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**UNTIL WEDNESDAY, JULY 20, 2011, 10:30 AM CEST (4:30 AM ET/USA)**

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AAIC 2011 press room, July 16-21: +33 (0)1 57 25 20 35

**INTERNATIONAL STUDY OF GENETIC ALZHEIMER'S DISEASE  
GIVES CLUES TO PRESYMPTOMATIC DETECTION AND  
PROGRESSION OF THE DISEASE**

**- Population Destined to Get Alzheimer's is Ideal to Study Prevention; Trials Being Planned -**

PARIS, July 20, 2011 – Measurable brain chemistry changes may appear 10 to 20 years before the first detectable memory and thinking impairments among people with a rare genetic form of Alzheimer's, according to new research presented today at the Alzheimer's Association International Conference 2011 (AAIC 2011) in Paris. According to the researchers, the results demonstrate the feasibility and promise of performing Alzheimer's prevention studies in this special population.

“We want to prevent damage and loss of brain cells by intervening early in the disease process – even before outward symptoms are evident, because by then it may be too late,” said Randall Bateman, MD, Assistant Professor of Neurology at the Washington University School of Medicine, Associate Director of the Dominantly Inherited Alzheimer Network (DIAN), and leader of DIAN's Clinical Core. “We propose accelerating efforts to prevent Alzheimer's by treating people at highest risk for dementia caused by Alzheimer's.”

This research focuses on a form of Alzheimer's caused by rare genetic mutations that guarantee a person will develop the disease. Because inheriting a single copy of these genes from either parent causes Alzheimer's, this form of the disease is called “dominantly inherited.” It's also known as “autosomal dominant” or “familial” Alzheimer's. People with dominantly inherited Alzheimer's develop symptoms at a young age – usually when they are in their 40s and 50s, but sometimes as early as their 30s. This form of Alzheimer's comprises about 1 percent of cases worldwide.

The genes that guarantee a person will develop Alzheimer's are known as “deterministic” genes. There are also “risk” genes that increase the likelihood a person will develop Alzheimer's, but don't guarantee that it will happen. In the vast majority of people with Alzheimer's, the disease results from complex interactions among genes, life experiences and other factors.

In 2008, the U.S. National Institute on Aging (NIA) at the National Institutes of Health (NIH) funded the establishment of the DIAN study, conducted by an international network of 11 leading research centers to investigate Alzheimer's caused by the rare, dominantly inherited genetic mutations. Directed by John C. Morris, MD, of Washington University School of Medicine, DIAN now has the largest and most extensive worldwide research network investigating dominantly inherited Alzheimer's at research facilities in the U.S., U.K. and Australia.

People from families with known gene mutations that cause Alzheimer's represent an ideal study group to determine the sequence and rate of Alzheimer's brain changes that occur before detectable memory and thinking changes appear. Asymptomatic mutation carriers – all of whom are destined to develop symptomatic Alzheimer's – can be compared with their noncarrier siblings. However, no single research center has sufficient numbers of familial Alzheimer's individuals to conduct a big enough study to generate meaningful results, underscoring the value of DIAN.

“By studying the cause, progression, detection, treatment and prevention of Alzheimer's in those rare individuals who are destined to get the disease because of their genes, we believe we can learn a great deal more about the vast majority of people whose Alzheimer's develops as a result of complex interactions among their genes, life experiences and other factors,” said William Thies, PhD, Chief Medical and Scientific Officer at the Alzheimer's Association. “In particular, earlier detection and treatment are crucial if we are to curb the growing epidemic of Alzheimer's disease.”

### **Details of the DIAN Trial and Interim Results**

At AAIC 2011, the DIAN researchers presented the clinical, cognitive, MRI, PET, cerebrospinal fluid (CSF), and blood biomarkers from the first cohort of DIAN participants with respect to the expected age of onset and suggestions on how these measures may be utilized in the design of trials. The DIAN registry will eventually total 400 individuals; at AAIC 2011, the scientists reported data from the initial 150 enrollees.

