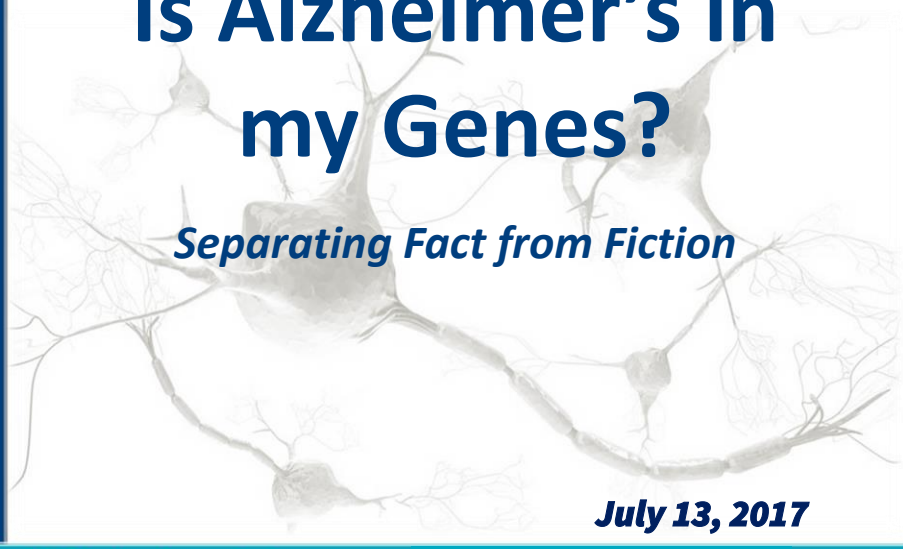
Is Alzheimer's in my Genes?

Separating Fact from Fiction



July 13, 2017

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The Heart of Alzheimer's Care & Cure

Our Mission: to provide San Diego families with care and support, while advancing critical local research for a cure.

100% OF DOLLARS RAISED STAY IN **SAN DIEGO**

Local & Independent

Alzheimer's San Diego is NOT affiliated with a national organization or association.

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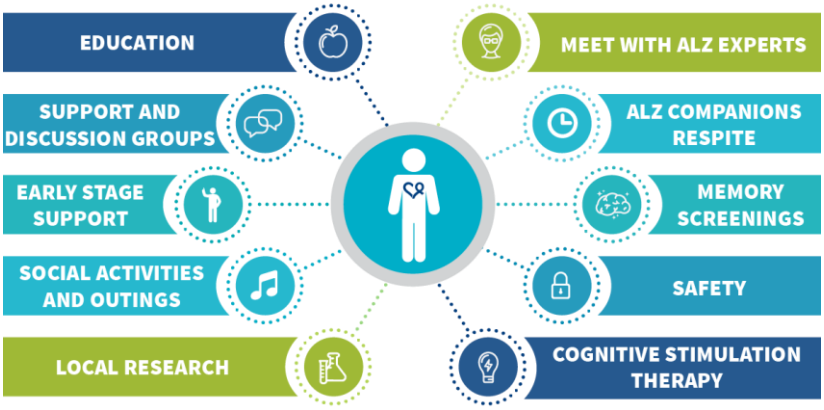
The Heart of Local Care & Cure



Free in-person support from local experts

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Meet the Experts

Dr. Michael Lobatz
Medical Director,
Scripps Health
Neurosciences

Dr. William Mobley
Associate Dean,
UCSD Dept. of
Neurosciences

Dr. Terry Gaasterland
Director, Scripps
Genome Center

Dr. Lisa Madlensky
Genetic Counselor &
Professor, UCSD

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Introduction to Genetics of Alzheimer's Disease

Dr. Michael Lobatz
Medical Director, Scripps Health Neurosciences

"Age carries all things away, even the mind"
Virgil 70 B.C. – 17 B.C.

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A Local Epidemic

65K
LIVING WITH **ALZHEIMER'S** IN SAN DIEGO

#3
CAUSE OF **DEATH IN** SAN DIEGO

+200K
SAN DIEGANS **CARING FOR A** LOVED ONE

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The most expensive disease in America

National cost of caring for people with Alzheimer's and other dementias

$226 billion in 2015

that number is set to reach

$1.1 trillion in 2050

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Terminology

Dementia

- An acquired syndrome consisting of a decline in memory and other cognitive functions
- Dementia is a word for a group of symptoms caused by disorders that affect the brain. It is not a specific disease.

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Types of Dementia

- Alzheimer's disease is the most common type of dementia
- Lewy body disease is one of the leading causes of dementia in elderly adults
- Many small strokes - vascular dementia

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RECOMMENDED SCREENING ALGORITHM FOR ADULT COGNITIVE IMPAIRMENT

NOTE: Cognitive screening may be a part of a regular annual physical exam.

10 WARNING SIGNS

1. Memory loss disrupts daily life
2. Challenges in planning or problem solving
3. Difficulty completing familiar tasks
4. Confusion with time or place
5. Trouble understanding visual images or spatial relationships
6. Problems with words
7. Misplacing items and inability to retrace steps
8. Decreased or poor judgment
9. Withdrawal from work or social activities
10. Changes in mood and personality

THE ALZHEIMER'S PROJECT CLINICAL ROUNDTABLE

LIVE WELL SAN DIEGO

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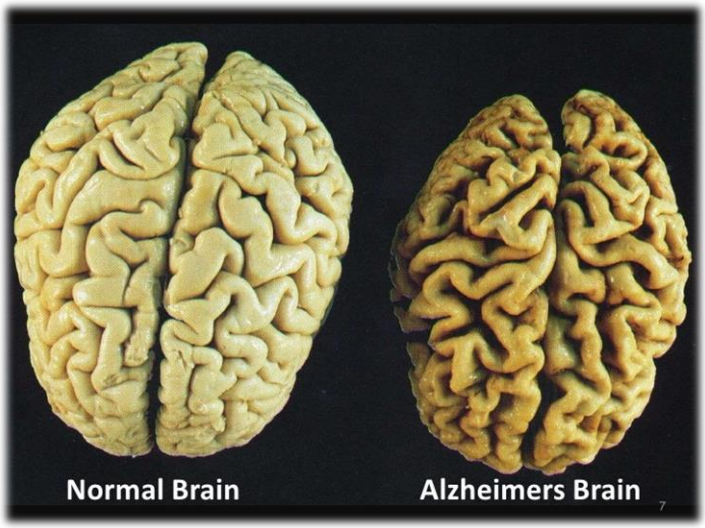
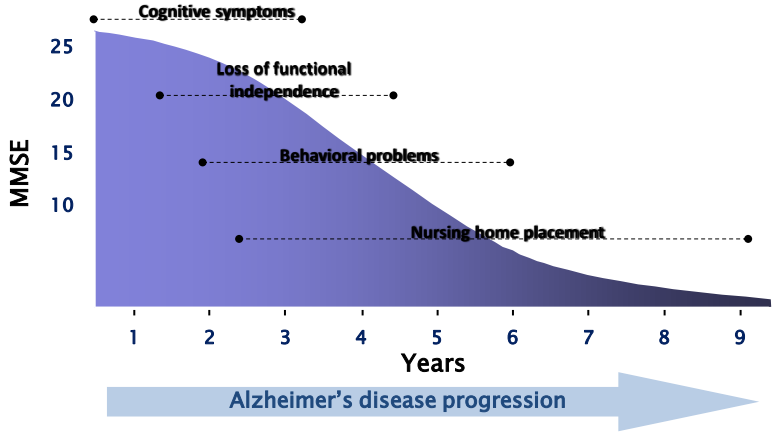


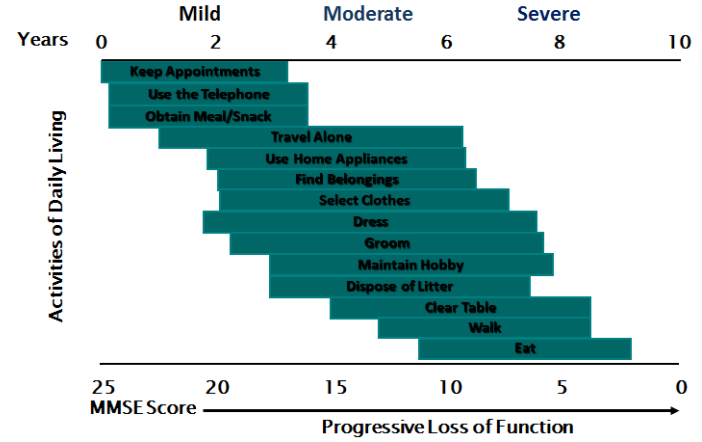
Symptomatic Progression



MMSE = Mini-Mental State Examination

Adapted with permission from Feldman et al. *Clinical Diagnosis and Management of Alzheimer's Disease.* 1999:249-268.

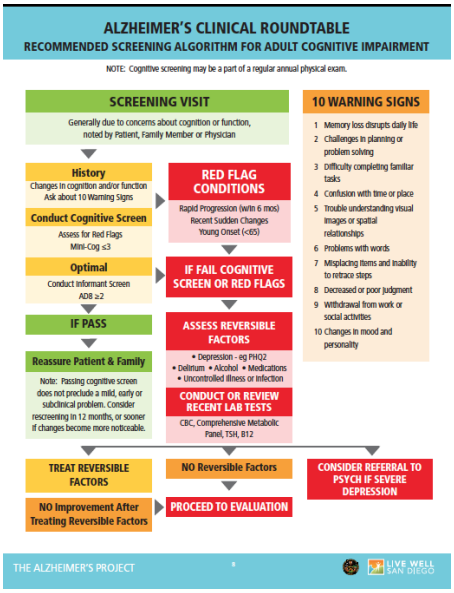
Progressive Loss of Activities of Daily Living



Adapted from Galasko D, et al. *Eur J Neurol.* 1998;5(suppl 4):S9–S17.

Getting a Diagnosis

- A physician should be consulted
- For people with dementia and their families, an early diagnosis has many advantages:
  - time to make choices that maximize quality of life
  - lessened anxieties about unknown problems
  - a better chance of benefiting from treatment
  - more time to plan for the future



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Current FDA Approved Treatments

Not Disease Modifying

Agent	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine (Razadyne)	Memantine (Namenda)
Dose Range	5-23mg/d	3-12mg/d	8-24mg/d	5-20mg/d
Target Dose	5-10mg/d	6-12mg/d or Patch	16-24mg/d	10-20mg/d
Most Common Adverse Events (Drug-Placebo)	Nausea (13%) Diarrhea (10%) Insomnia (8%)	Nausea (35%) Vomiting (25%) Dizziness (10%)	Nausea (12%) Vomiting (9%) Anorexia (6%)	Headaches(3%) Dizziness (2%) Constipation(2%)

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Manage the Patient and Caregiver

- Schedule follow-up visits (at least every 6 months)
- Repeat assessment of cognition, function, and behavior
- Monitor patient safety and caregiver burden
- Refer to specialists when necessary
  - eg, refractory behavioral disturbances, emergent neurologic symptoms

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Support Caregivers and Families

- Provide information on the disease process
- Introduce respite care early and describe full range of benefits available
- Identify members of a healthcare team (physician, nurse, social worker, psychologist) and support services
  - Refer caregivers for planning for future financial and legal issues
- Contact **Alzheimer's San Diego**

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Alzheimer's Disease: Biology of Memory Loss

William C Mobley M.D., Ph.D.
Department of Neurosciences
University of California, San Diego

Exploring the Causes of Alzheimer's

- Reduced brain size – atrophy
- Changes in microscopic structure – synaptic and neuronal loss with reduced brain metabolic activity
- Neuropathological markers – plaques, tangles, etc
- Disruption of cellular and molecular structure and function
- Genetic risk factors

