Is Alzheimer’s in my Genes?

Separating Fact from Fiction

July 13, 2017

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.
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
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.

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
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

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.
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

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
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

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
Current FDA Approved Treatments

Not Disease Modifying

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Range</th>
<th>Target Dose</th>
<th>Most Common Adverse Events (Drug-Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>5-23mg/d</td>
<td>5-10mg/d</td>
<td>Nausea (13%) Diarrhea (10%) Insomnia (8%)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>3-12mg/d</td>
<td>6-12mg/d or Patch</td>
<td>Nausea (35%) Vomiting (25%) Dizziness (10%)</td>
</tr>
<tr>
<td>Galantamine</td>
<td>8-24mg/d</td>
<td>16-24mg/d</td>
<td>Nausea (12%) Vomiting (9%) Anorexia (6%)</td>
</tr>
<tr>
<td>Memantine</td>
<td>5-20mg/d</td>
<td>10-20mg/d</td>
<td>Headaches (3%) Dizziness (2%) Constipation (2%)</td>
</tr>
</tbody>
</table>
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

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
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
Information Flow in Brain: Supports Neuron Function

Information Flow in Brain: Critical Role for the Synapse
Information Flow in Brain: Synapse Under Attack

Information Flow in Brain: Supports Neuron Function

Short Circuit & loss of function
Noticeable Brain Atrophy

Brain Pathology in Alzheimer’s disease

Cortex

$\text{A\beta}$

$p$-Tau

$\text{A\beta}$
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

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
Tau PET Imaging

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

Current Diagnosis and Treatment May Come Too Late

Current Diagnosis and Treatment May Come Too Late

Abnormal

- Aβ
- Tau-mediated neuronal injury and dysfunction
- Brain structure
- Memory
- Clinical function

Normal

Cognitively normal

MCI

Dementia

Clinical disease stage
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
AD Genetic Landscape

 Causes of Alzheimer's

 High risk

 DS/APP

 Med risk

 ADAM10, PLD1, TREM2

 Low risk

 Rare

 Frequency in the population (%)

 Common

 DNA the molecule of life

 Trillions of cells
 Each cell:
 - 46 human chromosomes
 - 2 meters of DNA
 - 3 billion DNA subunits (the bases: A, T, C, G)
 - Approximately 30,000 genes code for proteins that perform most life functions
Decoding a genome

sagtggdaagtgktqoqhmseagtgnqsagtggdbgagtdkkkhagtrhagtgmsagttggdactgmb

agtg → “ “
“s gda ktdqhmse nqs gdc dkhk 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

```
sagtggdaagtgktdoqhmseagtgnqsagtggdcagtgdkkhagtgrhagtgmsagtggdcagtgmbsagtggdaagtgktdoqhmseagtgnqsagtggdagnostgnqsagtggd
```

```
agtg → " "

"s gda ktdoqhmse nqs gdb dkkh rh ms gdb cgtgmb"
```

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 the eddhuhna”
```

“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


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

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

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Alzheimer’s | San Diego | UC San Diego Health | Scripps
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

If several genes lead to disease/trait:

Identical twins: Concordance HIGHER AND
Fraternal twins: Concordance LOWER

Discordant = one twin
Concordant = both twins
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**

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**Alzheimers Disease in Twins**

- 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
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.

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 ~30,000 controls. Case-control comparisons identified 24 independent association signals at P < 5 x 10^-8 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^-7 and 5 x 10^-8) 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.
Genetic Risk in Alzheimer's

- **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.

90% - 95% EOAD unexplained
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

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
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

Genes so far are just the beginning
Genetic Counseling and Testing

Lisa Madlensky, PhD, CGC
Program Director & Genetic Counselor
Family Cancer Genetics Program
Moores UCSD Cancer Center

Professor
Division of Medical Genetics, Dept. of Medicine
University of California San Diego

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
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.

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.


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**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.
Questions?