“Based on what we see in our population, brain chemistry changes can be detected up to 20 years before the expected age of onset,” said Bateman. “These Alzheimer's-related changes can be specifically targeted for prevention trials in these patients with genetic Alzheimer's.”

Each DIAN site enrolls eligible individuals, who then complete the 4-day DIAN testing battery, including clinical assessment (e.g., the Clinical Dementia Rating), standard and novel psychometric measures, blood (plasma) and CSF assays for amyloid-beta and tau, structural and functional magnetic resonance imaging (MRI), and positron emission tomography (PET) with Pittsburgh Compound-B (PiB), an amyloid imaging agent.

Asymptomatic DIAN participants have a mean age of 37 years at entry into the study; just over half (51percent) carry the Alzheimer's gene mutation. The average age at which their parent with Alzheimer's started experiencing symptoms is 45.8 years. Of those people in the study who are symptomatic, mean age of symptom onset is 46.1 years.

To date, the researchers have analyzed samples of CSF and blood from approximately 130 DIAN participants for proteins known to be related to Alzheimer's. These proteins include:

- amyloid-beta42, the primary component of amyloid plaques in the Alzheimer's brain
- tau and phosphorylated tau (or ptau), the primary components of neurofibrillary tangles

Previous research has shown that levels of CSF amyloid-beta42 are *decreased* in people who have Alzheimer's dementia compared those without Alzheimer's, reflecting the presence of amyloid plaques in the brain. Levels of tau are *elevated*, reflecting the presence of neurofibrillary tangles and/or brain cell death. The DIAN researchers asked whether these same patterns of biomarker changes are observed in Alzheimer's mutation carriers while they are still cognitively normal, and when such changes can be detected, with the goal of being able to determine (1) who is in the very earliest (preclinical) stages of the disease and (2) where they are along the course of the disease.

They found that, overall, asymptomatic Alzheimer's mutation carriers in DIAN had lower levels of CSF amyloid-beta42 and higher levels of tau compared to family members who did not have the mutation; this is consistent with the presence of Alzheimer's plaques and tangles even in the preclinical phase of the disease – before there are memory and thinking changes.

Importantly, when they looked at the relationship of these changes in protein levels to the person's expected age of dementia onset (defined as the age of dementia onset of their parents), they found that these biomarker changes were detectable at least 10 years before the expected age of dementia onset. They did not observe this pattern in family members who did not have mutations. These findings suggest that CSF amyloid-beta and tau are useful Alzheimer's markers in individuals destined to develop Alzheimer's dementia, and that absolute levels of these markers may indicate how far along in the disease process these individuals are before cognitive symptoms become apparent.

“This suggests that we can measure brain chemistry abnormalities in the Alzheimer's gene carriers that begin at least 10 years, and maybe even 20 years, before the age that their parents saw Alzheimer's symptoms and when they too would be expected to see them,” Bateman said. “As a result, we believe that the DIAN results will help to elucidate the chronology of Alzheimer's disease progression prior to its symptomatic stages.”

Note: New criteria and guidelines for the diagnosis of Alzheimer's disease were recently published by the National Institute on Aging and the Alzheimer's Association in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. These new criteria and guidelines describe three stages of the disease – including a research agenda for a proposed preclinical stage to be diagnosed solely by biomarkers. The work being carried out by the DIAN team coincides strongly with the research agenda outlined in those documents and supports the viability of preclinical detection of Alzheimer's.

### *Imaging*

Results in the DIAN population from brain amyloid imaging with C-11 PiB PET suggest that the deposition of amyloid begins many years before the development of dementia symptoms. They also reveal distinct differences in the regional distribution of beta-amyloid in the brain in dominantly inherited Alzheimer's compared to the much more common sporadic late onset Alzheimer's.

“We don't know yet why there are these differences,” Bateman said. “For now, it is an observation of one of the few consistent differences between autosomal dominant and sporadic Alzheimer's.”

### *Clinical and Cognitive Assessment*

For participants in DIAN, the initial cognitive and clinical assessment included a medical and neurological history and detailed neurological examination, the Clinical Dementia Rating (CDR), a cognitive battery including the Mini Mental State Exam (MMSE), and a variety of other memory and thinking tests. The MMSE and CDR in mutation carriers show the first signs of decline approximately five years before the estimated age of onset (EAO) and begin to separate from non-carriers approximately five years before EAO.

### **Ideal Platform for Prevention Trials**

“The DIAN study and findings provide the most extensive data on brain structural and pathologic biomarkers, blood and CSF biomarkers, and cognitive and clinical measures in pre-clinical and symptomatic early onset autosomal dominant Alzheimer's disease. This information fills a gap in the cascade of events causing Alzheimer's and represents a unique opportunity for prevention trials in Alzheimer's disease,” Bateman said.

Leveraging the study's existing infrastructure, the DIAN Therapeutic Trials Unit (TTU) plans to implement prevention trials. The U.S. Food and Drug Administration and European Medicines Agency – both government agencies that regulate drug trials – have expressed support for prevention trials in this special population. Eleven compounds have been nominated by the pharmaceutical industry for use in these trials; discussions are ongoing.

“Clinical trials in people with genetic Alzheimer's will pioneer the way to prevention trials for all forms of Alzheimer's,” Bateman said.

### **About AAIC**

The Alzheimer's Association International Conference (AAIC) is the world's largest conference of its kind, bringing together researchers from around the world to report and discuss groundbreaking research and information on the cause, diagnosis, treatment and prevention of Alzheimer's disease and related disorders. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

### **About the Alzheimer's Association**

The Alzheimer's Association is the leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit [www.alz.org](http://www.alz.org) or call 800-272-3900.

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- Randall Bateman, MD, et al. The Dominantly Inherited Alzheimer Network Interim Results (AAIC 2011 Featured Research Session). (Funder: U.S. National Institutes of Health)

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AAICAD 2011, Featured Research Session F4-02  
Wednesday, July 20, 2011, 10:30 am-12:30 pm  
Proposal ID: 14973  
Chair: Randall Bateman, MD, Washington University School of Medicine, St. Louis, MO  
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**The Dominantly Inherited Alzheimer Network Interim Results**

**Abstract Details**

**Topics**

|                           |  |
|---------------------------|--|
| <b>Topic:</b>             | Genetics                               |
| <b>Genetics Subtopic:</b> | Genetic factors of Alzheimer's disease |
| <b>Biomarkers:</b>        | Biomarkers                             |

**Background:** Autosomal-dominant Alzheimer's disease has provided significant understanding of the pathophysiology of Alzheimer's disease. The international Dominantly Inherited Alzheimer Network (DIAN) aims to determine the pathophysiological changes in clinical, cognitive, imaging, biochemical and pathology measures. The first interim analysis of the progress, results and future studies will be presented.

**Methods:** The DIAN study enrolls individuals with or at-risk for an autosomal dominant Alzheimer's disease causing mutation for longitudinal assessments. Eleven international DIAN sites recruit and enroll participants for uniform clinical, cognitive, imaging, CSF and blood collection. All measures are quality controlled across sites and collected in a uniform manner with the Alzheimer's Disease Cooperative Study.

**Results:** The Featured Research Session will summarize the clinical, cognitive, pathology, imaging, biochemical, and molecular studies of autosomal-dominant Alzheimer's disease, highlighting the similarities and differences between the dominantly inherited form of Alzheimer's disease and the more common sporadic form of Alzheimer's disease.

Six sessions will be presented:

- 1) Overview of the DIAN cohort, aims, and progress
- 2) History, Genetic, and Pathology overview and update
- 3) MRI - structural, functional and other
- 4) Amyloid Imaging
- 5) CSF and blood biomarkers
- 6) DIAN clinical and prevention trials

**Conclusions:** The DIAN has been established and provides the first international study on familial Alzheimer's disease. The results indicate autosomal dominant AD is similar to later-onset sporadic AD with common pathophysiological mechanisms. The DIAN provides a model framework for discovering the chronological changes of Alzheimer's disease and offers a unique opportunity for future prevention trials.