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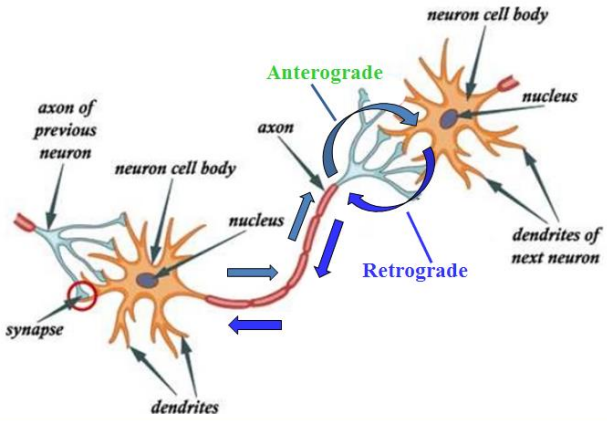
Information Flow in Brain: Supports Neuron Function



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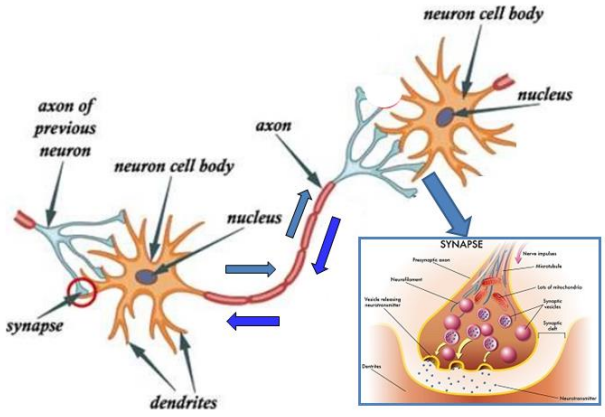
Information Flow in Brain: Critical Role for the Synapse



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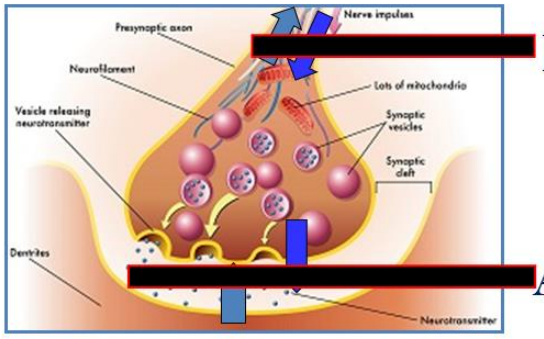
Information Flow in Brain: Synapse Under Attack



p-Tau

Aβ

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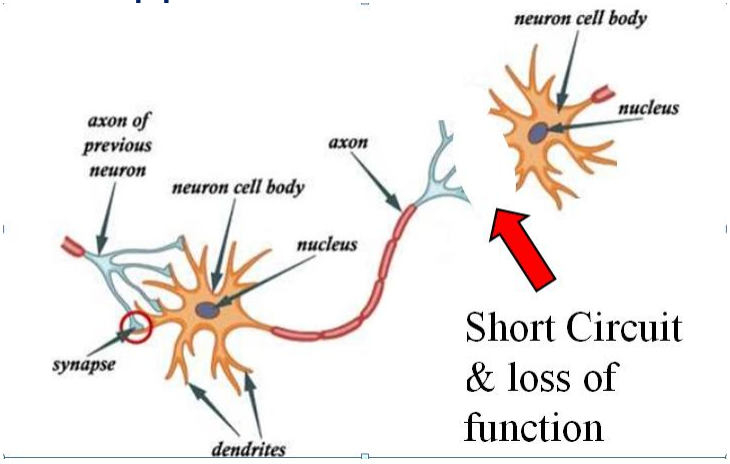
Information Flow in Brain: Supports Neuron Function



Short Circuit & loss of function

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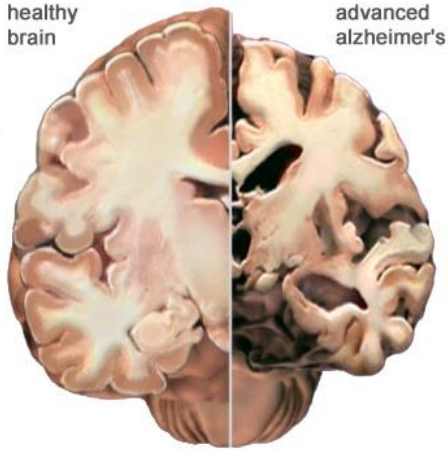
Noticeable Brain Atrophy



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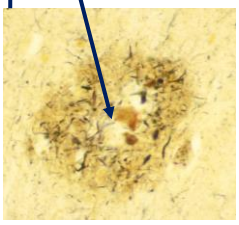
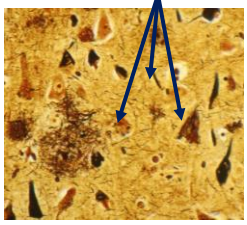
Brain Pathology in Alzheimer's disease

Cortex

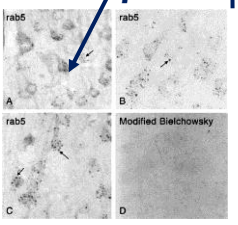
Aβ



p-Tau



Aβ



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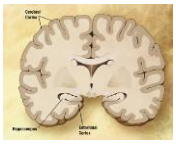
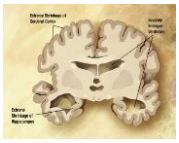
Biomarkers to Aid in Diagnosis and Treatment



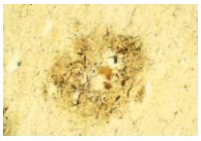


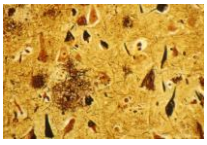
Structure:

MRI	whole brain atrophy
	regional atrophy
	connectivity - DTI

Function:

fMRI	↓ activation/ default network
PET, SPECT	↓ glucose use

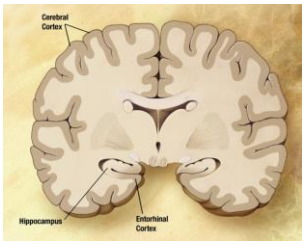


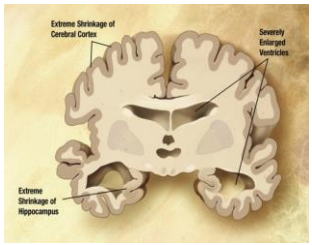


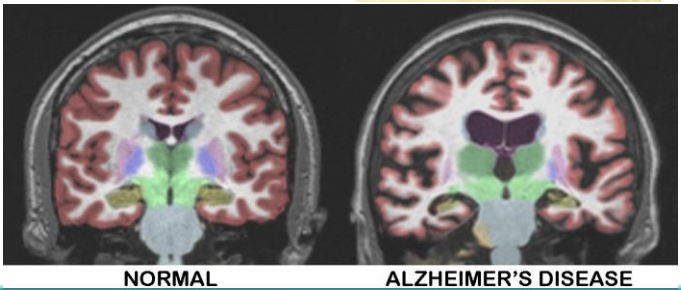
Biochemistry:

CSF	Aβ42 ↓
	tau, P-tau ↑
PET	amyloid deposition
	tau deposition
Plasma	Aβ

Volumetric MRI

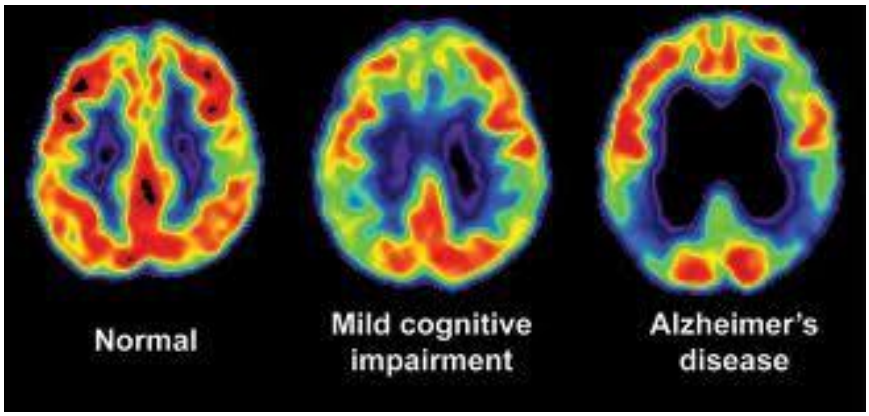






NORMAL ALZHEIMER'S DISEASE

FDG PET Scans are Abnormal in AD



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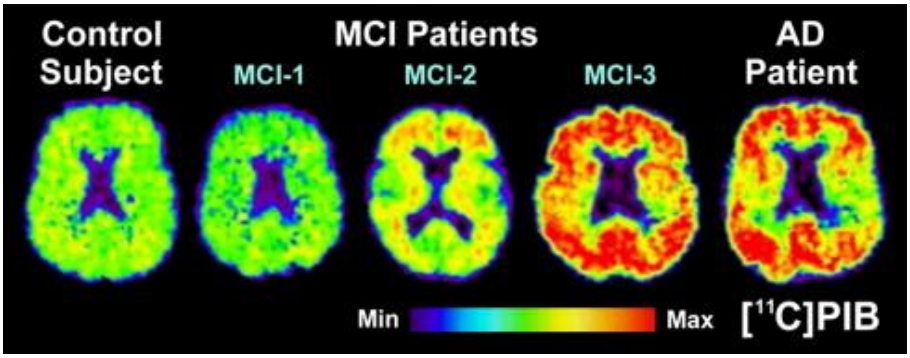
PET Imaging to Detect Amyloid



Amyloid imaging detects fibrillar deposits of Aβ in plaques.

These arise years before people develop memory loss

About 30% of people aged 70 have positive scans

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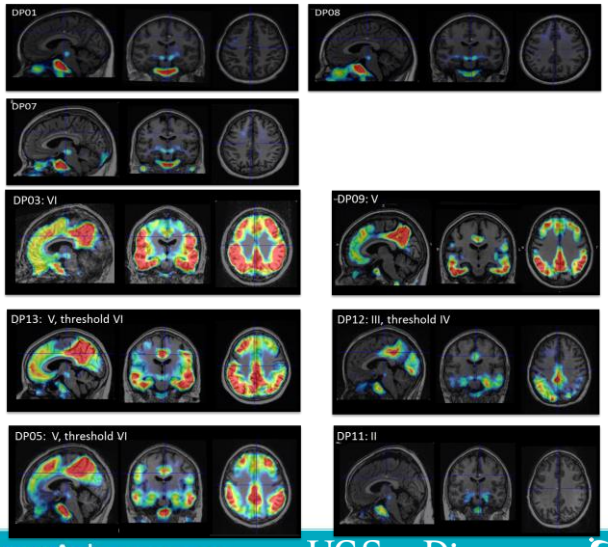
Tau PET Imaging



Rafii et al., J Alz Dis, In press.

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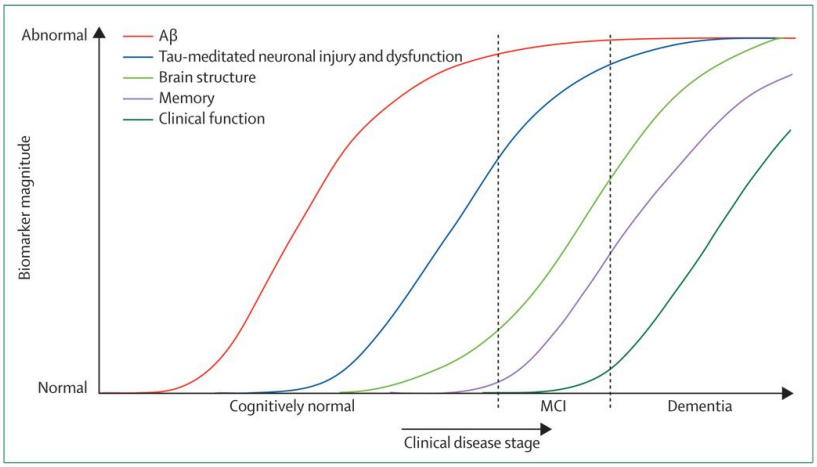
Current Diagnosis and Treatment May Come Too Late



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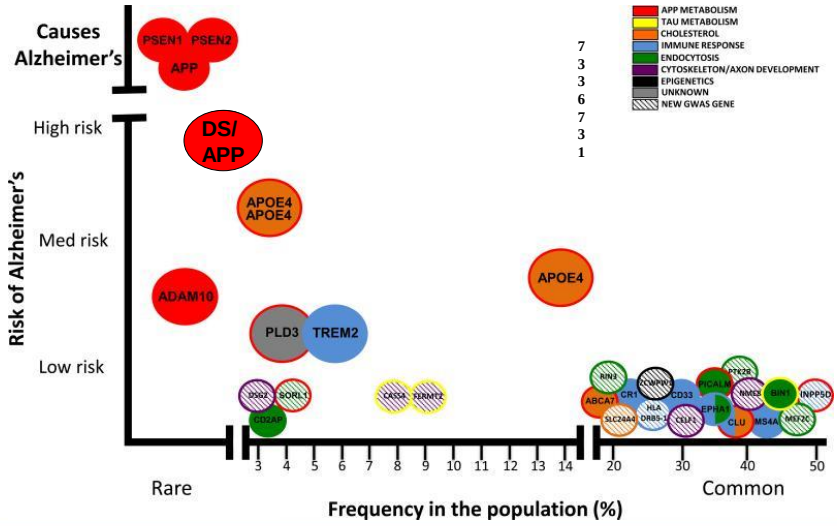
AD Genetic Landscape



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Understanding Neurodegenerative Disease through Genomics and Genetics

Terry Gaasterland, PhD
Director, Scripps Genome Center
Professor, Genomics & Computational Biology
Bioinformatics & Systems Biology Program
Institute for Genomic Medicine
Scripps Institution of Oceanography
University of California San Diego

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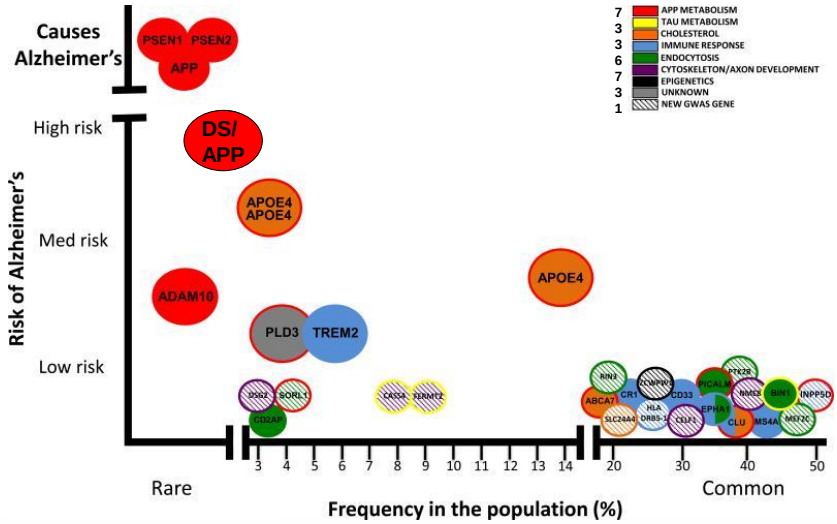
AD Genetic Landscape



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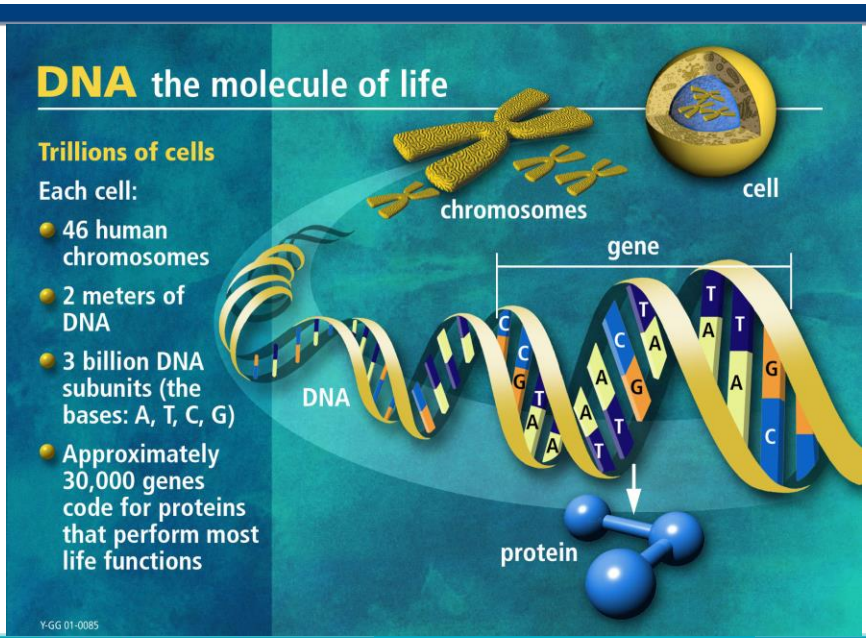

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Decoding a genome

sagtggdaagtgktdoqhmseagtgnqsagtggdbagtgdkkhagtgrhagtgmsagtggdcagtgmb

agtg → " "

"s gda ktdoqhmse nqs gdc dkkh rh ms gdc mb"

Add 1 to every letter: a → b … s → t…

"t heb lueprintf ort hec elli si nt hed na"

Shift " " left

"the blueprint for the cell is in the dna"

