Biological Underpinnings of Genetic Risk Factors in Alzheimer’s disease (BGF)

**Competition objectives:** The present Request for Applications [RFA] by the Alzheimer’s Association aims to promote further understanding of the underlying biological mechanism of ‘genetic risk’ factors, identified by Genome Wide Association Studies (GWAS), rare-variant studies, DNA sequence-based approaches, or other genomic approaches, associated with Alzheimer’s disease (AD) and related dementia. The overall objective of this RFA is to enable the formulation of ‘testable hypotheses’ along with proof-of-concept preliminary studies to potentially identify functional variants, explain the molecular linkages, cascades of biological events, and to understand the connections between genetic phenotypes and clinical or behavioral expression of the disease. The pilot research supported by this RFA should provide good quality data for further research support by other funding agencies.

**Background:** Single nucleotide variants in multiple identified genetic loci have now reproducibly been shown to be associated with AD. Some of these variants affect protein coding sequences while others are either in regulatory elements, or in linkage disequilibrium with regulatory and/or coding elements. For a given associated variant, it is often not clear what gene is being affected. The details of the molecular events that link the genetic variants to the biological and/or clinical-behavioral phenotype are for the most part lacking or poorly understood. For example, many of the genetic variants identified to date may be related to inflammation and immune system dysfunction, yet it is unclear how each contributes to the risk of AD pathogenesis and cognitive decline. The identification of the various biological pathways and a better understanding of the sequence of critical steps in translation of genetic codes into pathophysiological mechanism will no doubt provide key insights into the etiology or mechanism of disease progression thus opening the prospects for identification of novel therapeutic targets.

**Potential themes:** Some of the potential themes applicants might consider may include the following; they are not limited to those listed here. Studies may include:

1. Investigations into the potential molecular linkages of genetic loci.
2. Understanding the functional effects and functional variants within a given loci (e.g functional effects of SNPs, efforts to identify functional coding or regulatory variants).
3. Studies that investigate genetic loci associated cascade of biological events that are linked to disease mechanisms.
4. Investigations regarding the connections between genetic phenotypes and clinical or behavioral expression of the disease.
5. Studies that examine genotype-phenotype correlations with imaging or fluid based biomarkers, in postmortem brain tissue, or in novel model systems.
6. Approaches that attempt to understand the cumulative effect of the genetic variants on risk.
7. Approaches aimed at understanding the biological pathways revealed by genetic studies. For example the role of Alzheimer’s disease risk variants/genes in inflammation and immune dysfunction and their potential crosstalk with neurons.
**General considerations:** All proposals must clearly and explicitly outline the hypothesis to be investigated, the methods for study, sample, outcomes, etc. The ultimate goal is to move understanding and knowledge of the biological relevance of the biological underpinnings of genetic risk factors identified for AD. Applicants must present the genetic evidence that supports the study of a particular gene or pathway. Applications targeting neuroinflammation and innate immunity are especially encouraged.

The Association strongly encourages submissions from collaborative research teams (e.g., basic scientists and clinical researchers). In addition, while novel and creative ideas are sought, proposals also need to demonstrate feasibility. The Alzheimer's Association recognizes the need to increase the number of scientists from underrepresented groups in the research enterprise. Researchers from these groups are encouraged to apply.

**Funding and award period:** Each award is limited to $250,000 (direct and indirect costs) for two to three years. Requests in any given year may not exceed $100,000 (direct and indirect costs). Indirect costs are capped at 10 percent (rent for laboratory/office space is expected to be covered by indirect costs paid to the institution).

**Eligibility:** Researchers with full-time staff or faculty appointments (Assistant Professor and above) are encouraged to apply. Applications from post-doctoral candidates will not be accepted.

*Please note:* If the applicant institution does not have an Assistant Professor Position, the letter of employment should include sufficient information to allow the Alzheimer's Association staff to evaluate the eligibility of the applicant.

**Ineligibility:** The Alzheimer's Association will not accept new grant applications from currently funded investigators who are delinquent in submitting required reports and other deliverables on active grants. Investigators that have previous Alzheimer's Association awards closed as 'Incomplete' are not eligible to apply without exception. This policy will be strictly adhered to with no exceptions.

**Submission and Review Procedures:** The grant submission process will follow a two stage procedure. First, applicants will submit an LOI. These LOIs will be reviewed and a select number of the top rated LOIs will be invited to submit full grant applications. The exact number of full applications invited for full submission will be determined by available funding, with a target that more than ten percent (10%) funding rate for full submission.

**Both LOI and the full submissions will be reviewed based on:**
1) Alignment with the research priorities as outlined in the RFA.
2) Demonstrable innovation/novelty of the proposed project (especially in the context of the PIs recently funded work).
3) Impact of project on Alzheimer’s disease and related dementia research.
4) Established investigators from other fields new to Alzheimer’s and related dementia research.
5) Evidence of methodological rigor that address the research question(s) being proposed.

**Deadlines and award dates:** Letters of Intent must be received by 5:00 PM EASTERN STANDARD TIME, March 6, 2015. Letters of Intent will not be accepted after this date. No exceptions will be made.

Applications must be received by 5:00 PM EASTERN STANDARD TIME, May 1, 2015.

Scientific and technical review will be conducted from May through June 2015. The second-level review by the Medical and Scientific Advisory Council will be conducted during June 2015. Funding will be awarded by August 30, 2015.

**Mechanism of award, reporting requirements and allowable costs:** The mechanism of the award is the individual research grant. The maximum allowable duration is three years. Annual progress and financial reports are required. Continuation of the grant over the awarded duration is contingent upon the timely receipt of scientific and financial reports.

**Budget:** A budget summary for the proposed research project is required and must be submitted with the application and within the allowable page limits. However, if the application is to be awarded, a more detailed budget will be required and must be approved before the disbursement of funds. Your budget must not exceed the maximum amount of the award ($250,000 for *Biological Underpinnings of Genetic Risk Factors in AD*).

**Allowable costs under this award:**
It is required that most of the funds awarded under this program be used for direct research support. Allowable costs under this award include:

- Computer equipment if used strictly for data collection
- Travel (up to $1,000 per year)
- Salary for the principal investigator, scientific (including post-doctoral fellows) and technical staff (including interviewers, interventionists, data entry staff, technicians, and administrative support staff whose work is directly related to the funded project)
- Manual production/development/website, etc.

**Costs not allowed under this award include:**

- Tuition
- Computer hardware or software for investigators
- Rent for laboratory/office space
- Construction or renovation costs