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**Dominantly Inherited Alzheimer Network (DIAN): Overview, Aims, and Progress**

**Background:** We hypothesize that the pathological process of Alzheimer's disease (AD), as detected by molecular and other biomarkers, begins in asymptomatic individuals at least a decade, if not longer, before detectable cognitive symptoms appear. To determine the sequence and rate of biomarker abnormalities antecedent to symptomatic AD, individuals from families with known pathogenic mutations causing AD represent an ideal study cohort. Asymptomatic mutation carriers (all of whom are destined to develop symptomatic AD) can be compared with their noncarrier siblings. However, no single center has sufficient numbers of familial AD individuals to conduct an appropriately powered study of antecedent biomarkers for AD.

**Methods:** We develop standard and uniform protocols for the longitudinal evaluation of clinical, cognitive, personality, genotype, biofluid (plasma; cerebrospinal fluid [CSF], and structural and molecular imaging variables at ten sites that study English-speaking members of families with known pathogenic mutations for AD. Each site enrolls into the DIAN study individuals, both asymptomatic and symptomatic and mutation carriers and noncarriers, from families with PSEN1, PSEN2, and APP mutations. These individuals complete the 4-day DIAN battery, including clinical assessment (eg, the Clinical Dementia Rating), standard and novel psychometric measures, blood (plasma) and CSF assays for amyloid-beta and tau, structural and functional magnetic resonance imaging (MRI), and positron emission tomography (PET) with Pittsburgh Compound-B (PIB). The frequency of longitudinal follow-up is indexed to the participant's age in relation to the age of onset (AAO) of symptomatic AD of their affected parent. The total registry will total 400 individuals; we report here data from the initial 150 enrollees.

**Results:** Virtually all DIAN participants have completed the clinical, cognitive, personality, and genotyping procedures. Completion rates are approximately 92% for MRI, 84% for PET PIB, and 68% for CSF collection. Asymptomatic participants have a mean age of 37y at entry; 51% are mutation carriers. The mean AAO of their affected parent is 45.8y. The mean age of symptomatic participants is 46.1y. Seventy-five per cent of mutation carriers have a PSEN1 mutation. Other sample and biomarker characteristics will be presented.

**Conclusions:** DIAN is now well-established. Preliminary molecular biomarker analyses suggest that abnormalities begin at least 10-20 years before the parent's AAO of symptomatic AD, suggesting that DIAN can help to elucidate the pathological chronology of AD prior to its symptomatic stages. Supported by National Institute on Aging grant U01AG032438

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### **DIAN: History Genetic and Pathology Overview and Update**

**Background:** Dominantly inherited Alzheimer's disease (AD) is rare, comprising less than 1% of cases. Although families had been identified as early as the 1930s it was not until 1991 that the first mutations were identified in the APP gene and in presenilin 1 and 2 genes in 1995; APP locus duplication causing AD with cerebral amyloid angiopathy was reported in 2006. Presenilin 1 genes comprise the majority of cases. The study of dominantly inherited AD has led to important insights into the molecular pathology and clinical features of AD and directly to animal models. It has also provided an opportunity to study pre-symptomatic mutation carriers to identify the early natural history of the disease.

**Methods:** Review of published literature on dominantly inherited AD exploring the history, the identification of candidate genes and the key clinicopathological features. Results Studies to date have involved relatively small numbers of patients affected by nearly 200 different presenilin1 mutations and over 30 APP gene mutations. The three different disease genes and the site of mutation within each gene influences the pathology and the clinical features. For example, presenilin 1 mutations beyond codon 200 tend to have larger amyloid plaques and more amyloid angiopathy, the latter also being a prominent feature of APP mutations within the A $\beta$  coding sequence. Although there is pathological and clinical heterogeneity amnesic presentation remains the commonest and the small number of longitudinal studies of at risk individuals suggest a progression similar to sporadic disease.

