Functional Screen of Autism-Associated Variants Request for Applications

SFARI mission
The Simons Foundation Autism Research Initiative (SFARI) seeks to improve the understanding, diagnosis and treatment of autism spectrum disorders by funding innovative research of the highest quality and relevance.

Objective of the Functional Screen of Autism-Associated Variants Award
Grants awarded through this request for applications (RFA) are intended to advance our understanding of the genetic basis of autism, and in particular the potential role of missense and in-frame deletion variants in conferring risk.

Data to be analyzed under this RFA will come in part from the exome sequencing of more than 2,500 families from the Simons Simplex Collection (SSC), which is now complete^1. Although much attention has been focused on de novo mutations that clearly disable protein function — nonsense, splice-site, and frameshift mutations — the majority of what has been identified in the SSC falls into the category of missense variants of uncertain significance. The sequencing of additional large cohorts may help to distinguish pathogenic from benign variants on a purely statistical basis, but it is clear that these efforts will have to be complemented by screens to test such variants for functional relevance.

To this end, we seek proposals for the development and application of medium- or high-throughput screens to test for the functional effects of missense and in-frame deletion variants identified in the SSC and other autism collections. In addition to establishing the functional impact of de novo missense mutations, one key goal will be to compare the impact of such variants when inherited in individuals with autism vs. unaffected siblings (or those with autism vs. unrelated controls), to support a case for particular genes in autism susceptibility.

We envision awards proceeding in two stages. In the first stage, investigators would establish the effectiveness of their proposed screen in assessing a small number of variants. Contingent upon the success of this pilot stage, to be completed in one year, and after discussions with the Simons Foundation, a subset of the awarded pilots would expand to a larger number of variants. Applications should include a plan for the full three years of funding.

Successful proposals will include:
• A discussion of the rationale for selecting the genes and variants to be tested in the functional screen. These may include bioinformatic, genetic or functional considerations.
• A justification for the suite of assays to be included in the screen. Such assays could include cell-based or whole-organism-based approaches.
• A discussion of the proposed methods for introducing the variants into the cells or organisms to be used in the screen.
• Evidence for the potential scalability of the screen.
• A discussion of the potential use of SSC phenotypic data to enable genotype-phenotype correlations based on the functional effects observed in the screen.
Recognizing that successful screens will likely involve multiple approaches, we encourage collaborations between investigators with complementary expertise.

**Eligibility and collaboration**

All applicants and key collaborators must hold a Ph.D., M.D. or equivalent degree and have a faculty position or the equivalent at a college, university, medical school or other research facility. Applications may be submitted by domestic and foreign nonprofit organizations; public and private institutions, such as colleges, universities, hospitals, laboratories, units of state and local government; and eligible agencies of the federal government. Applications may also be submitted by for-profit companies, in which case the funds provided for the grant are to be used only for charitable purposes toward research related to autism spectrum disorders. There are no citizenship or national residence requirements.

If the proposal includes investigators at more than one site, all investigators should have demonstrated prior success in similar collaborations.

**Funding period and budget**

The pilot-grant period is for one year, and a subset of selected pilots will be awarded an additional two years of funding. Continued funding beyond this is possible, when justified by scientific progress. Applications should include a plan for the full three years of funding. During this initial three-year period, SFARI plans to commit up to $2 million annually to support projects funded as a result of this RFA.

**Application requirements**

Applications should include the following:

1. Narrative, not exceeding six (6) pages (excluding references and figures). Proposals should include specific aims, background relevant to the application, significance of the proposed studies, preliminary results, experimental design, pitfalls and alternative strategies, and a timeline with milestones.

2. Biosketches for Principal Investigator(s) and Key Collaborators.

3. Current and pending support for Principal Investigator(s) and Key Collaborators.

4. Budget. While there are no budget caps on the individual applications, budgets will strongly factor into the competitiveness of an application. Budgets of more than $250,000 annually will need convincing justification. It is unlikely that SFARI will make an award larger than this amount. Proposals should include a realistic budget sufficiently detailed for evaluation of needed resources. SFARI will work closely with investigative teams with competitive applications to arrive at a suitable budget. Indirect costs are limited to 20 percent of the modified total direct costs (see SFARI policies).

Applications with multiple Principal Investigators from different institutions that would like to be paid separately must include a signed budget template and budget justification for each Principal Investigator’s institution. Applications with subcontracts must include a
budget and budget justification. The budget template and budget justification are available for download in the proposal attachments section of proposalCENTRAL’s full application.

5. Research environment and resources. Investigators should demonstrate access to appropriate resources for high-capacity data collection and analysis, although SFARI will work with awarded investigators to provide additional informatics support as needed.

6. Data-sharing plan. The plan should include sharing of raw and analyzed data. SFARI will work closely with awarded investigative teams to ensure that the plan includes timely dissemination of data with reasonable embargo provisions.

7. 501(c)(3) determination or equivalency letter (foreign institutions only). The Simons Foundation requires a determination letter from the U.S. Internal Revenue Service (IRS) stating exemption under 501(c)(3) and furthermore, either a 509(a)(1), (2) or (3) classification. If an international institution is selected for funding and does not have the aforementioned documentation, the Simons Foundation will require the institution to complete an equivalency determination with NGOsoacrie (see SFARI policies).

For more details, see the Instructions document, which is available for download in the “Proposal Attachments” section of proposalCENTRAL.

Application deadline
We request that investigators who intend to submit a proposal send an email by 27 March 2015 with the intended investigators’ names and affiliations and their intended proposal’s title to grants@simonsfoundation.org with the subject line: SFARI RFA Notice of Intent.

The deadline for full proposal submission is 10 April 2015, 5:00 p.m. Eastern. No extensions will be given. If you have any difficulties, please contact grants@simonsfoundation.org.

Competitive applications will receive external peer review. SFARI will make final funding decisions; notification of award is expected by 1 July 2015, with funding expected to begin 1 August 2015.

Instructions for submission
Applications must be completed electronically and submitted using forms provided at proposalCENTRAL. Please log in as an applicant, scroll to “Simons Foundation” and click on the program.

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References: