Dominantly Inherited Alzheimer Network Trials: An opportunity to prevent dementia

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Brain atrophy of Alzheimer’s disease

AD brain

normal brain

Courtesy of ADRC Neuropathology Core
Microscopic Pathology of Alzheimer’s Disease
Evidence for a presymptomatic Alzheimer’s disease phase

• Incidence of dementia is delayed by 10-15 years from the prevalence of Alzheimer’s pathology in population pathological studies.

• Alzheimer’s disease biomarkers are abnormal in asymptomatic individuals in an age dependent fashion (e.g. low CSF Aβ42, fibrillar amyloid deposition are rare <50 years, ~10% 60’s, ~25% 70’s and above).

• Given the long pathobiological progression, observational studies needed over many years, unless we can predict who will have AD and when.
## Comparison of Autosomal Dominant and Sporadic AD

<table>
<thead>
<tr>
<th>Measure</th>
<th>Autosomal Dominant AD</th>
<th>Sporadic AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Amnestic</td>
<td>Amnestic</td>
</tr>
<tr>
<td>Cognitive deterioration</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
</tr>
<tr>
<td>MRI</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
</tr>
<tr>
<td>PiB PET</td>
<td>Cortex plus basal ganglia</td>
<td>Cortex</td>
</tr>
<tr>
<td>FDG PET</td>
<td>Parieto-occipital hypometabolism</td>
<td>Parieto-occipital hypometabolism</td>
</tr>
<tr>
<td>CSF Aβ 42</td>
<td>Decreased by 50%</td>
<td>Decreased by 50%</td>
</tr>
<tr>
<td>CSF tau</td>
<td>Increased by 2-fold</td>
<td>Increased by 2-fold</td>
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</tbody>
</table>
Original Article

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer’s Disease

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for the Dominantly Inherited Alzheimer Network

New England Journal of Medicine

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer’s Disease
Amyloid deposition begins at least 15 years prior to dementia onset in mutation carriers

Courtesy of Tammie Benzinger and Tyler Blazey
DIAN amyloid deposition by estimated age of onset
How does Aβ relate to other AD processes: tau, brain atrophy, cognitive and clinical impairment?
Comparison of Aβ, tau, brain atrophy, metabolism, and clinical impairment

The DIAN; Bateman et. al NEJM 2012
Altered Aβ42 to Aβ40 kinetics in Presenilin 1 and Presenilin 2 mutation carriers

Average Aβ 42:40

Aβ 42:40 Ratio

Time point (hours)

MC PIB+

MC PIB-

NC
24% increased Aβ42:40 production (p<0.0001) in Presenilin mutation carriers.
21 years from the discovery of a detrimental APP mutation to beneficial mutation

Nature 349, 704 - 706 (21 February 1991)

Nature (2012) Accepted 06 June 2012

LETTER

A mutation in APP protects against Alzheimer’s disease and age-related cognitive decline

Thorlakur Jonsson¹, Jasvinder K. Atwal², Stacy Steinberg¹, Jon Snaedal³, Palmi V. Jonsson³,⁸, Sigurbjörn Bjornsson³, Hreinn Stefansson¹, Patrick Sulem¹, Daniel Gudbjartsson¹, Janice Maloney², Kwame Hoyte², Amy Gustafson², Yichin Liu², Yanmei Lu², Tushar Bhagade², Robert R. Graham², Johanna Huttenlocher¹,⁴, Gyda Bjornsdottir¹, Ole A. Andreassen⁵, Erik G. Jönsson⁶, Aarno Palotie⁷, Timothy W. Behrens², Olafur T. Magnusson¹, Augustine Kong¹, Unnur Thorsteinsdottir¹,⁸, Ryan J. Watts² & Kari Stefansson¹,⁸
Interim Conclusions

• Currently more than 280 participants enrolled in DIAN

• The clinical, cognitive, imaging, and biochemical biomarkers of AD in mutation carriers is similar to late-onset sporadic Alzheimer’s disease and can be detected at least 20 years before estimated age of onset of dementia.

• The first clinical and cognitive changes begin at least 5 years prior to estimated age of onset of dementia.

• The DIAN cohort is well-suited for proof-of-concept studies (drug effect on biomarkers) and for dementia prevention studies in pre-symptomatic carriers.
Rationale for treatment trials in individuals at risk for Autosomal Dominant Alzheimer’s disease

- **Current therapeutic trials may be too late:** proposed therapeutics for Alzheimer’s disease currently target slowing or halting the underlying disease (disease modifying), but are not likely reverse the extensive neuronal death present at the onset of symptoms.

- There is **certain risk** (~100% with known mutation in PS1, PS2 or APP) of the disease which enables prevention studies and increases the power of treating minimally symptomatic patients.

- **Disease modifying therapeutics are largely developed with animal models based on human disease causing mutations.** Thus, AD caused by known autosomal dominant mutations is most likely to respond to these proposed disease modifying treatments.