Single Nucleotide Polymorphism (SNP) truisms

- One base difference amongst individuals (*e.g.*, **A** instead of **G**)
- About **one per 1000** base pairs in human genome
- **~3 million "common" SNPs** in human genome
- Many, many more **"rare"** SNPs
- Each SNP's **frequency** is stable in a population
- Many SNPs **occur in or near genes**

Decoding a genome with SNPs

sagtggdaagtgktdoqhmseagtgnqsagtggdcagtgdkkhagtgrhagtgmsagtggdcagtgmb
sagtggdaagtgktdoqhmseagtgnqsagtggdbagtgdkkhagtgrhagtgmsagtggdccgtgmb

agtg → " "

"s gda ktdoqhmse nqs gdb dkkh rh ms gdccgtgmb"

Add 1 to every letter: a → b … s → t…

"t heb lueprintf ort heb elli si nt heddhuhna"

Shift " " left

"the blueprint for the bell is in theddhuhna"

"Complex" genetics = many genes + environment

- Childhood diseases tend to be "**monogenic**"
  - One gene, **one copy : dominant**
  - One gene, **both copies : recessive**
- Later onset diseases tend to be "**complex**"
  - **Multiple genes**
    - **+ Environment**
      - **+ Somatic mutations + …**

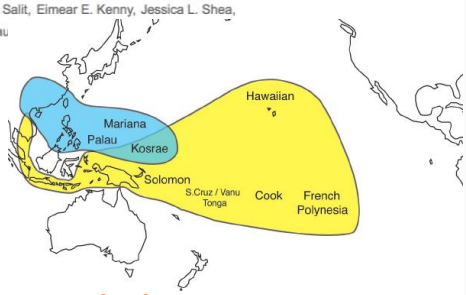
Insights from Island Populations

Genome-Wide Association Studies in an Isolated Founder Population from the Pacific Island of Kosrae

Jennifer K. Lowe, Julian B. Maller, Itsik Pe'er, Benjamin M. Neale, Jacqueline Salit, Eimear E. Kenny, Jessica L. Shea, Ralph Burkhardt, J. Gustav Smith, Weizhen Ji, Martha Noel, Jia Nee Foo, Mau
[view all]

Published: February 6, 2009 • https://doi.org/10.1371/journal.pgen.1000365

PLOS | GENETICS



- Genes for diabetes, obesity, hypertension
- Required an environmental change
- Western diet (e.g., potato chips...)!

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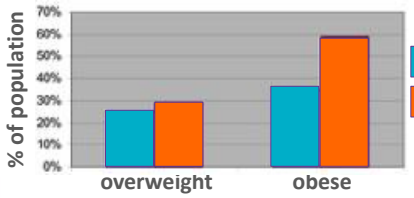
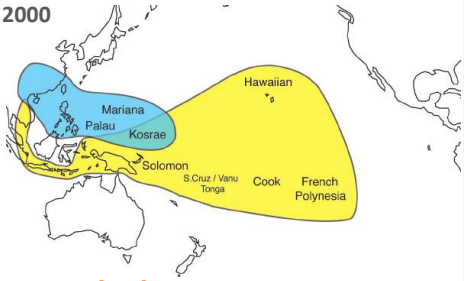
Insights from Island Populations





- Genes for diabetes, obesity, hypertension
- Required an environmental change
- Western diet (e.g., potato chips...)!

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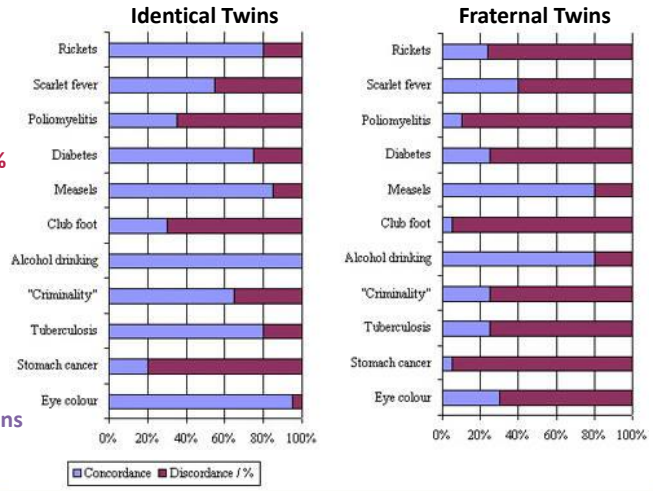
Clues to genetics from twins

If one SNP leads to disease/trait:

Identical twins: Concordance = 100%
AND
Fraternal twins: Concordance = 50%

Discordant = one twin

Concordant = both twins



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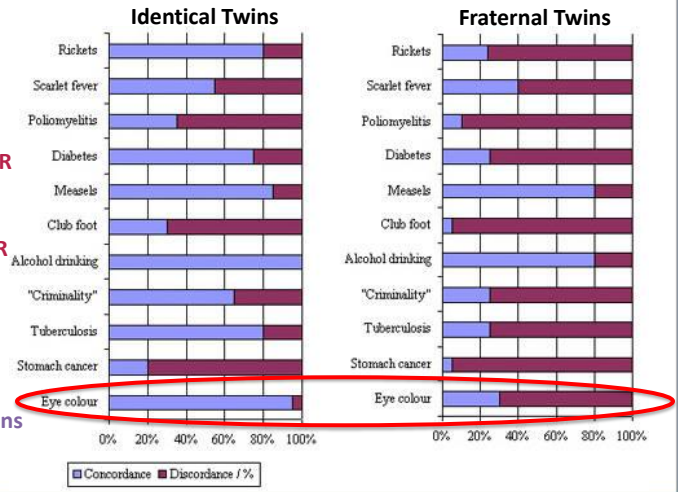
Clues to genetics from twins

If several genes lead to disease/trait:

Identical twins: Concordance HIGHER
AND
Fraternal twins: Concordance LOWER

Discordant = one twin

Concordant = both twins



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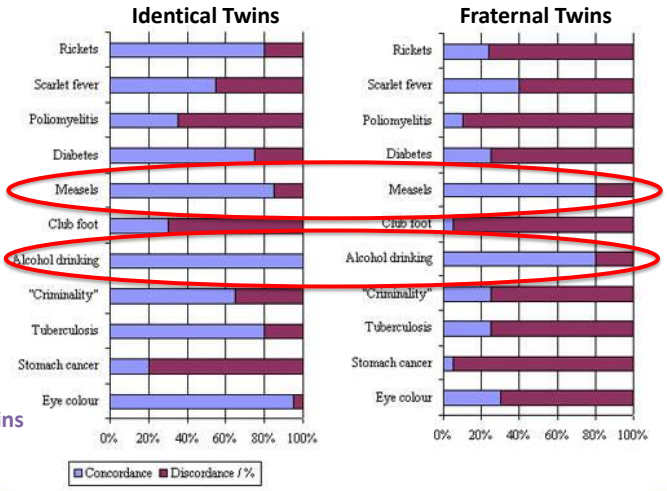
Clues to genetics from twins

If environment contributes to disease/trait:

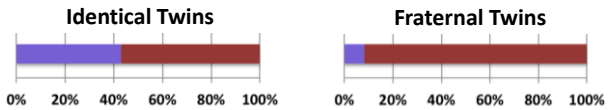
Difference between Identical twins AND Fraternal twins shrinks

Discordant = one twin

Concordant = both twins



Alzheimers Disease in Twins



Concordant = both twins

Discordant = one twin

- 392 twin pairs, one or both with AD
  (drawn from Swedish Twin Registry, 11 884 pairs)
- Estimated heritability: **58%**
- Gender independent
- Genetic influence on age of onset

Role of Genes and Environments for Explaining Alzheimer Disease
Gatz et al, 2006, Arch. Gen. Psych.

Population truisms

- Any one population includes ~90% of genetic variation found worldwide
- Common SNPs - in all human populations
- Thus, a map of SNPs can be developed with samples from any one population

BUT! SNP frequencies differ.

Vol 447|7 June 2007|doi:10.1038/nature05911 nature

Insights from Many Genomes

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 5×10^{-7}) likely to yield additional susceptibility loci. The importance of appropriately large samples was confirmed by the modest effect sizes observed at most loci identified. This study thus represents a thorough validation of the GWA approach. It has also demonstrated that careful use of a shared control group represents a safe and effective approach to GWA analyses of multiple disease phenotypes; has generated a genome-wide genotype database for future studies of common diseases in the British population; and shown that, provided individuals with non-European ancestry are excluded, the extent of population stratification in the British population is generally modest. Our findings offer new avenues for exploring the pathophysiology of these important disorders. We anticipate that our data, results and software, which will be widely available to other investigators, will provide a powerful resource for human genetics research.

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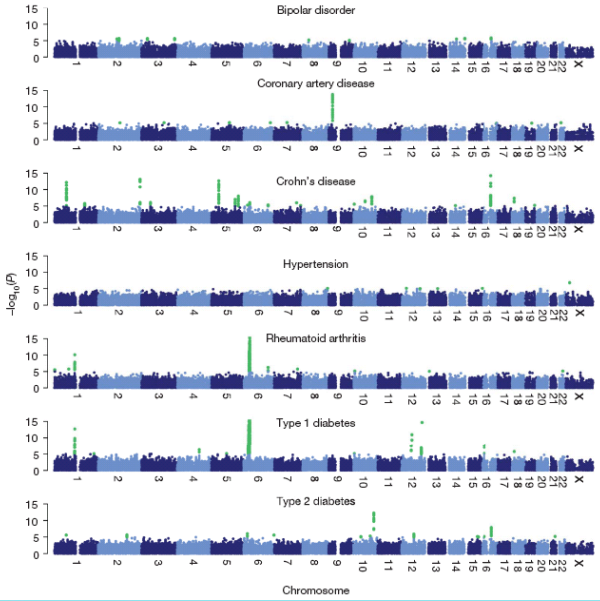

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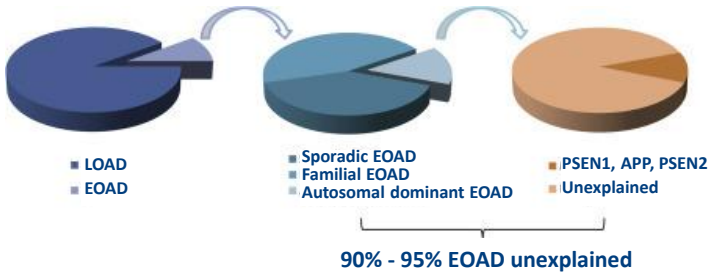
Genetic Risk in Alzheimers



- **Early onset:**
  3+ genes,
  hardly explained

  Cacace et al, 2016, Alzheimers Dement.

- **Later onset:**
  20+ genes by GWAS
  28% of heritability

  Van Cauwenberghe et al, 2016, Genetic Med.

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APOE algebra

- Everyone has 2 copies of APOE
- APOE4 **14%** *(European population copies)*
- APOE4,4 = 14%*14% = **2%** **higher risk**
- APOE2 **7%**
- APOE2,2 = **0.5%** **later onset**
- APOE2,4 = **1%** **mixed**

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What does "higher risk" mean?

Alzheimer's Disease Sequencing Project

>10,000 genomes

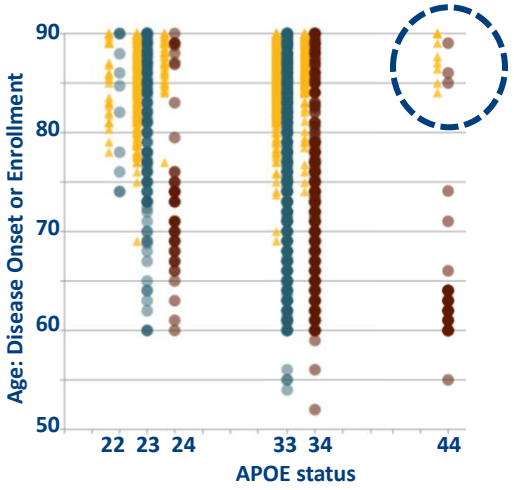
no AD n = 4,107

autopsied cases, Braak 4+

E4-- n = 1,585

E4+ n = 1,007

https://www.niagads.org/adsp



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Alzheimer's Disease has "Complex" Genetics = many genes + environment

For a complete genome picture, we need to

- **Study more families**
- **Especially people with 1st-degree family history**
- **Compare frequencies in many populations**
- **Develop a multi-gene genetic risk calculator**

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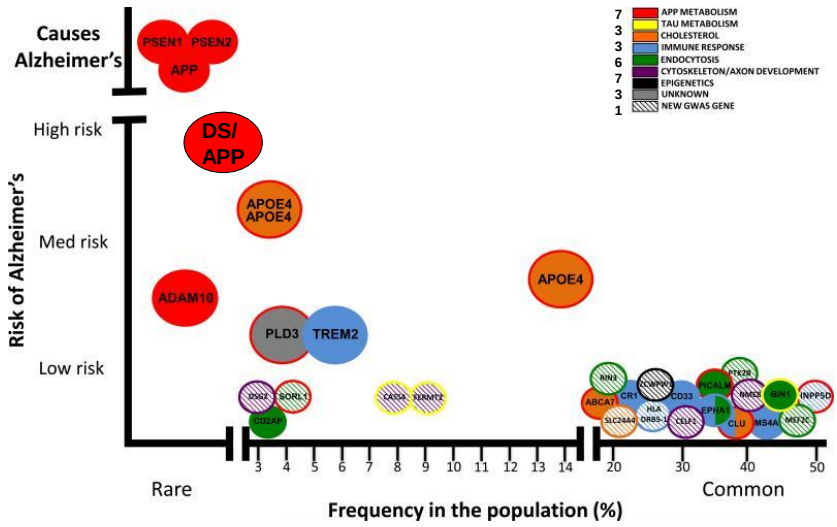
Genes so far are just the beginning



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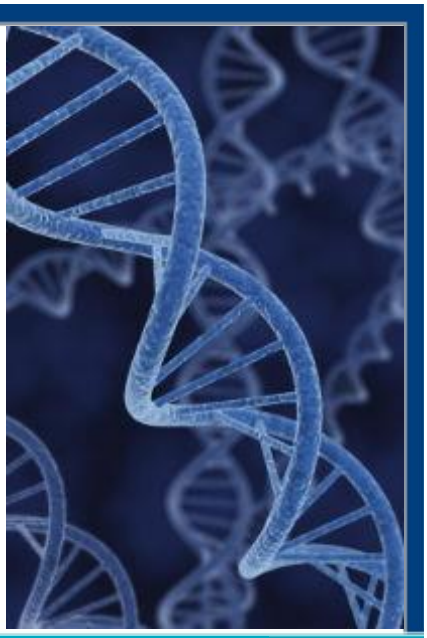
Genetic Counseling and Testing



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Genetic Counseling and Testing

- We are here to help!
- May be challenging to find a clinic; now online/telephone genetic counseling is widely available
- Identify goals, talk through pros and cons.
- Is this really "testing"? Or one component of a risk assessment?
- You can always consider testing in the future… but once you have tested you can't go back

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Genetic test results

- Once you look, you can't "unsee" the results
- Are you able to set the information aside? Or will you worry more?
- Everyone hopes to see no increase in risk…
  - But what if you do have an increased risk?
  - What if results aren't what you expected?
  - What if family members do this together?

Direct-to-consumer testing

I recently sent my personal raw data file, from 23andMe, to Promethease.com, for health-related information based on my genome.

In my Promethease report, I received some alarming information related to my risk of developing Alzheimer's Disease (AD). I appear to have two copies of the APOE e4 gene, which gives me an 11x greater-than-average chance of developing Late Onset AD.

There was other unsettling and also confusing information in my report.

I'm interested in meeting with a genetic counselor to 1) receive instruction on how to read and understand my Promethease report and 2) better understand the implications of my homozygous APOE e4 status, as well as the other health risks flagged.

-email to me from a patient

Things to consider

- What is the goal of testing?
- What would you do differently if increased risk? If decreased risk?
- Individuals with anxiety, depression, *prior to testing* are more likely to experience increased anxiety, depression
- *"I just wanted to do ancestry testing; I didn't know I could look at my APOE results"*

Results from the REVEAL study (2009)

Conclusions

The disclosure of *APOE* genotyping results to adult children of patients with Alzheimer's disease did not result in significant short-term psychological risks. Test-related distress was reduced among those who learned that they were *APOE* ε4–negative. Persons with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure.

Green et al, N Engl J Med 2009; 361:245-254

Results from the REVEAL study (2009)

Methods

Study Population and Instruments

We recruited adult children of a living or deceased parent with Alzheimer's disease through self-referral or telephone calls to families in research registries. As part of the screening process, we interviewed the subjects and administered standardized tests to evaluate their cognitive ability, academic achievement, and levels of anxiety and depression. We excluded subjects who scored 1.3 SD below norms on the Repeatable Battery for the Assessment of Neuropsychological Status or the Wide Range Achievement Test 3; higher than 20 on the Beck Anxiety Inventory (BAI), which ranges from 0 to 63, with higher scores indicating greater anxiety; or higher than 26 on the Center for Epidemiological Studies Depression Scale (CES-D), which ranges from 0 to 60, with higher scores indicating greater depression

Green et al, N Engl J Med 2009; 361:245-254

Summary

- Know yourself- do a thought experiment
- Have genetic counseling at the ready
- It may be difficult to obtain pre-test genetic counseling in San Diego; easier to obtain post-test
- APOE status is a risk/protective factor. Not a diagnosis.

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Questions?

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