**Conclusions:** The study of dominantly inherited AD provides the opportunity to explore the effect of specific mutations on disease expression but importantly the similarity of dominantly inherited AD in general to sporadic disease supports the view that this is a valid model. Longitudinal studies of presymptomatic carriers provide a valuable opportunity to study the onset and progression of earliest disease. The international collaboration afforded by DIAN provides the numbers of patients needed to build on previous preliminary observations.

**Conflicts:** No conflicts of interest

**Plasma and cerebrospinal fluid markers in the DIAN study of autosomal-dominant Alzheimer's disease**

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**Background:** Alzheimer's disease (AD) pathology begins years before cognitive signs/symptoms, thus offering a potential window for disease-modifying therapies. AD biomarkers are needed to identify individuals in this "preclinical" stage. Since individuals with gene mutations in APP, PSEN1 or PSEN2 will develop AD dementia with virtually 100% penetrance, they comprise a unique cohort to study the chronology of biomarker changes antecedent to estimated onset of dementia. To this end, the Dominantly Inherited Alzheimer Network (DIAN), an international consortium of 10 AD centers, is collecting longitudinal clinical, cognitive and biomarker data in such a cohort.

**Methods:** Groups to date include cognitively normal (Clinical Dementia Rating=0, CDR 0) mutation non-carriers (NC, n=26), cognitively normal (CDR 0) asymptomatic (n=29) and symptomatic (CDR>0, n=29) mutation carriers (MC). Plasma analytes include A 40 and A 42. CSF analytes include A 1-42, tau and p-tau181. CSF A 1-40 measures are in progress. "Normalized" age is defined as participant's age in relation to parental age of dementia onset (reported by family members). Group differences were analyzed by ANOVA. Slopes of the "analytes x normalized age" linear regression lines provided an estimate of biomarker change over time in this cross-sectional dataset.

**Results:** Preliminary analyses revealed higher mean levels of plasma A 42 in MCs (asymptomatic and symptomatic) compared to NCs ( $p < 0.001$ ), whereas levels of plasma A 40 did not differ between groups ( $p > 0.72$ ). Mean levels of CSF A 1-42 were decreased, and tau and p-tau181 were increased, in symptomatic MCs compared to NCs and asymptomatic MCs. However, levels of CSF analytes were related to normalized age. NCs showed little to no difference in CSF measures as a function of normalized age. In contrast, levels of CSF A 1-42 in asymptomatic MCs declined, and levels of tau and p-tau181 increased, during the long presymptomatic period (0-32 years prior to parental dementia onset).

**Conclusions:** Plasma A 42 levels reflect mutation status in autosomal dominant AD, whereas CSF A 1-42, tau and p-tau181 likely reflect the presence/absence of early AD pathology in the brain. Ongoing studies are investigating mutation-specific effects, effects of APOE genotype, longitudinal change in biomarkers within individuals, and correlation of fluid markers with other cognitive and imaging variables.

Support: U01AG032438

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**DIAN: MRI of familial AD**

**Background:** Dominantly inherited Alzheimer's disease (although rare) provides the opportunity to examine pre-symptomatic changes by studying at-risk individuals. MR imaging allows non-invasive assessment of structural, micro-structural and functional cerebral change. MRI may therefore provide a means of indentifying individuals who are near to symptom onset ("proximity" markers) for inclusion in trials. Imaging may also be used to track progression and provide "outcome" measures that predict (later) clinical response.

**Methods:** Review of published literature on the structural and functional MR studies in dominantly inherited AD exploring early change and measures of progression. Preliminary MRI results from DIAN will be set in this context.

**Results:** There have been relatively few MR-based studies of familial AD to date. These have usually involved small numbers of subjects and cross-sectional imaging. Nonetheless volumetric MRI studies have suggested that gene-carriers have increased cerebral atrophy: larger ventricular volumes and smaller hippocampal and entorhinal cortex volumes. Diffusion imaging studies have shown that mutation carriers have reduced fractional anisotropy in the fornix and other relevant tracts – diffusivity changes within grey matter structures including thalamus have also been reported. Magnetisation transfer ratios appear to be reduced in the temporal lobe – at least by the time individuals are symptomatic. Studies of mutation carriers prior to expected age-at-onset have shown increased fMRI activity in temporal gyri during encoding tasks; similarly MR spectroscopy has shown NAA/MI reductions near to age-at-onset. Serial studies show that rates of atrophy (e.g hippocampus) increase up to 5 years prior to symptom onset.

