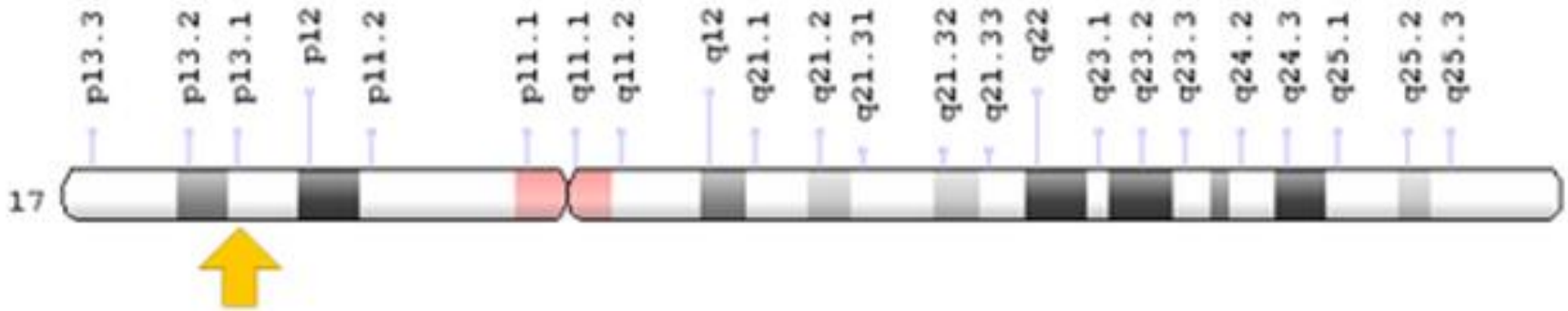
GENE: SLC2A4 (GLUT4)

Chromosomal Location

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

https://ghr.nlm.nih.gov/gene/SLC2A4#location

17

81 million base pairs

Canavan disease
Ovarian cancer
Miller-Dieker syndrome
Retinitis pigmentosa
Tumor protein p53
Colorectal cancer
Li-Fraumeni syndrome
Cystinosis, nephropathic
Diabetes mellitus, noninsulin-dependent
Cone dystrophy
Myasthenic syndrome
Deafness, autosomal recessive
Smith-Magenis syndrome
VLCAD deficiency
Maturity Onset Diabetes of the Young, type V
Hypertension, essential, susceptibility to
T-cell immunodeficiency, alopecia, and nail dystrophy
Chondrosarcoma, extraskeletal myxoid
Neurotransmitter transporter, serotonin (anxiety-related)
Neurofibromatosis, type 1
Watson syndrome
Leukemia, juvenile myelomonocytic
HIV-1 disease, delayed progression of
Meesmann corneal dystrophy
Muscular dystrophy, limb-girdle
Epidermolysis bullosa simplex, recessive
Pachyonychia congenita, Jackson-Lawler type
Steatocystoma multiplex
Wilms tumor, type 4
Glycogen storage disease (von Gierke disease)
Parkinsonism-dementia
Epidermolytic hyperkeratosis
Patella aplasia or hypoplasia
Osteogenesis imperfecta
Ehlers-Danlos syndrome, types I and VIIA
Osteoporosis, idiopathic
Ovarian carcinoma antigen
Neuroblastoma
Glanzmann thrombasthenia, type A
Thrombocytopenia, neonatal alloimmune
CLL/lymphoma, B-cell
Retinitis pigmentosa
Pituitary tumor, invasive
Myocardial infarction, susceptibility to
Alzheimer disease, susceptibility to
Myotonia congenita, atypical
Cramps, familial
Fetal Alzheimer antigen
Lung cancer, small-cell
Campomelic dysplasia with autosomal sex reversal
Apoptosis inhibitor
Diabetes mellitus, type II
Radical fringe

Bernard-Soulier syndrome
Breast cancer-related regulator of TP53
Hypermethylated in cancer
Lissencephaly
Subcortical laminar heterotopia
Leber congenital amaurosis, type I
Medulloblastoma
Cataract, anterior polar
Myasthenia gravis, familial infantile
Bruck syndrome
Sjogren-Larsson syndrome
Charcot-Marie-Tooth neuropathy
Dejerine-Sottas disease
Van der Woude syndrome modifier
Choroidal dystrophy, central areolar
Huntingtin-associated protein
Psoriasis susceptibility
Epidermolysis bullosa
Alzheimer disease, susceptibility to
Van Buchem disease
Malignant hyperthermia susceptibility
Leukemia, acute promyelocytic
Epidermolytic palmoplantar keratoderma
Pachyonychia congenita, Jadassohn-Lewandowsky type
Keratoderma, nonepidermolytic palmoplantar
Sclerosteosis
Muscular dystrophy, Duchenne-like, type 2
Adhalinopathy, primary
Breast cancer, early onset
Ovarian cancer
Leukemia, myeloid/lymphoid or mixed-lineage
Breast cancer, sporadic
Gliosis, familial progressive subcortical
Pseudohypoaldosteronism type II
Spherocytosis, hereditary
Hemolytic anemia
Renal tubular acidosis, distal
T-cell leukemia virus (I and II) receptor
Dementia, frontotemporal, with Parkinsonism
Trichodontoosseous syndrome
Glanzmann thrombasthenia, type B
Symphalangism, proximal
Synostoses syndrome, multiple
Mulibrey nanism
Growth hormone deficiency
Myeloperoxidase deficiency
Cataracts
Tylosis with esophageal cancer
Adrenoleukodystrophy, pseudoneonatal
Deafness, autosomal dominant
Leukemia, acute myeloid, therapy-related
Myasthenic syndrome, slow-channel congenital
Sanfilippo syndrome, types A and B

TRIPLET REPEATS

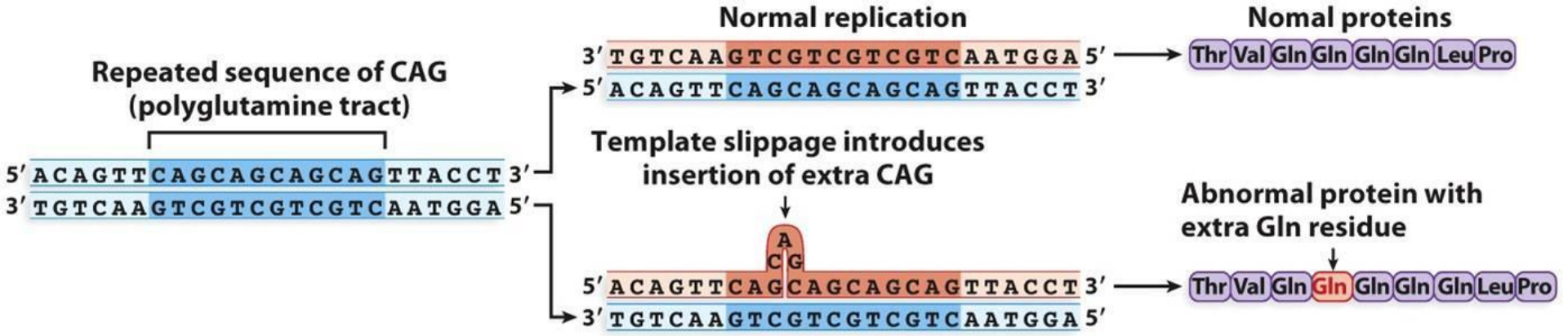
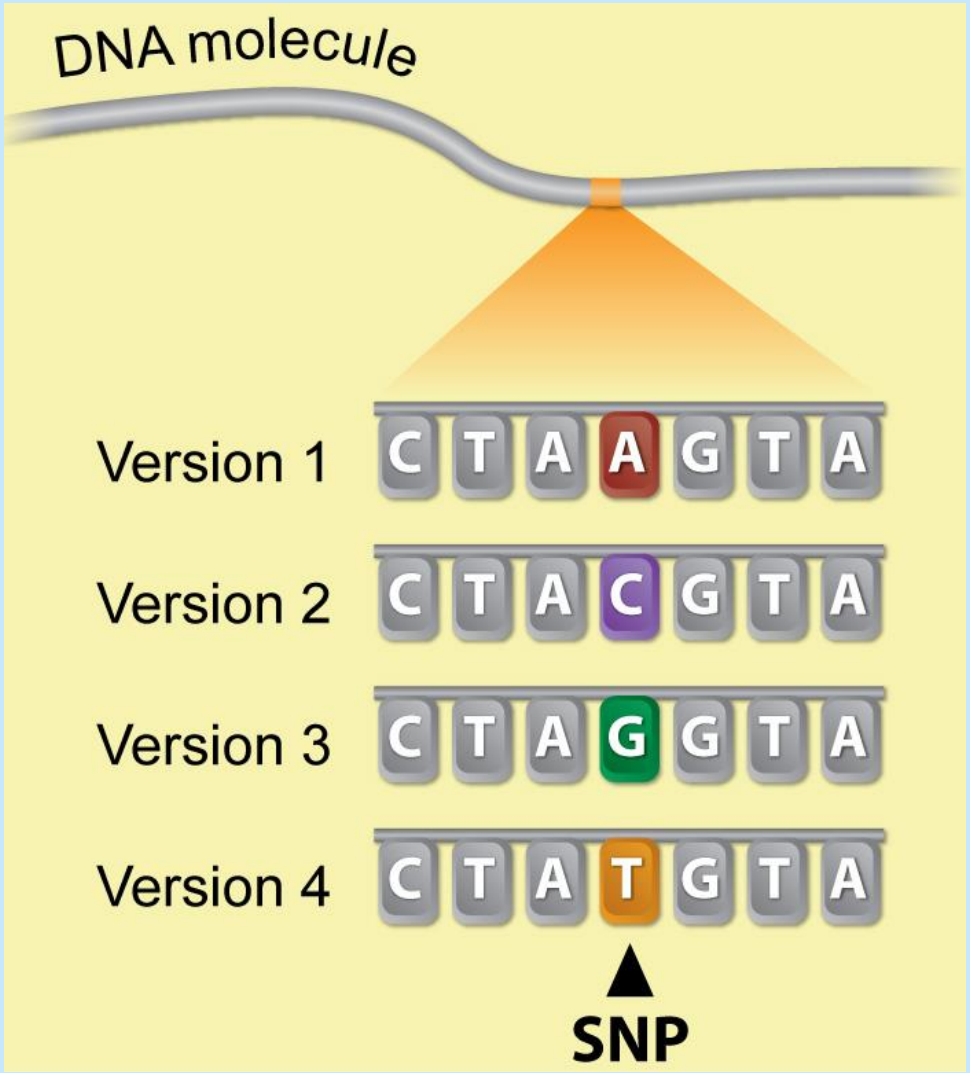
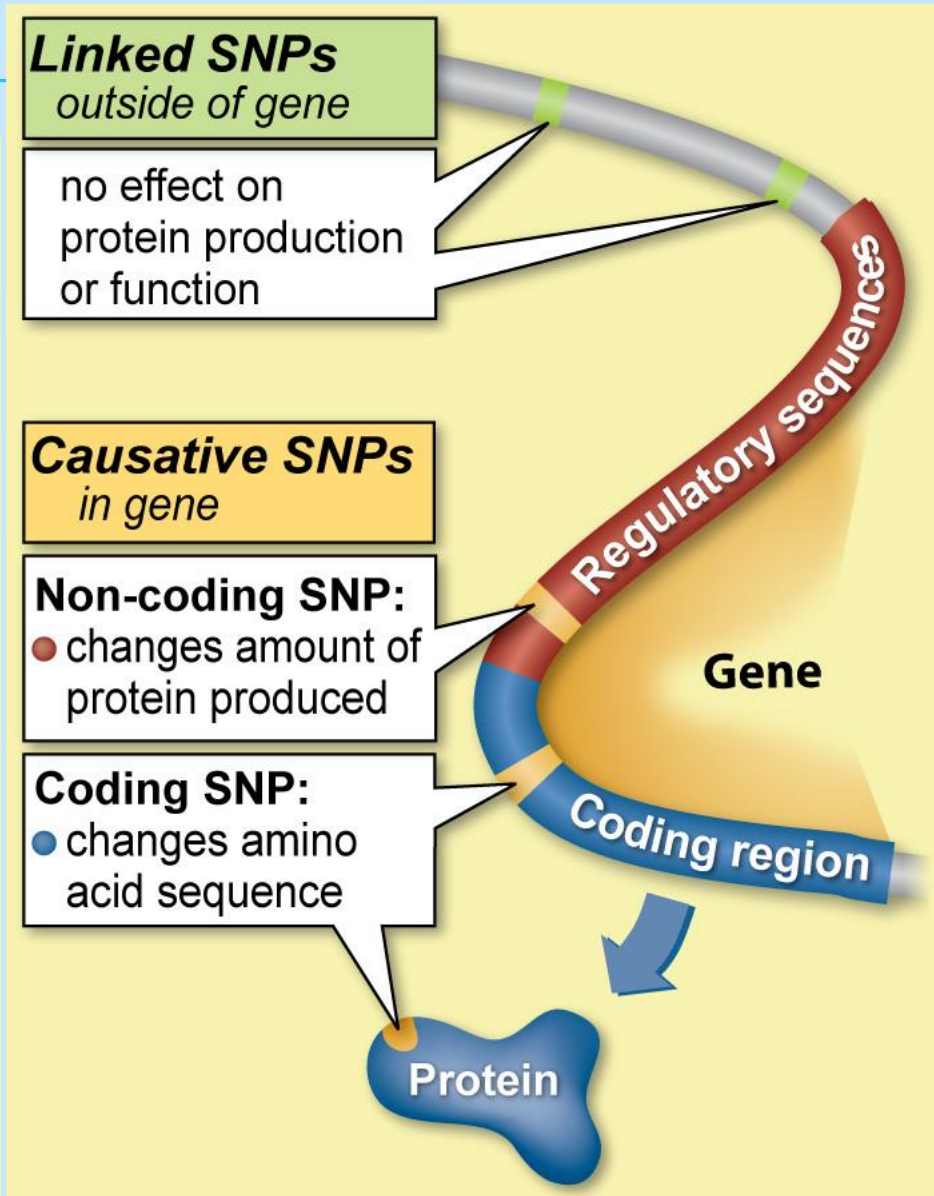


Figure 12-4
Molecular Biology: Principles and Practice

		Normal	Disease	Gene
Huntington disease	CAG	9-35	37-100	Huntingtin
Kennedy disease	CAG	17-24	40-55	androgen receptor
Spino-cerebellar Ataxia	CAG	19-36	43-81	Ataxin 1
Machado Joseph D	CAG	12-36	67-75	SCA
Myotonic dystrophy	CTG	5-35	50-400	DM
Fragile X	CGG CCG GCC	6-50	200-1000	FMR1

SINGLE NUCLEOTIDE POLYMORPHISMS

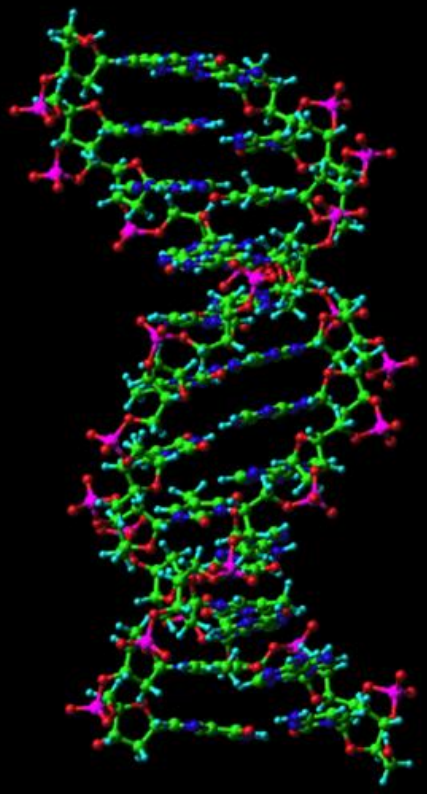




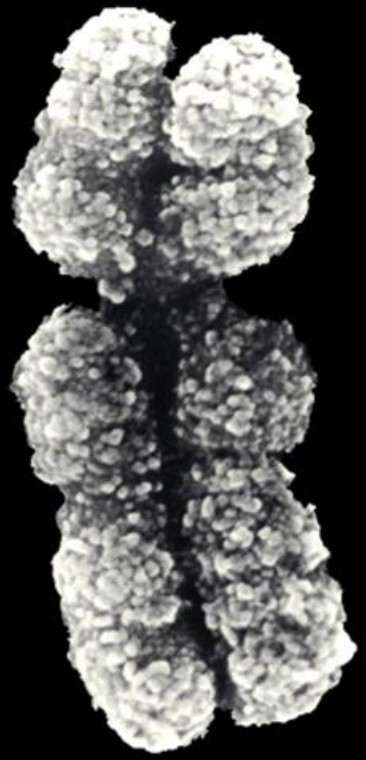
http://learn.genetics.utah.edu/

EPIGENOME

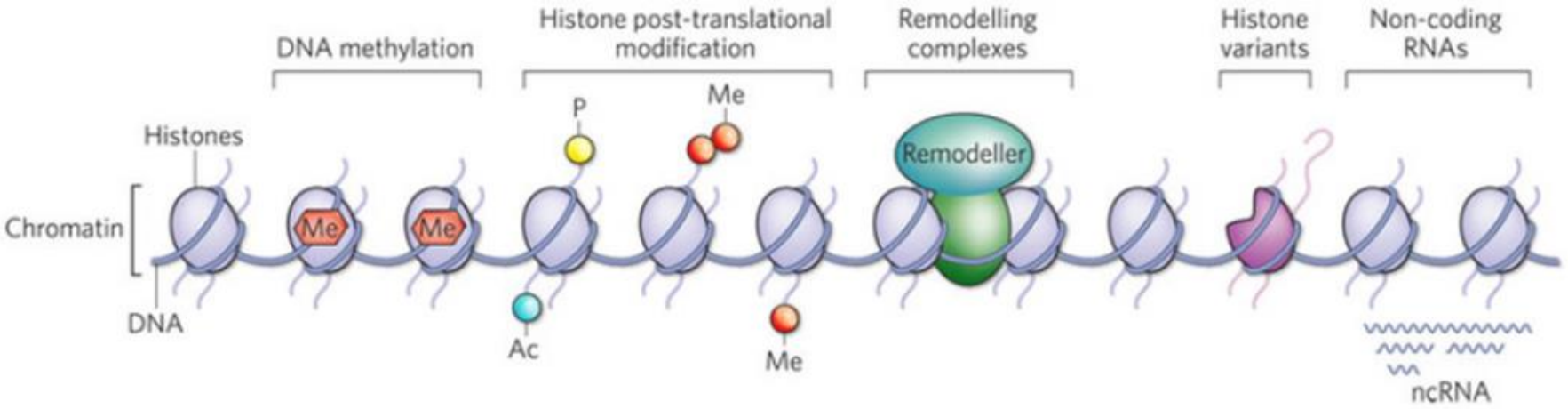
Nature (genome)
Inherited



Nurture (epigenome)
Acquired



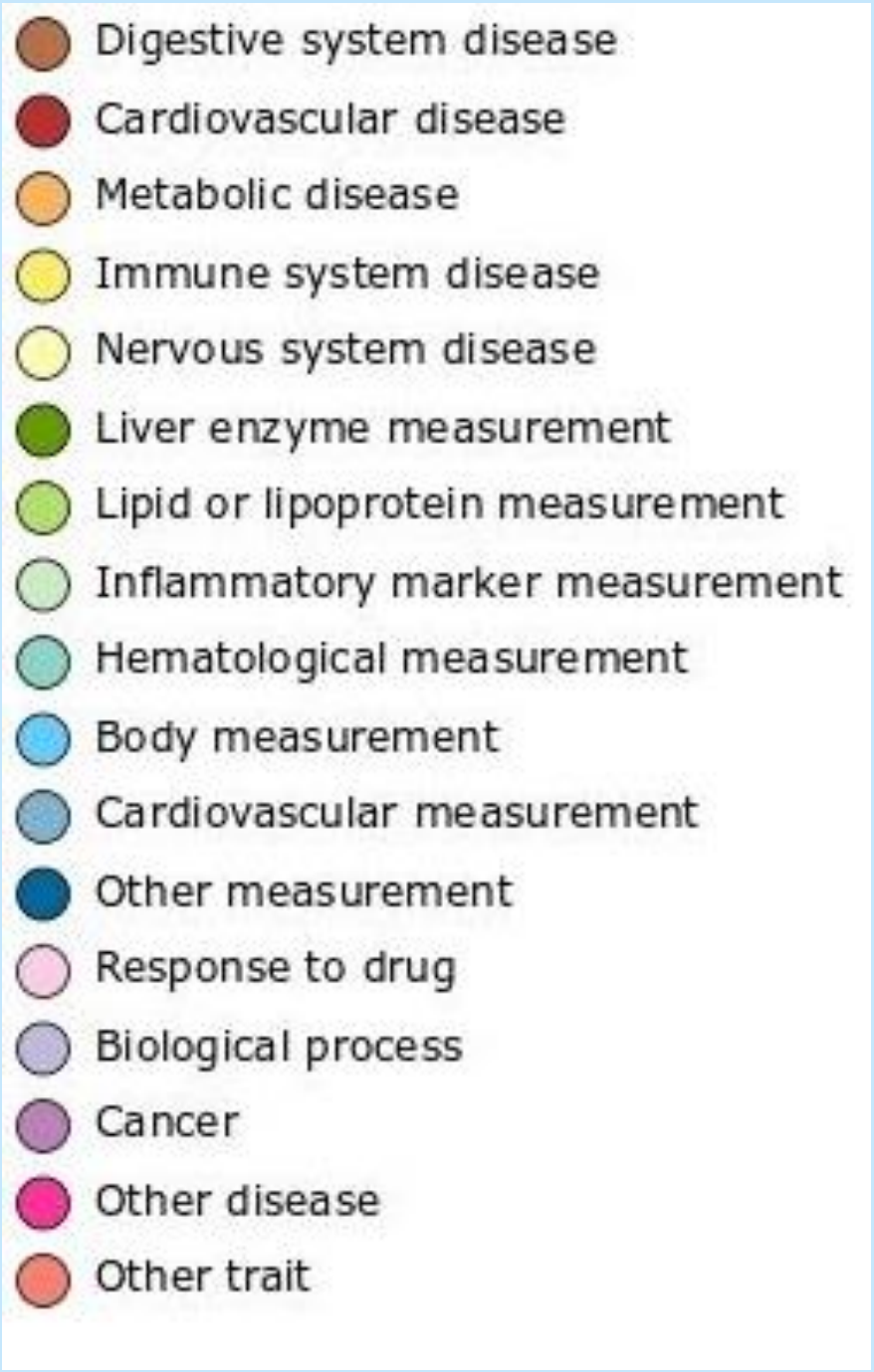
EPIGENETIC MODIFICATIONS



C. Dulac, Nature 465:7299 (2010)

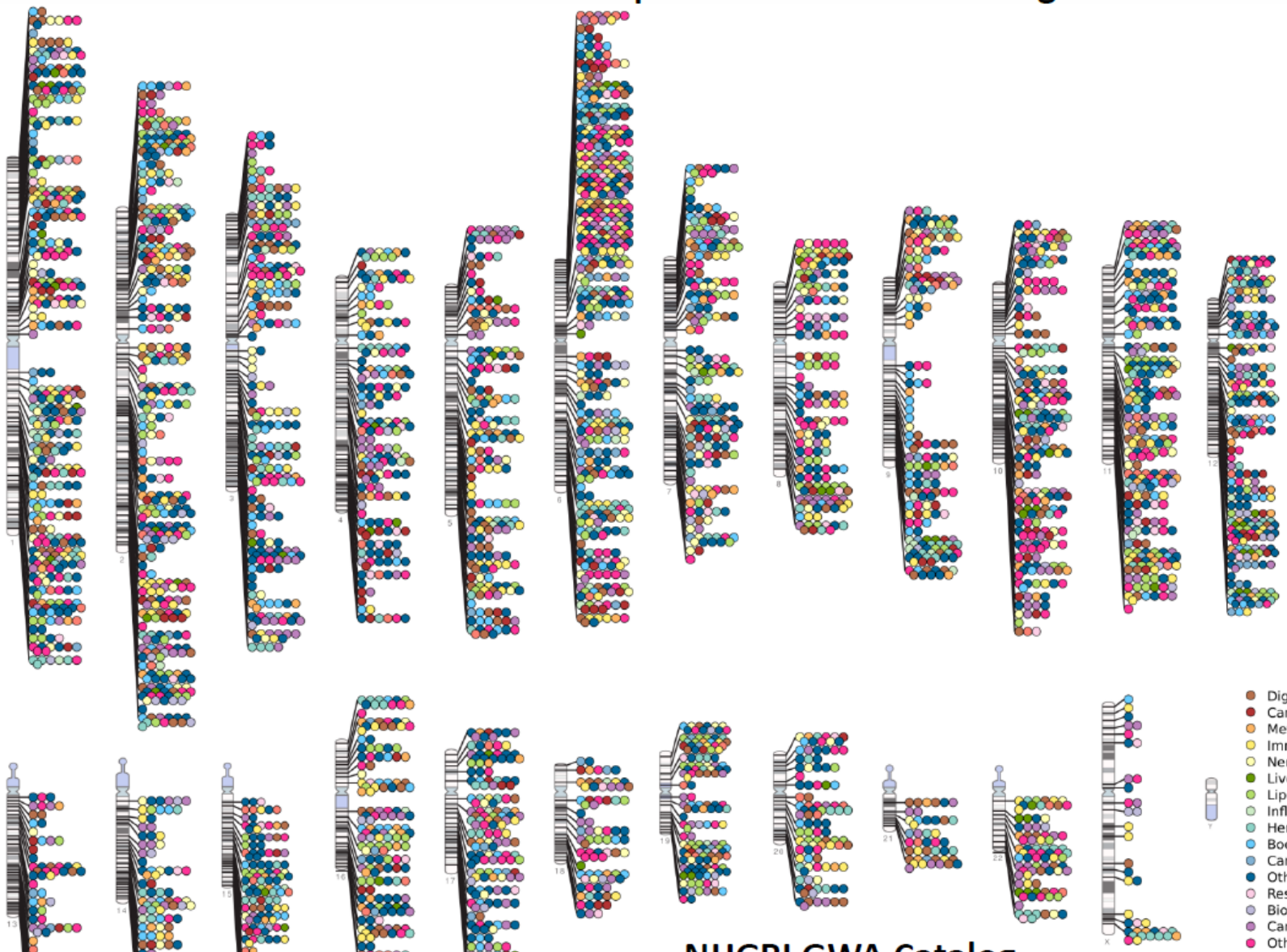
Factors Influencing Epigenetic Modifications

- **Developmental program (includes aging)**