- Results from treatment trials in autosomal dominant AD will bridge cellular and mouse therapeutic research with sporadic AD therapeutic research.
DIAN Trials Unit (TU)

The DIAN TU scientific and medical aims include:

1. Determine the **timing of treatment** important for improved clinical outcomes.

2. Determine **changes in physiologic or pathologic biomarkers** that can be used to track therapeutic effectiveness of treatments.

3. Test **Alzheimer’s disease hypotheses** (e.g. amyloid hypothesis) through therapeutic treatment trials.
Through public/private support and partnership, DIAN TU will launch trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer’s disease drug developments.
The Alzheimer’s Association supported the DIAN TU and DIAN Trial with the largest Association grant ever given ($4.2M).

**Scope of Work:**

- Accelerating launch of the DIAN trial
- Non-profit patient advocacy support
- Enabled expansion and outreach efforts
- Association continues to support autosomal dominant AD Forum
The DIAN Pharma Consortium is a collaboration of the DIAN with pharmaceutical companies and research institutions to advise on the design and implementation of DIAN therapeutic trials and support the DIAN Trials Unit.
**DIAN Pharma Consortium**

• **Scope of Work**
  – Tri-annual meetings with the DIAN TU, regulatory agencies, scientific experts, patient groups, consultants, others
  – Participation in non-therapeutic longitudinal DIAN interim data reviews to inform on trial design, staging and process of AD
  – Participation in working groups to provide recommendations for clinical trial designs
  – Nominate therapeutic agents for inclusion in DIAN therapeutic trials
  – Increase the DIAN participant pool to increase power and numbers of clinical trials in DIAN
ADAD Forum

- Website launched in February, 2011
- Currently 87 members, 1043 user logins, 9518 page views and 96 posts.
- The ADAD Forum has had multiple teleconferences and a webinar with the DIAN TU to facilitate participant and family member input into the design of DIAN clinical trials and to inform participants about trial design issues (e.g. placebo, genetic blinding, randomization).
- Ongoing webinars planned approximately every 4 months.
If you do not have an ADAD diagnosis or do not have ADAD in your family, we ask that you respect the purpose of this forum and do not join. How do I know if I have ADAD?

Join the Conversation

**Autosomal Dominant Alzheimer’s Disease Forum**

Autosomal Dominant Alzheimer’s Disease, also known as Familial Alzheimer’s disease is a rare form of Alzheimer’s disease.

The [ADAD Forum](https://www.alz.org) connects people with Autosomal Dominant Alzheimer’s Disease and their family members and provides information, peer support and engagement.
**DIAN Expanded Registry**

- Provides an overview of Autosomal Dominant Alzheimer’s disease (ADAD), links to other web resources (alzforum.org).
- Operational as of Feb 2012, announced in April
- ~313 registered:
  - Potential participants: 285
  - Researchers & Physicians: 28
- Registrants:
  - Current DIAN observational study participants, family members and those interested in future trials are registering on the website
  - Physicians and researchers interested in participating as an investigator or referring potential patients from their practice are also registering
Participant Interaction and partnership

Close partnership with an autosomal dominant AD support group and the Alzheimer’s Association with teleconferences and webinars every 4 months to facilitate participant and family member input into the design of DIAN clinical trials and to inform participants about trial design issues (e.g. placebo, genetic blinding, randomization).

The DIAN Expanded Registry
Register at www.DianXR.org
or 800-747-2979 toll free
Historical Precedent:
Treatment of inherited high cholesterol with statin drug

Pre-treatment

Post-treatment
Amyloid deposition in the 30’s and 40’s in people with ADAD Mutations

15 years prior to estimated symptoms  
10 Years prior to estimated symptoms  
~5 years after Alzheimer’s disease symptoms

Courtesy of Mark Mintun and Randy Bateman
**DIAN Biomarker Trial Design**

- 3 different **drugs** each with a unique target to alter the disease course
- 4 arms: 3 active drug, 1 placebo (75\% chance of active drug)
- 160 mutation carriers, 40 per arm
- Estimated 80 non-carriers (placebo)
- Drug treatment duration = 2 years
- **Extend study if positive results**
Biomarker Outcomes

Primary biomarker outcome
• Based on drug mechanism of action and CNS target engagement

Secondary ‘downstream’ biomarker outcomes
• CSF tau
• CSF p-tau
• Volumetric MRI
• FDG PET
• Functional connectivity MRI
Subject Randomization from DIAN and DIAN Expanded Registry

DIAN Observational Recruitment:

n=290 → n=130

Active & Trial Eligible

RANDOMIZATION #1

Drug A:B:C
1:1:1

n=160

RANDOMIZATION #2

Drug A: Placebo A
3:1

n=40

Drug B: Placebo B
3:1

n=40

Drug C: Placebo C
3:1

n=40

Identified Additional Participants:

n=2972+

N=40
Operational execution for remote subjects

Remote consenting by ‘Home’ DIAN Site

Home healthcare nurse (GCP trained) visits participant’s home [blood draws]