**Conclusions:** MRI studies show that individuals at risk of familial AD have increased rates of atrophy several years prior to symptom onset. These changes are accompanied (and may be preceded by) microstructural and functional MR alterations. Determining how best to use these methods to track change at this early stage will be important to guide pre-symptomatic trial design.

**Conflicts:** No conflicts of interest

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**Amyloid Imaging in Dominantly Inherited AD**

**Objectives:** To track the deposition of beta-amyloid in carriers of gene mutations known to cause dominantly inherited Alzheimer's disease and relate this to change in cognition, blood and CSF biomarkers, brain atrophy and hypometabolism in order to better understand the pathogenesis of familial AD.

**Methods:** Individuals with or at-risk for autosomal dominant Alzheimer's disease from 11 international sites are being recruited and receive clinical, cognitive, imaging, CSF and blood collection. C-11 PiB PET is acquired 40-70 minutes postinjection of 10-15 mCi PiB. All measures are quality controlled across sites and collected in a uniform manner with the Alzheimer's Disease Cooperative Study.

**Results:** Initial analysis has revealed a variety of patterns of PiB binding but with prominent striatal uptake and in some families, marked occipital binding. In asymptomatic carriers of a gene mutation, PiB binding is a common finding and often associated with normal FDG PET.

**Conclusion:** Imaging with C-11 PiB PET has revealed distinct differences in the regional distribution of fibrillar beta-amyloid in dominantly inherited AD compared to sporadic late onset AD with marked uptake in the striatum especially in presymptomatic carriers. These studies also suggest that the deposition of amyloid commences many years before the development of dementia and may be associated with normal cognition and normal brain metabolism on FDG PET at this early, preclinical stage of the disease.

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### **Dominantly Inherited Alzheimer's Network Clinical Trials: A Model for Prevention Trials**

**Background:** Autosomal dominant Alzheimer's disease has provided significant understanding of the pathophysiology of Alzheimer's disease. Clinical trials in autosomal dominant Alzheimer's disease may test the amyloid hypothesis, determine the timing of treatment, and lead the way to Alzheimer's disease prevention. The Dominantly Inherited Alzheimer Network (DIAN) study and findings provide the most extensive data on brain structural and pathologic biomarkers, blood and CSF biomarkers, and cognitive and clinical measures in pre-clinical and symptomatic early onset autosomal dominant Alzheimer's disease. This information fills a gap in the cascade of events causing Alzheimer's disease and represents a unique opportunity for prevention trials in Alzheimer's disease. Issues involved in the design and implementation of treatment trials in the DIAN study will be reviewed.

**Methods:** The clinical, cognitive, MRI, PET, CSF, and blood biomarkers from the first cohort of participants of the Dominantly Inherited Alzheimer's Network will be presented with respect to the expected age of onset and how these measures can be utilized in the design of therapeutic trials. Treatment trial issues of power analysis, timing of treatment, choice of target and therapy, and stage of disease for treatment trials will be presented.

**Results:** Changes in clinical, cognitive, MRI, PET, CSF, and blood biomarkers relative to the expected age of onset indicate a sequence of events in the pathophysiologic cascade of Alzheimer's disease. Results indicate that changes can be detected up to 20 years before the expected age of onset. These changes of Alzheimer's disease can be specifically targeted for prevention trials in autosomal dominant Alzheimer's disease.

**Conclusions:** The Dominantly Inherited Alzheimer's Network provides a model framework for discovering the chronological changes of Alzheimer's disease and offers a unique opportunity for future prevention trials.

Study supported by: National Institutes of Health (NIH) grants NIA U-01 AG032438 and also grants from an anonymous foundation.