- **Genetic variation**
- **Nutrition**
- **Environment**
- **Drugs**
- **Others**


Digestive system disease
Cardiovascular disease
Metabolic disease
Immune system disease
Nervous system disease
Liver enzyme measurement
Lipid or lipoprotein measurement
Inflammatory marker measurement
Hematological measurement
Body measurement
Cardiovascular measurement
Other measurement
Response to drug
Biological process
Cancer
Other disease
Other trait

Published Genome-Wide Associations through 12/2013

Published GWA at $p \leq 5X10^{-8}$ for 17 trait categories

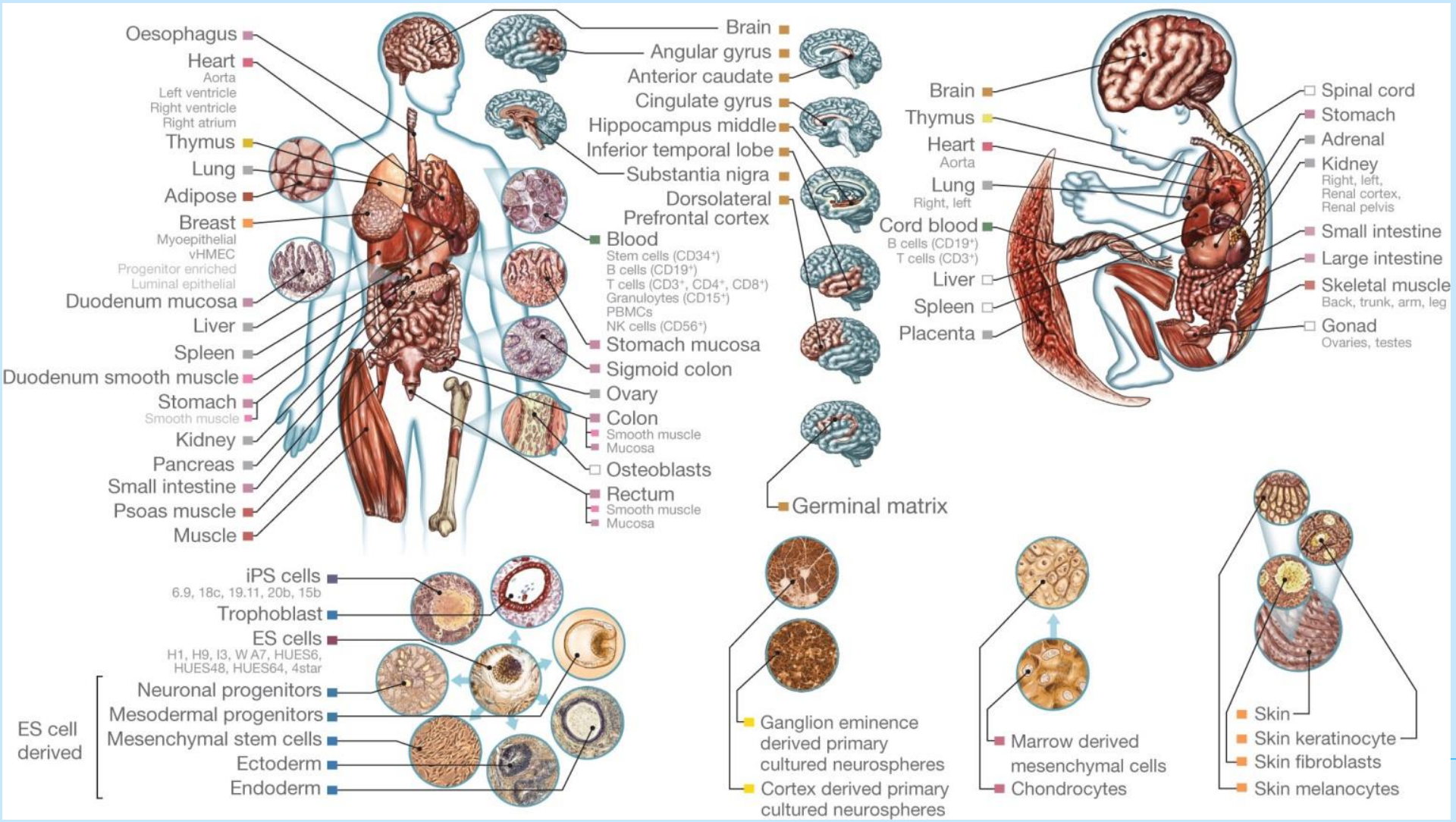


NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

EMBL-EBI

Tissues and cell types profiled in the Roadmap Epigenomics Consortium.



Roadmap Epigenomics Consortium *et al. Nature* **518**, 317-330 (2015) doi:10.1038/nature14248