Participant’s “HOME” DIAN Site [rand & 1st dose]

- Participant obtains local MRI scans [sent to Mayo for central read]
  - CSSR

Monthly

Monthly Home Nurse visit [AEs, drug admin]

q2-3 mo

Wk 0, Yr 1 & Yr 2

Year 1 & Year 2: ‘Full Assessment’ Visit at DIAN Site
Adaptive Design for drug(s) to continue to a Cognitive Endpoint Trial

Outcomes:

- If drug(s) demonstrate positive biomarker profiles, enrollment continues for a cognitive endpoint registration trial.
- If none of the three original drugs is successful, then new biomarker trials may be started.
## Biomarker Power Analysis*

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>Est’d power (n=32/arm)</th>
<th>2/3 redc’d effect size power (n=32/arm)</th>
<th>Reported effect size</th>
<th>Effect sizes @ 80% power</th>
<th>SD- rate of change/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIB SUVR</td>
<td>99.6%</td>
<td>86.5%</td>
<td>0.16 (p=0.003)</td>
<td>0.098</td>
<td>0.137</td>
</tr>
<tr>
<td>PIB SUVR</td>
<td>&gt;99.9%</td>
<td>&gt;99.9%</td>
<td>0.50 (p&lt;0.05)</td>
<td>0.098</td>
<td>0.137</td>
</tr>
<tr>
<td>Unbound Free CSF Aβ&lt;sub&gt;42&lt;/sub&gt;</td>
<td>&gt;99.9%</td>
<td>&gt;99.9%</td>
<td>230 (p&lt;0.001)</td>
<td>53.4</td>
<td>75</td>
</tr>
<tr>
<td>CSF tau</td>
<td>&gt;99.9%</td>
<td>&gt;99.9%</td>
<td>83.1 (p=0.09)</td>
<td>16.59</td>
<td>23.29</td>
</tr>
<tr>
<td>CSF ptau 181</td>
<td>84.1%</td>
<td>50.6%</td>
<td>9.0 (p=0.03)</td>
<td>8.52</td>
<td>11.94</td>
</tr>
</tbody>
</table>

*Analysis performed on published data and DIAN longitudinal data (C. Xiong).
References: Rinne, 2010; Ostrowitzki, 2011; Farlow, 2011; Blennow, 2012
Participants and patients eager for clinical trials.

Strong scientific rationale for DIAN treatment trials.

Regulatory agencies (FDA and EMA) supportive of autosomal dominant AD prevention trials.

Fifteen DIAN therapeutic nomination packets have been received from Pharma.

DIAN Pharma Consortium Formed to assist in clinical trial design – members currently include 10 pharmaceutical companies.

DIAN Trials Unit formed to design, implement and manage DIAN treatment trials.

First studies targeted to start in late 2012 or early 2013
Acknowledgements

The DIAN participants and family members

The Alzheimer’s Association, ADAD Forum, DIAN Pharma Consortium and regulatory representatives

DIAN TU
Randall Bateman, Virginia Buckles, Matt Carril, David Clifford, David Holtzman, Denise Levitch, Susan Mills, John C. Morris, Angela Oliver, Anna Santacruz, Wendy Sigurdson, Joy Snider

DIAN TU Cores
Admin – Randy Bateman  Biostatistics – Chengjie Xiong  Imaging – Tammie Benzinger
Clinical – Randy Bateman  Cognition – Peter Snyder  Informatics – Dan Marcus
Biomarkers – Anne Fagan  Genetics – Alison Goate  Neuropathology – Nigel Cairns

The DIAN Team and Performance Sites
The Dominantly Inherited Alzheimer’s Network (DIAN) and the DIAN Trials Unit (DIAN TU)

**DIAN Principal Investigator**
JC Morris

**DIAN TU Principal Investigator**
RJ Bateman

**Coordinating Center Cores**
- Admin – JC Morris
- Clinical – RJ Bateman
- Biomarkers – AM Fagan
- Biostatistics – C Xiong
- Genetics – AM Goate
- Imaging – T Benzinger
- Informatics – D Marcus
- Neuropathology – NJ Cairns

**Performance Sites**

- **United States:** Washington Univ (Bateman), MGH/BWH (Sperling), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti), UCLA (Ringman), U of Pittsburgh (Klunk), Mayo Clinic, Jacksonville (Graff-Radford)

- **Europe:** Institute of Neurology, Univ College London (Rossor), Ludwig-Maximilians-Universität München (Danek), University of Tübingen (Jucker)

- **Australia:** Prince of Wales Medical Research Institutes, Sydney (Schofield), Mental Health Health Research Institute, Melbourne (Masters), Edith Cowan Univ, Perth (Martins)