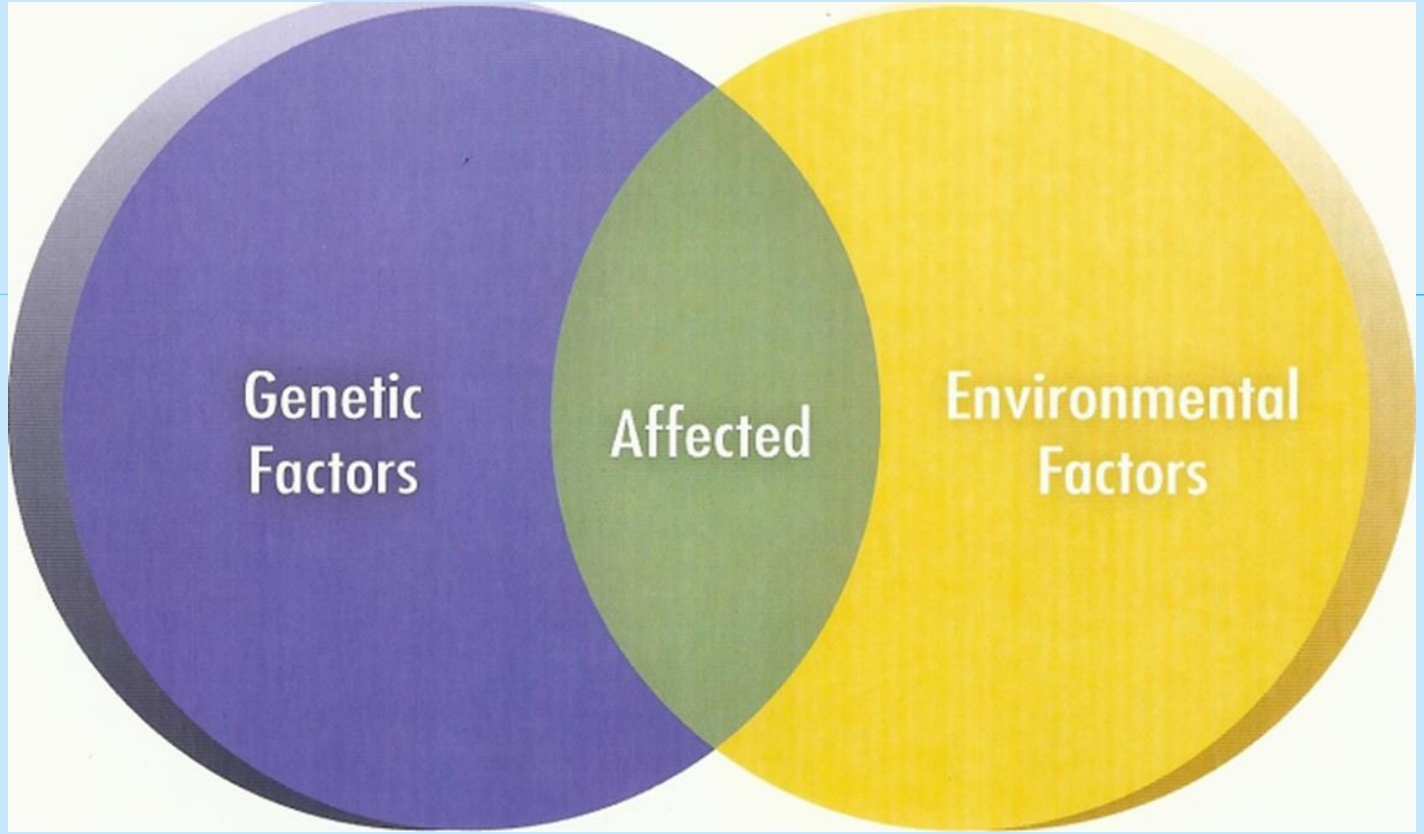
nature

THE REST OF THE STORY

Term	Definition	Examples of Techniques Used
Transcriptomics	"The quantitative study of all genes expressed in a given biological state"[25]	Gene expression microarrays; RNA sequencing[25]
Proteomics	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	Matrix-assisted laser desorption/ionization[28]; mass spectroscopy; electrospray ionization[29]
Metabolomics (metabolic profiling)	"Measurements of the metabolome, which represents the entire collection of all small-molecule metabolites present in any biological organism"[36]	Nuclear magnetic resonance; mass spectrometry[36]
Pharmacogenomics	"Pharmacogenomics is the study of an individual's interaction with a specific drug based upon the genetic make-up of the individual"[39]	"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]
Bioinformatics	"Information technology as applied to the life sciences, especially the technology used for the collection and analysis of genomic data"[118]	

Glauber, H. S., Rishe, N., & Karnieli, E. (2014). Introduction to personalized medicine in diabetes mellitus. *Rambam Maimonides Medical Journal, 5*(1), e0002. doi:10.5041/RMMJ.10136

DIABETES AND PERSONALIZED HEALTHCARE PERSPECTIVES

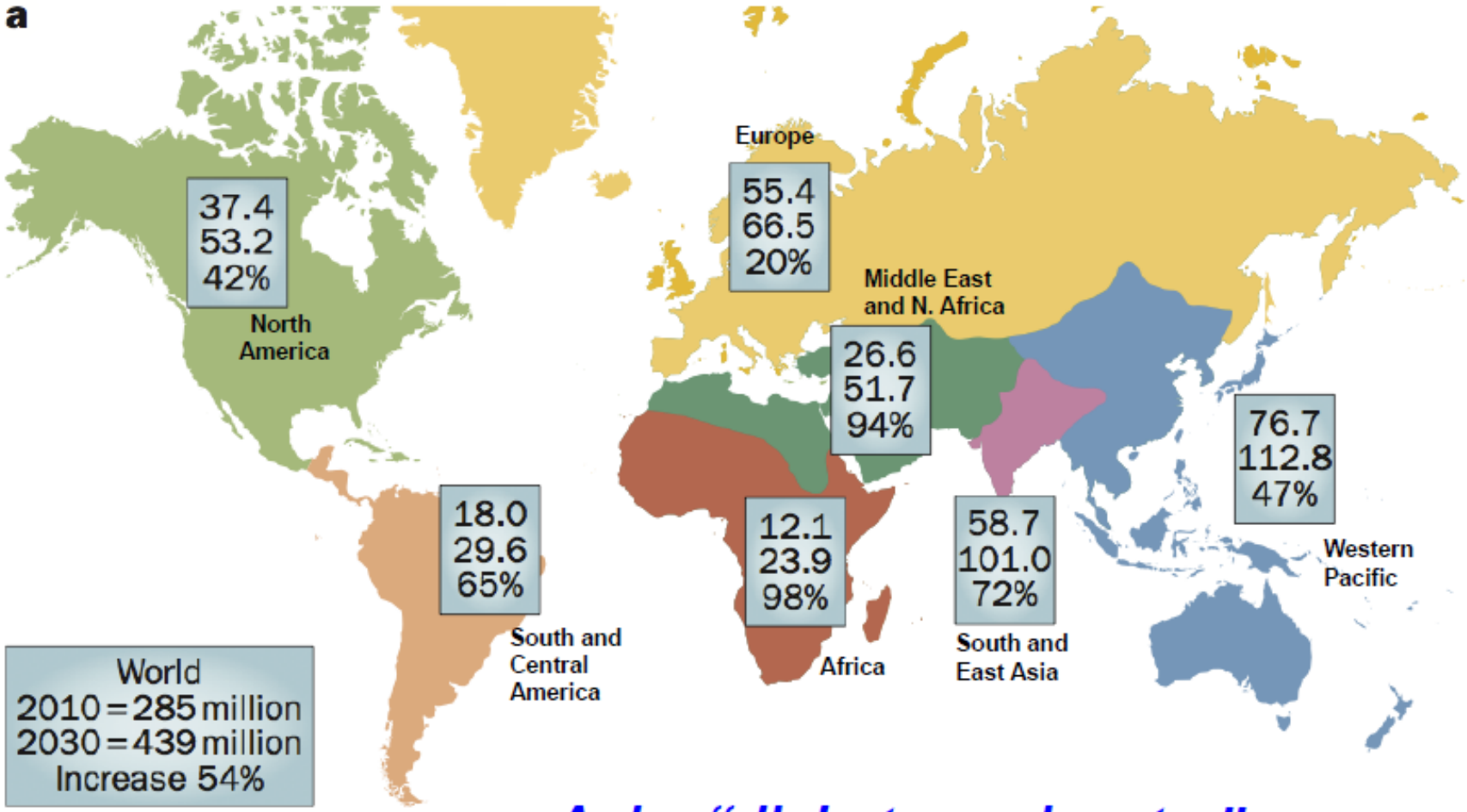


10 LEADING CAUSES OF DEATH, U.S.

- 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

Source: CDC, 2014 data http://www.cdc.gov/nchs/fastats/deaths.htm

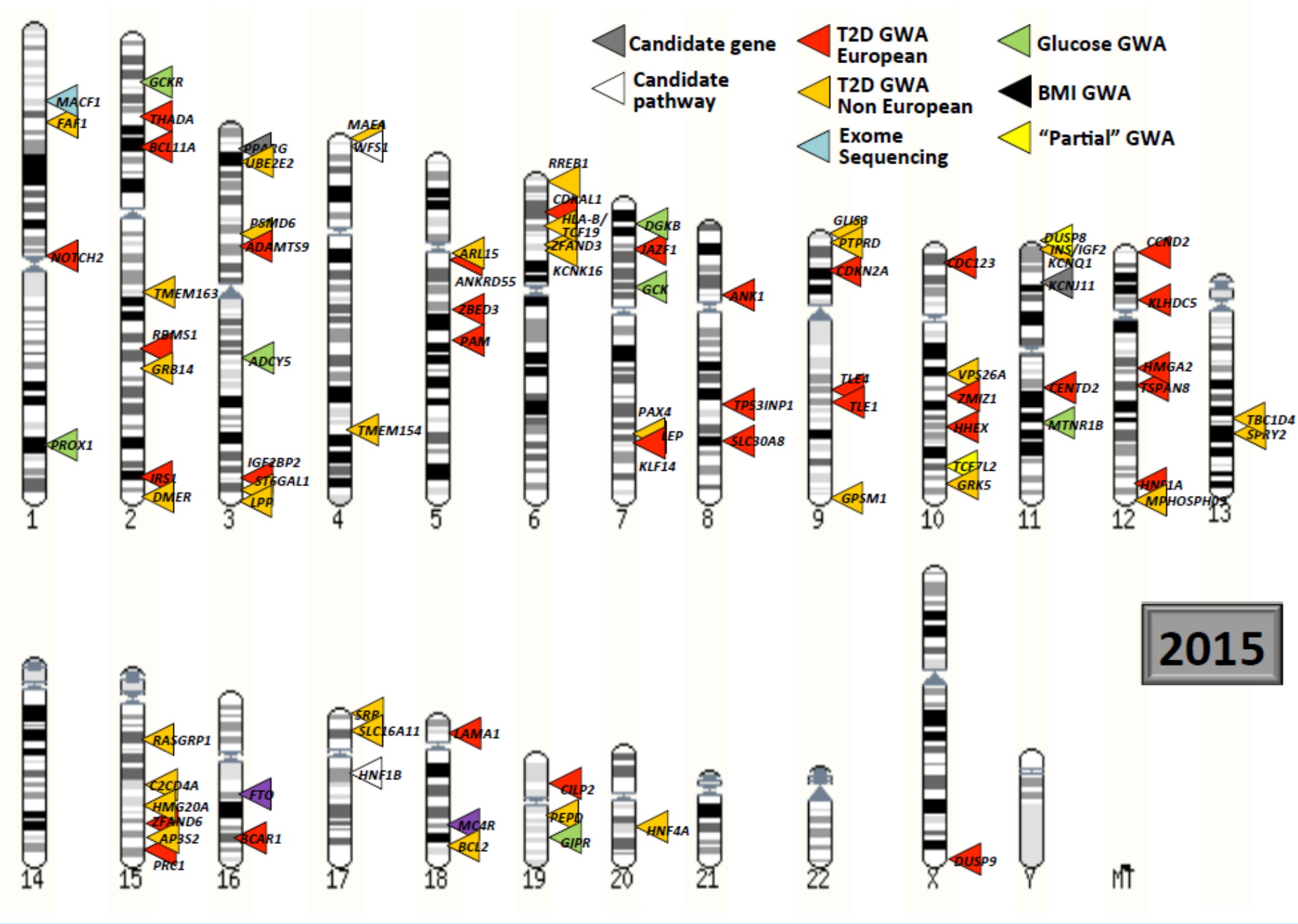
Global projections for the diabetes epidemic: 2010–2030



Asia: "diabetes epicenter"

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

Chen et al., Nat Rev Endocrinol. 2012



Mark McCarthy, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital

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Health Conditions | Genes | Chromosomes & mtDNA | Resources | Help Me Understand Genetics

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Search https://ghr.nlm.nih.gov/search?query=diabetes&start=0&tab=gene

diabetes

Filters

- All (162)
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Submit

MT-TE gene

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

IRS1 gene

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

GCGR 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

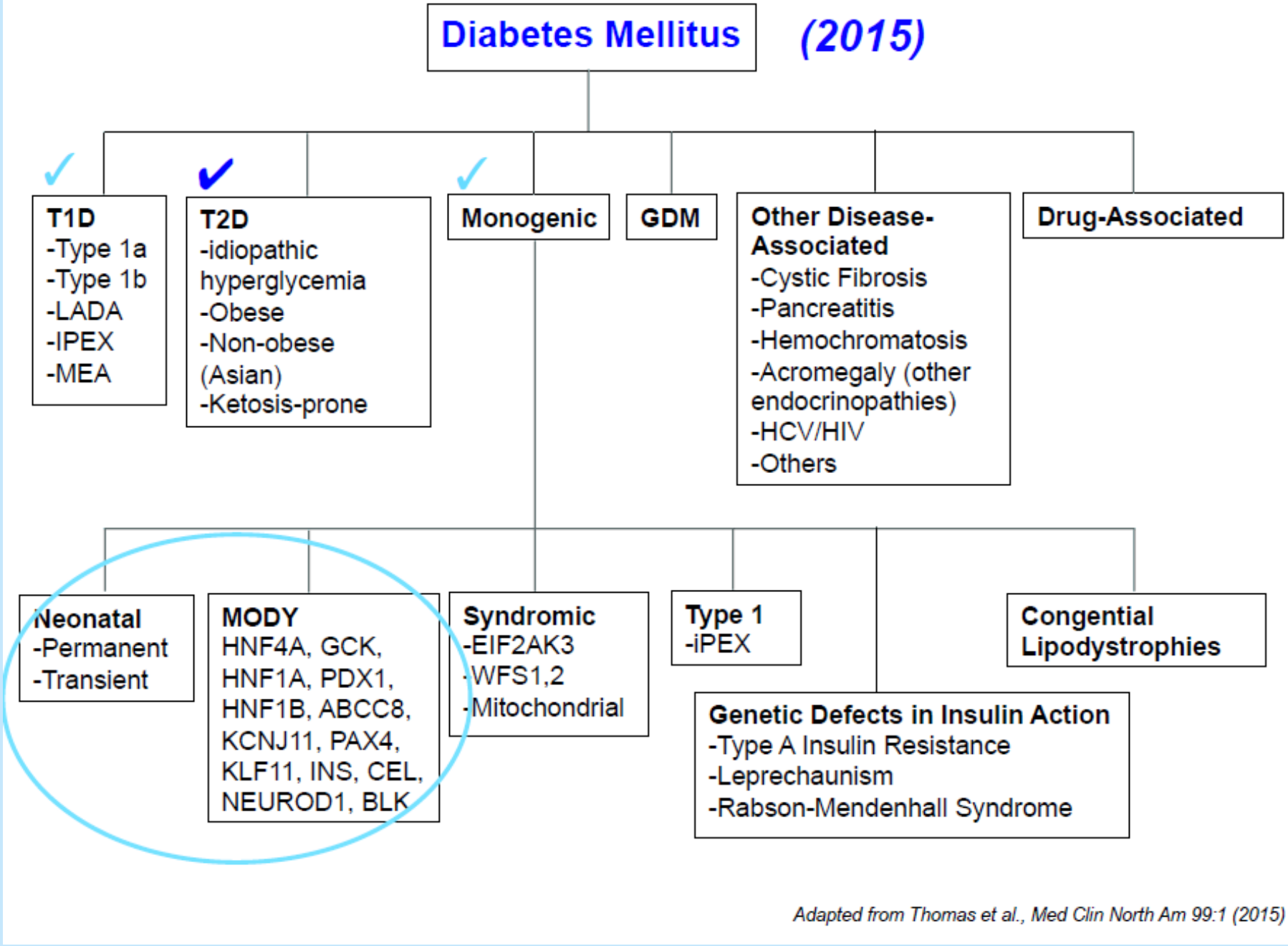
the embryonic pancreas. Mutations in this gene result in renal cysts and *diabetes* syndrome and

ESTABLISHED TYPE 2 DIABETES SUSCEPTIBILITY LOCI

Index SNP	Chromosome	Position	Region/gene	Identification	λ_s*
rs10010131	4	6343816	*WFS1*	Candidate gene	1.004
rs1801282	3	12368125	*PPARG*	Candidate gene	1.005
rs757210	17	33170628	*HNF1B (TCF2)*	Candidate gene	1.002
rs5219	11	17366148	*KCNJ11*	Candidate gene	1.005
rs7901695	10	114744078	*TCF7L2*	Linkage peak fine-mapping	1.022
rs10811661	9	22124094	*CDKN2A/B*	GWA	1.003
rs10946398	6	20769013	*CDKAL1*	GWA	1.002
rs13266634	8	118253964	*SLC30A8*	GWA	1.003
rs4402960	3	186994381	*IGF2BP2*	GWA	1.002
rs5015480	10	94455539	*HHEX/IDE*	GWA	1.002
rs8050136	16	52373776	*FTO*†	GWA	1.009
rs2237892	11	2796327	*KCNQ1*	GWA	1.031
rs10830963	11	92348358	*MTNR1B*‡	GWA	1.001
rs10923931	1	120319482	*NOTCH2*	GWA meta-analysis	1.001
rs12779790	10	12368016	*CDC123/CAMK1D*	GWA meta-analysis	1.002
rs4607103	3	64686944	*ADAMTS9*	GWA meta-analysis	1.002
rs7578597	2	43586327	*THADA*	GWA meta-analysis	1.002
rs7961581	12	69949369	*TSPAN8/LGR5*	GWA meta-analysis	1.001
rs864745	7	28147081	*JAZF1*	GWA meta-analysis	1.001

*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.

McCarthy, M. (2009). Genome wide association studies in type 2 diabetes. Current Diabetes Reports. 9: 164–171



Adapted from Thomas et al., Med Clin North Am 99:1 (2015)

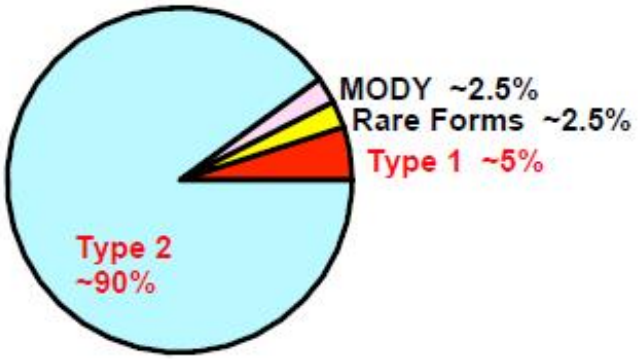
Optimal Treatments for Monogenic Diabetes by Subtype

Table 1. Optimal treatments for monogenic diabetes by subtype

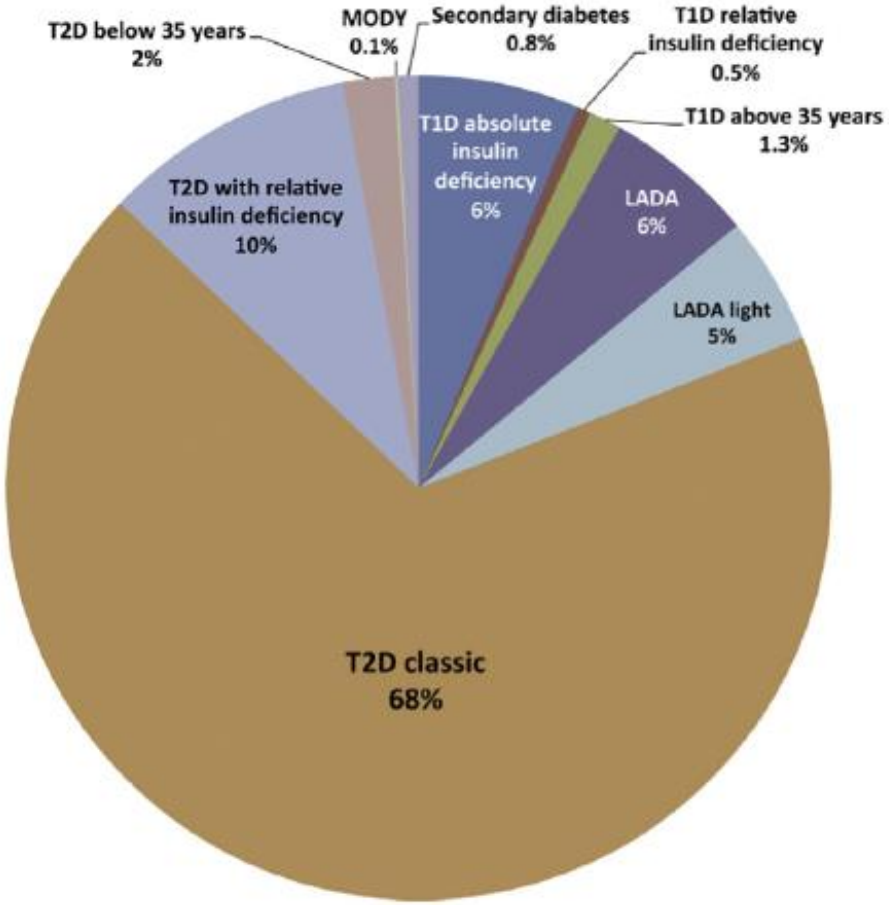
Monogenic diabetes subtype	Distinguishing clinical features	Examples of causal genes	Optimal treatment
Examples of more common subtypes			
GCK-MODY	Mild fasting hyperglycaemia	*GCK*	Diet alone
HNF1A-MODY	Young onset diabetes	*HNF1A*	Low dose sulphonylurea
Neonatal diabetes	Diabetes diagnosed before 6 months	*KCNJ11, ABCC8*	High dose sulphonylurea
		INS	Insulin
HNF4A-MODY	Young onset diabetes, increased birth weight and macrosomia	*HNF4A*	Low dose sulphonylurea
Examples of rarer subtypes with extrapancreatic features			
HNF1B-MODY	Renal cysts, genitourinary abnormalities, exocrine pancreatic insufficiency	*HNF1B*	Early insulin
Mitochondrial diabetes	Deafness, short stature, pigmentary retinopathy	*MTTL1*	Sulphonylurea initially but rapid progression to insulin requirement
Wolfram syndrome	Optic atrophy, diabetes insipidus, deafness, renal tract abnormalities, neurological abnormalities	*WFS1*	Insulin
TRMA syndrome	Megaloblastic anaemia, deafness	*SLC19A2*	Thiamine ± sulphonylurea ± early insulin

GCK, glucokinase; HNF4A, hepatocyte nuclear factor 4A; MODY, maturity-onset diabetes of the young; TRMA, thiamine responsive megaloblastic anaemia.

Pal et al., Clin Genet. 2013



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

Klonoff, D. C. (2015). Precision medicine for managing diabetes. *Journal of Diabetes Science and Technology, 9*(1), 3-7. doi:10.1177/1932296814563643

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

Glauber, H. S., Rishe, N., & Karnieli, E. (2014). Introduction to personalized medicine in diabetes mellitus. *Rambam Maimonides Medical Journal, 5*(1), e0002. doi:10.5041/RMMJ.10136


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

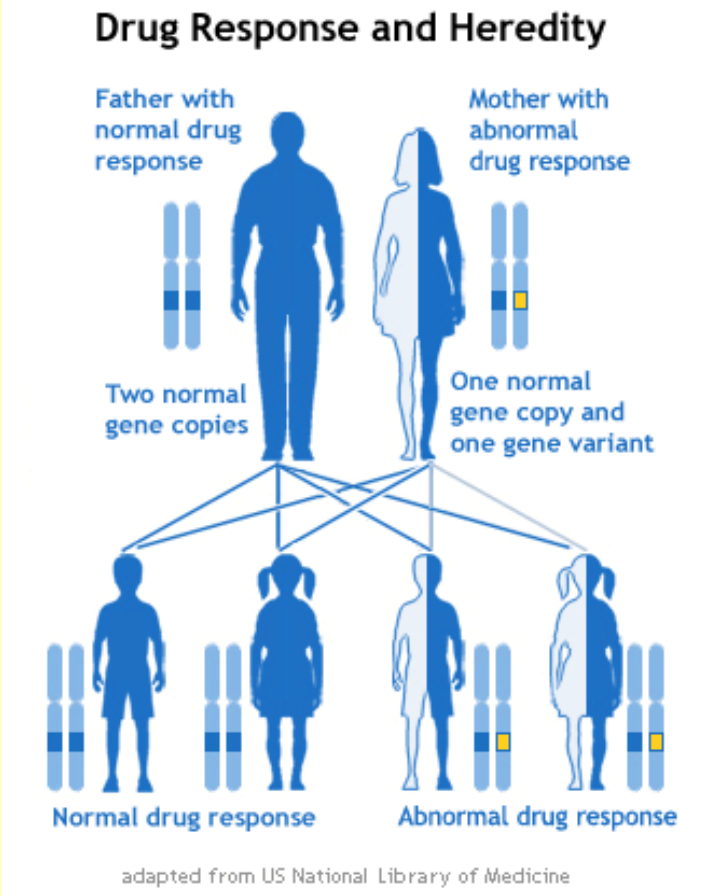
Pollin, T., Streeten, E. (2016). **A Case-Finding Approach to Screening for Monogenic Diabetes.** Research Protocol**.** Retrieved from: http://ummidtown.org/programs/diabetesendocrinology/research/clinical-trials

Think Genomics and Drugs!

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

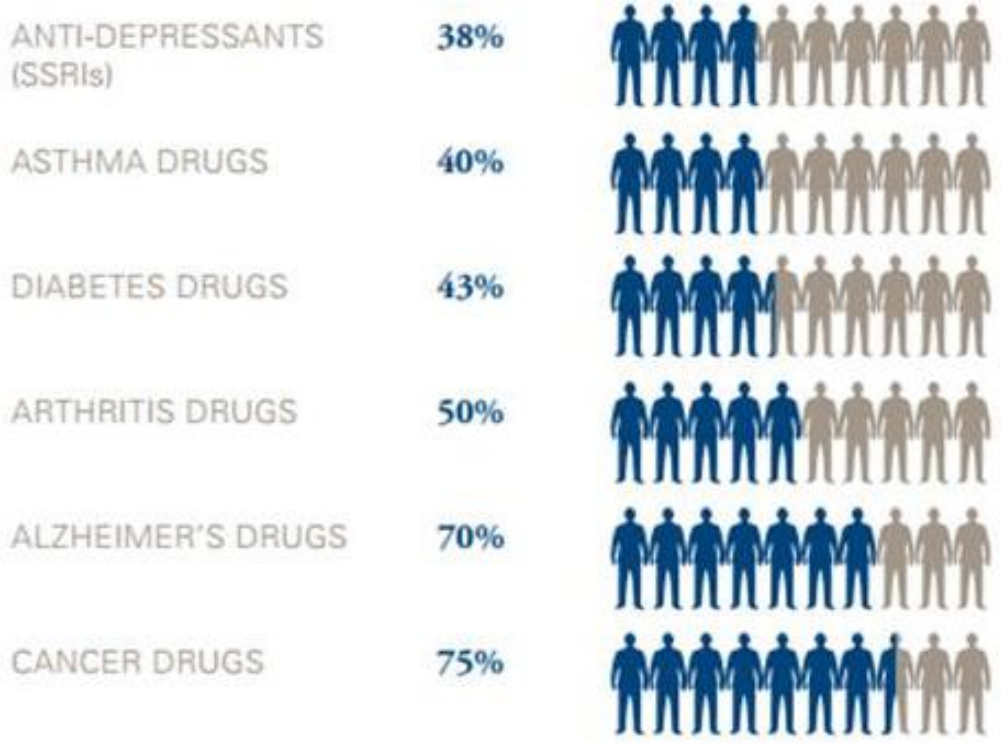
ANY OF THESE MEDICATION RESPONSES at RECOMMENDED DOSES

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



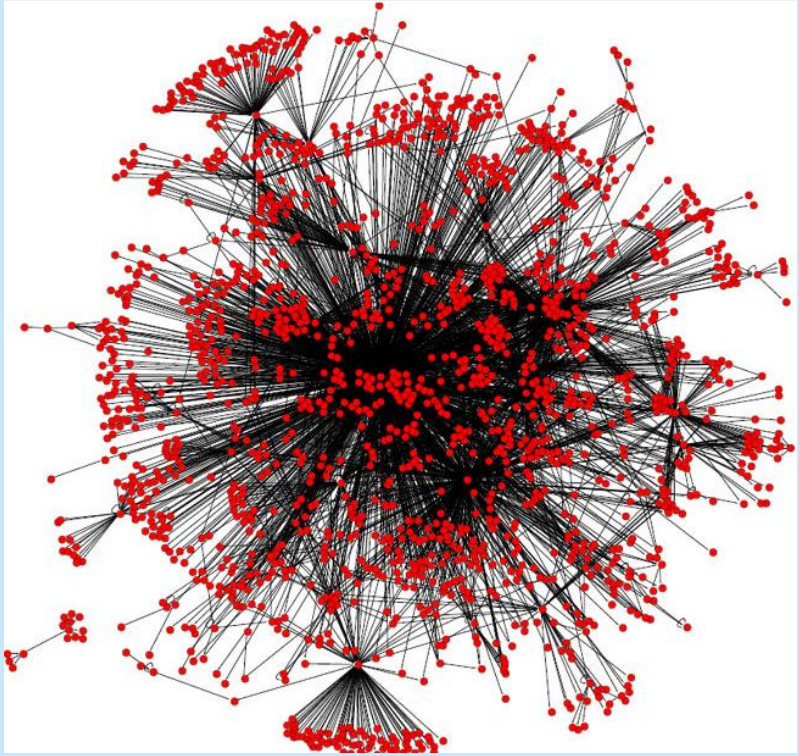
http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
https://www.pharmgkb.org/

DRUG RESPONSES



Spear B, Heath-Chiozzi M, Huff J (2001). Clinical application of pharmacogenetics. *Trends in Molecular Medicine.* 2001;7(5): 201-204.

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



Genetics and Complex Disease

CASE STUDY

Diabetes case Study. Retrieved from: http://www.nchpeg.org/dentistry/index.php?option=com_content&view=article&id=55&Itemid=56
Freyre-Gonzalez, J. A. & Trevino-Quintanilla, L. G. (2010) Analyzing Regulatory Networks in Bacteria. Nature Education 3(9):24

GENETICS AND COMPLEX DISEASE

- 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.

A DENTAL PRACTICE SERVING AN ADULT POPULATION OF 2,000 CAN EXPECT TO ENCOUNTER 40-80 PERSONS WITH DIABETES, ABOUT HALF OF WHOM WILL BE UNAWARE OF THEIR CONDITION

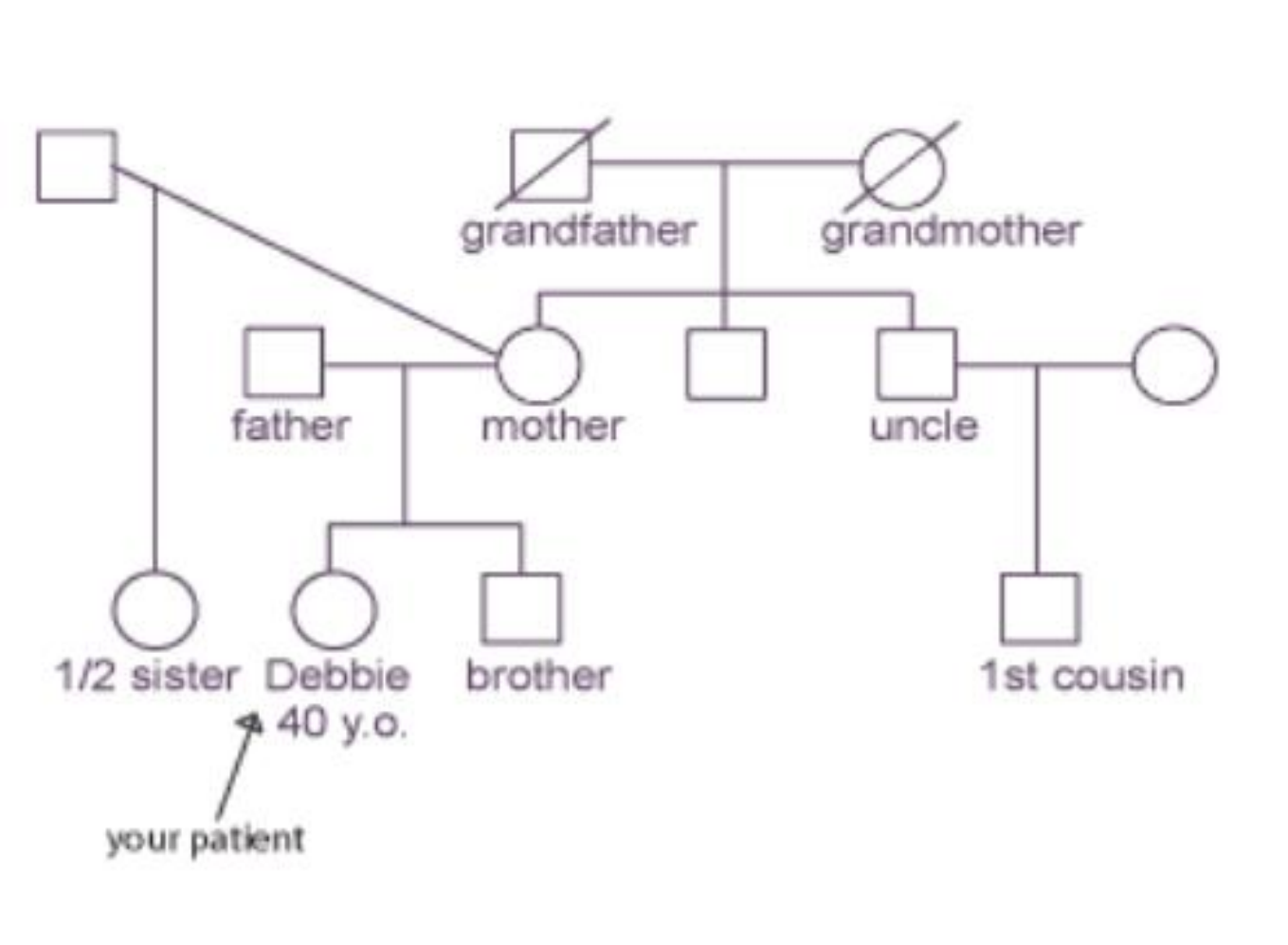
The most marked oral complications seen in uncontrolled diabetic patients includes:

- 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.

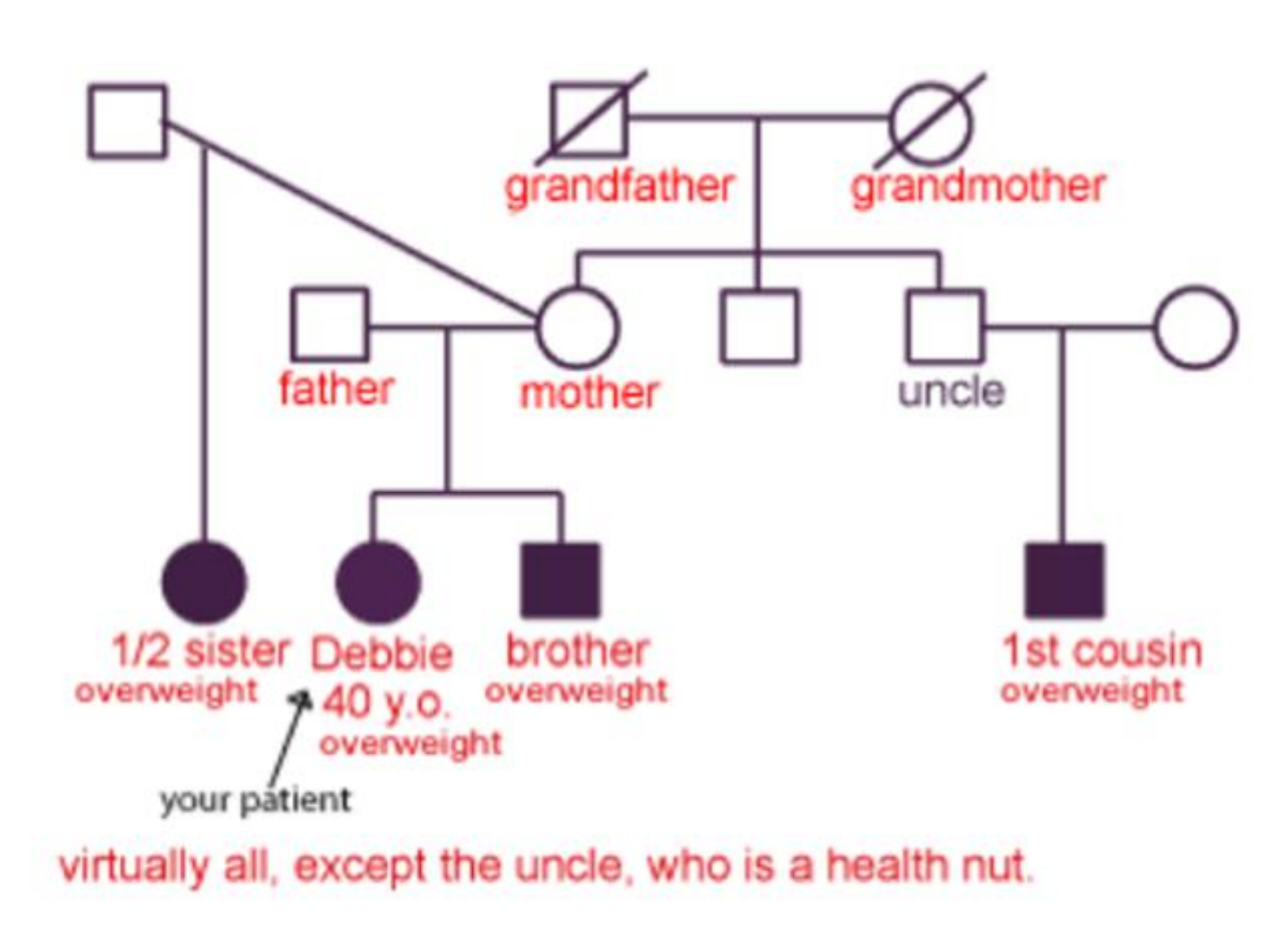
DEBBIE

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.

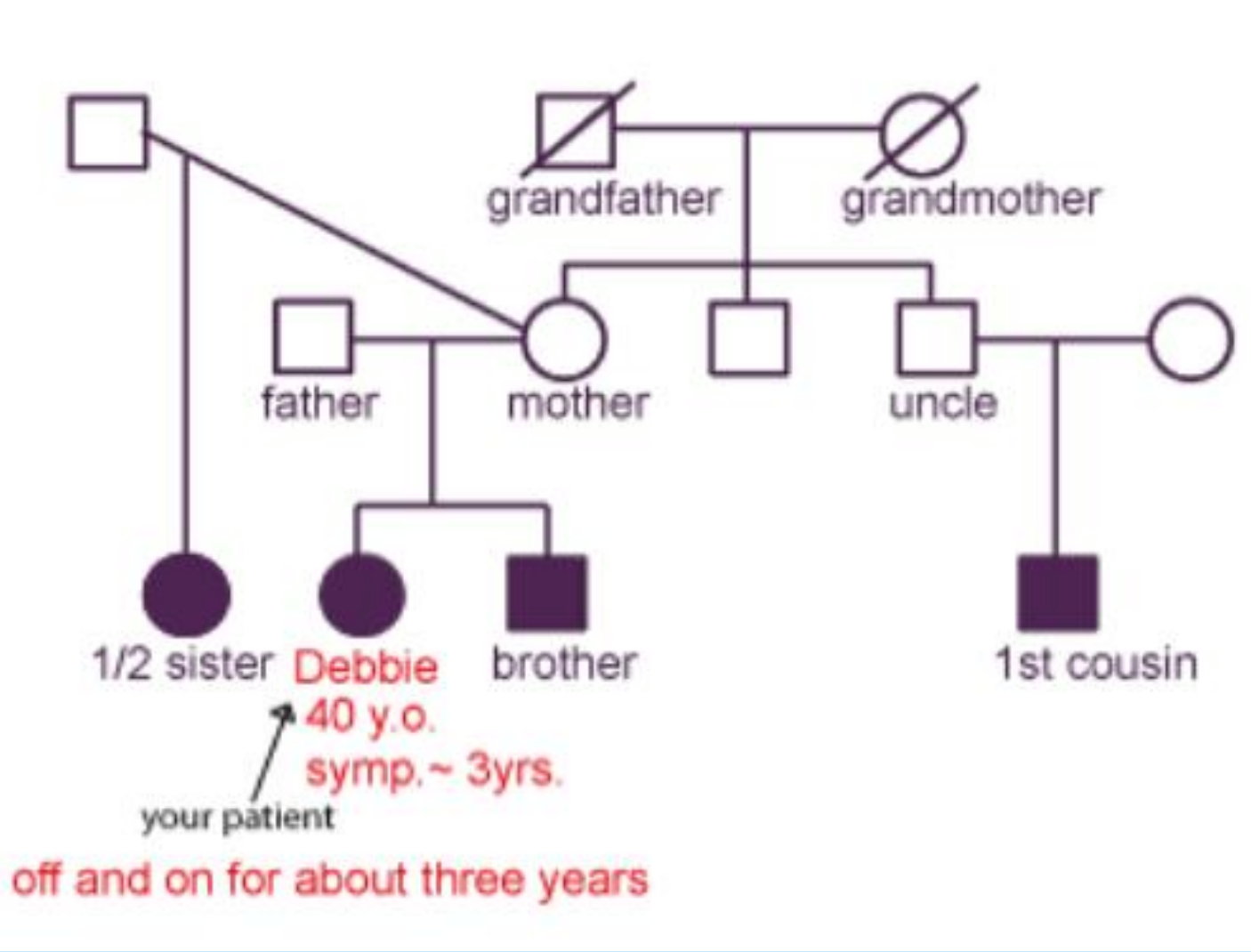
TAKING THE FAMILY HISTORY WILL HELP PUT DEBBIE'S INTRAORAL FINDINGS INTO A BROADER PERSPECTIVE. GO THROUGH THE QUESTIONS BELOW TO CONSTRUCT DEBBIE'S GENETIC FAMILY HISTORY.



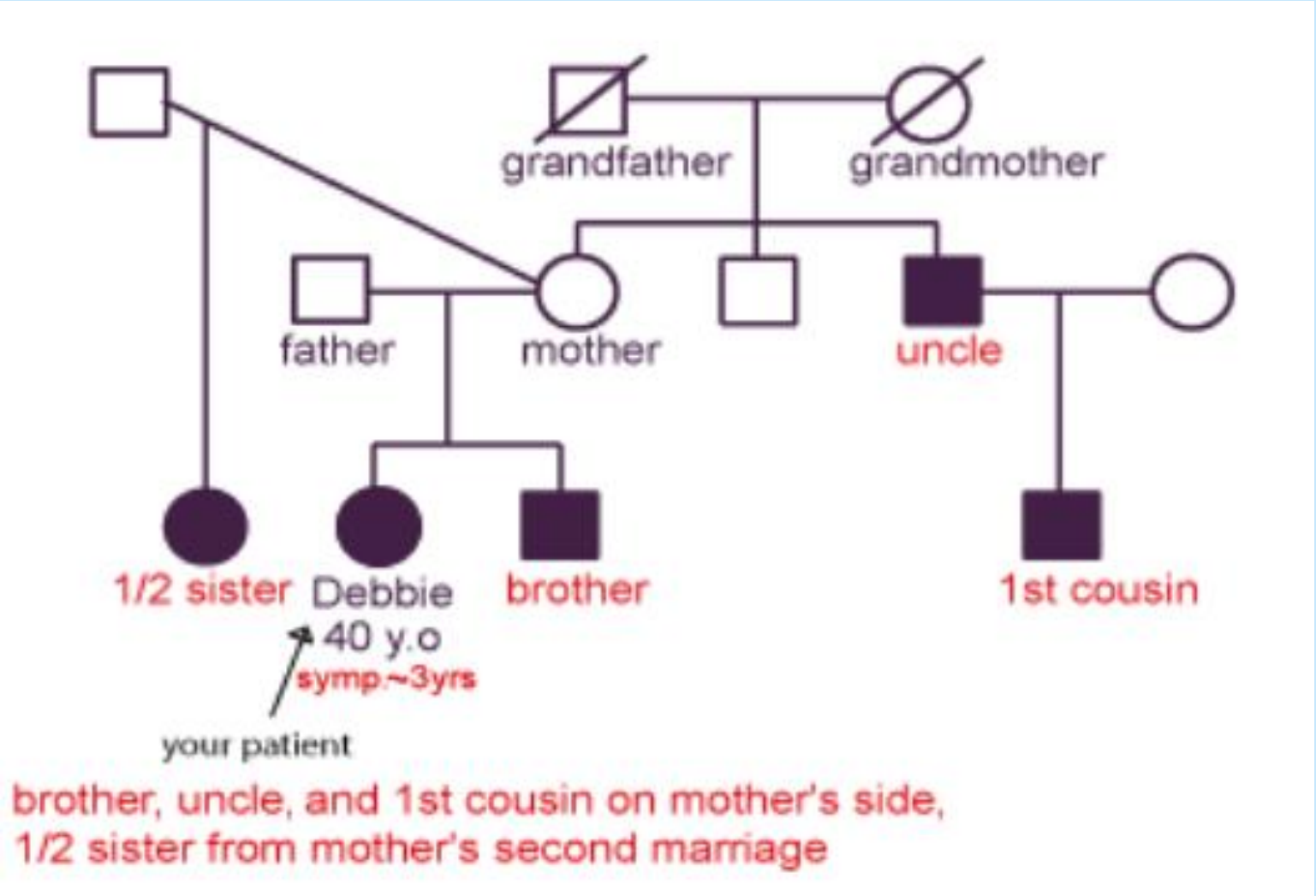
IS DEBBIE OVERWEIGHT?
IS THIS COMMON IN THE FAMILY?



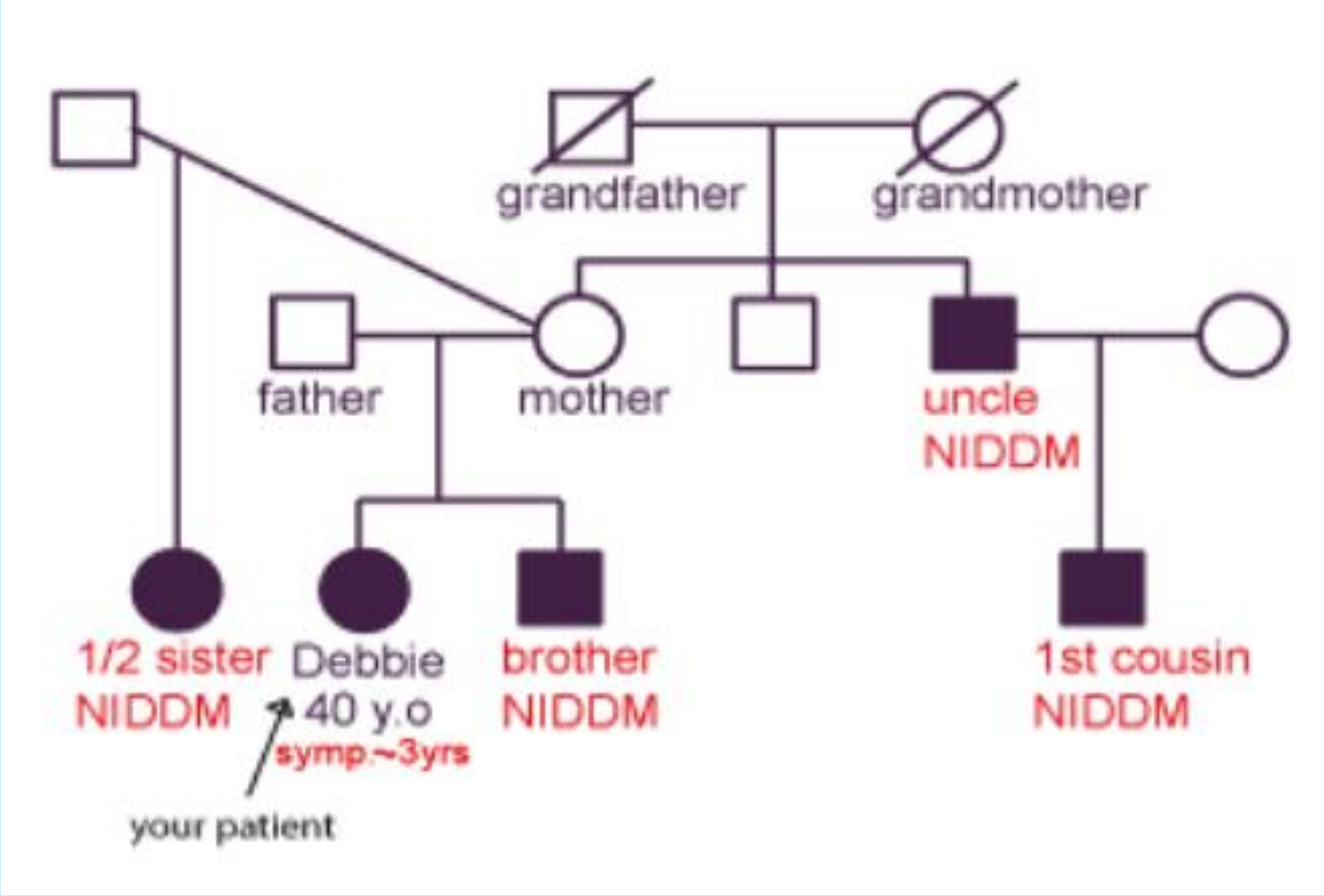
HOW LONG HAS DEBBIE HAD THESE SYMPTOMS?



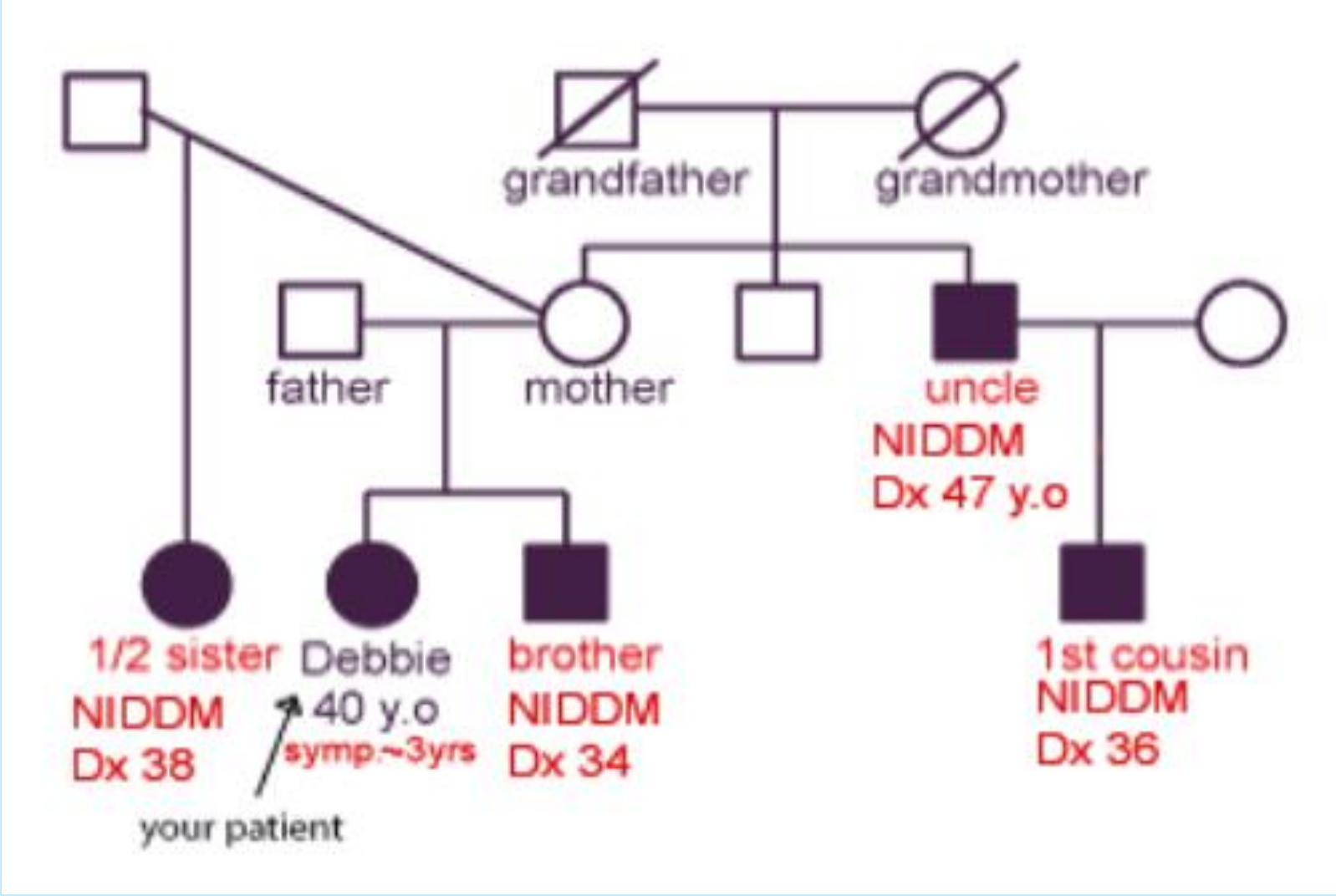
HAS DEBBIE OR ANYONE ELSE IN HER FAMILY BEEN DIAGNOSED WITH DIABETES?



WHAT TYPE - INSULIN DEPENDENT OR NON-INSULIN DEPENDENT?



HOW OLD WERE THEY WHEN THEY WERE DIAGNOSED?



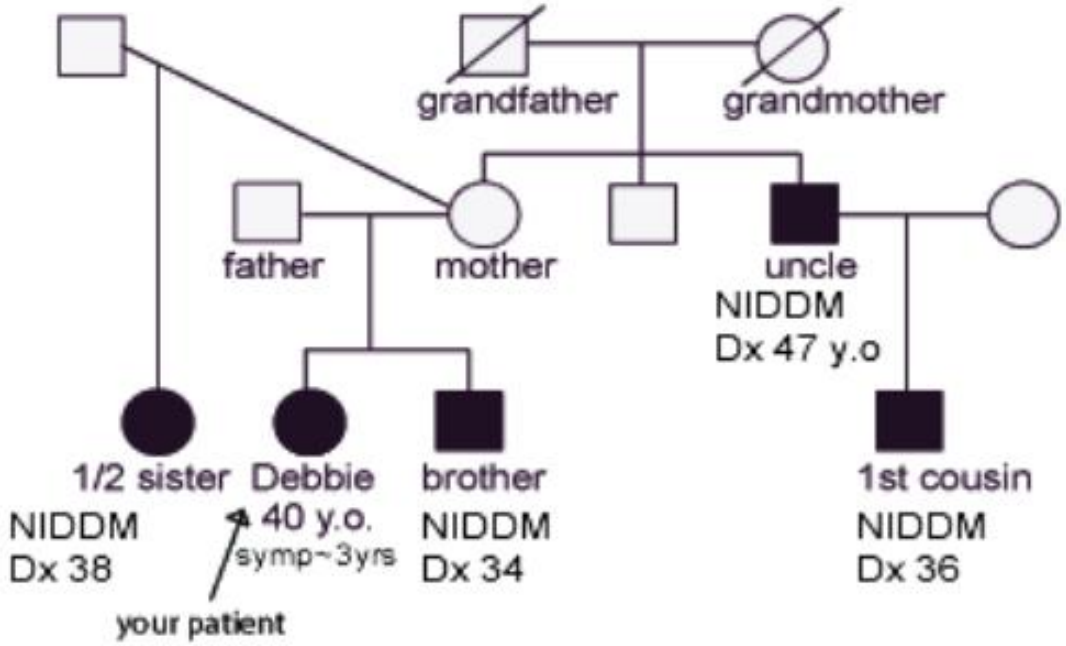
QUESTIONS: MONOGENIC DIABETES

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

Pollin, T., Streeten, E. (2016). **A Case-Finding Approach to Screening for Monogenic Diabetes.** Research Protocol**.** Retrieved from: http://ummidtown.org/programs/diabetesendocrinology/research/clinical-trials

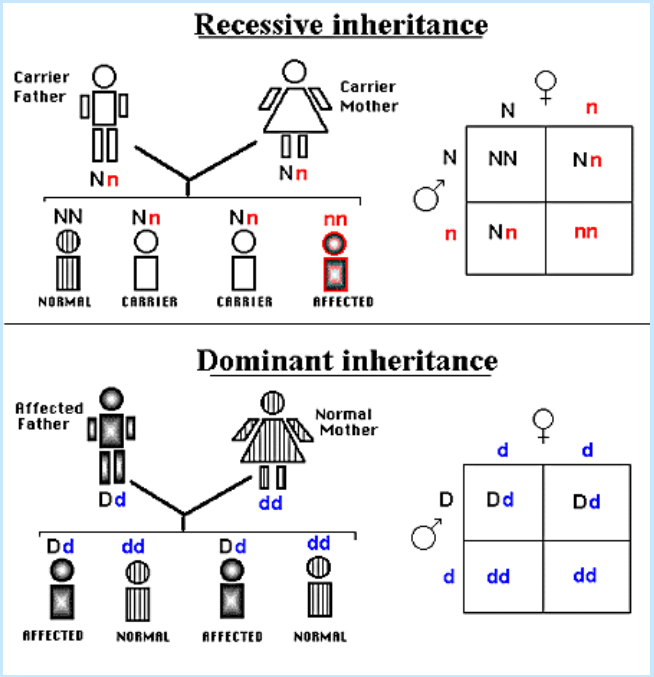
ENVIRONMENTAL CONSIDERATIONS:

- 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

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