Dup15q Alliance

FOR 15Q 11.2–13.1 MULTIPLICATIONS

Grant Application Instructions and Forms 2024

Background

We are excited by your interest in applying for a **DREAM** (**D**up15q **R**esearch **E**ngagement, **A**ctivities, and **Me**chanisms) **Fund** grant! The Dup15q Alliance is a 501(c)(3) non-profit organization empowering individuals with Dup15q syndrome and their caregivers to reach their full potential by advancing breakthrough research to identify life-changing curative treatments. It supports various research activities, including clinical studies, registry-based investigations that leverage LADDER, and preclinical or basic research. Please use the following instructions and forms to prepare your application.

If you have any questions about the required components or formatting, please contact ryan.rogers-hammond@dup15q.org.

ELIGIBILITY

The Dup15q Alliance DREAM Fund grant program is intended to fund small proof-of-concept studies to generate data for future large-scale research initiatives and funding. Applicants may request up to $50,000 in direct costs to be expended within 12 months. Applications are open to research investigators affiliated with an academic institution, hospital system, non-profit institution, or other accredited research institutions based in the United States (U.S.) or internationally. Eligible applicants include postdoctoral fellows, clinical fellows, researchers, physicians, or other associated research professionals with faculty appointments or research positions. The Alliance does not cover indirect costs for research grants. We are a small non-profit with limited funding, so every dollar allocated goes towards research.

Dup15q Syndrome

Maternal Dup15q Syndrome (Dup15q) is a rare neurodevelopmental disorder affecting up to 1 in 5,000 children worldwide. Dup15q syndrome is highly penetrant for Autism Spectrum Disorder (ASD), intellectual disability (ID), and epilepsy, with hypotonia affecting motor function and GI motility. While no single gene is responsible for the clinical features of Dup15q, some therapeutic targets of interest include the gene cluster encoding $GABA_A$ receptor subunits and UBE3A. The disease is further complicated by the fact that there are two primary genetic subtypes of Dup15q syndrome. Idic (15), which is caused by an isodicentric supernumerary chromosome that carries two or more extra copies of the 15q11.2-q13.1 region, accounts for ~60-80% of cases while a maternal interstitial duplication, or (int) dup(15), of the same region accounts for a smaller percentage of the population. Clinical presentation is heterogeneous, but there is a clear link between epilepsy and the severity of developmental disability in these individuals. Epilepsy occurs in 50% of individuals with idic (15) and less than 10% of individuals with int (15). Of particular interest in Dup15q syndrome is identifying a distinctive EEG biomarker that likely reflects alterations in GABA neurotransmission. This biomarker can be used as a marker of drug-target engagement or as a proximal endpoint in trials. A strong and tightly connected patient advocacy group (PAG) called Dup15q Alliance has created 14 multidisciplinary clinics. However, the management of Dup15q syndrome is limited to developmental interventions, symptomatic treatment, and supportive care.

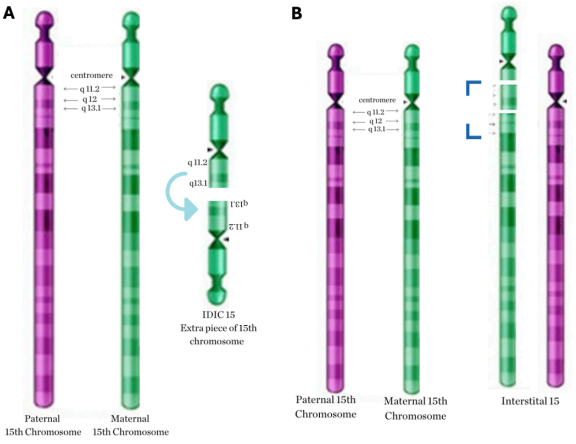

Figure 1: There are two primary genetic subtypes of Dup15q syndrome. (A) Idic (15), which is caused by an isodicentric supernumerary chromosome that carries two or more extra copies of the 15q11.2-q13.1 region, accounts for ~60-80% of cases. **(B)** Maternal interstitial duplication, (int) dup (15), of the 15q11.2-q13.1 region, accounts for ~20-40% of cases.

Research Areas of Interest

Biomarkers and clinical endpoints development.

Dup15q syndrome currently has a unique EEG biomarker, which is still being validated for drug trial utility. The Alliance is interested in identifying additional biomarkers, including CNS imaging, EEG, metabolomics, circulating molecular indicators, etc. Reductions in seizure activity and/or severity can be an important clinical endpoint for evaluating potential therapeutics; however, not all individuals with Dup15q syndrome experience seizures; therefore, developing other clinical endpoints is needed for future clinical trial design.

Molecular pathobiology and genotype-phenotype relationships.

Why duplication of the 15q11.2-q13.1 chromosome region causes the various phenotypes associated with the syndrome remains unclear. There are several genes in this region whose aberrant interactions likely drive the etiology of Dup15q syndrome, including those critical for brain development and synaptic function. Since this region is typically imprinted in neurons, maternally derived increases in copy number are thought to drive the disorder's clinical features. Of the genes, ubiquitin protein ligase E3A (Ube3a), SNRPN, Cytoplasmic FMR1 interacting protein 1 (CYFIP1), and three GABAA receptor genes (GABRB3, GABRA5, GABRG3) are highlighted as key instigators of the phenotype but how duplication affects interactions within key pathways remains poorly understood. Moreover, how aberrant interactions lead to seizures and the observed heterogeneity of seizures is unknown. Understanding the molecular basis of Dup15q will help identify potential therapeutic intervention targets.

The role of hypotonia in disease progression and outcomes.

While epilepsy and ASD are cited as the hallmarks of Dup15q syndrome, hypotonia is thought to drive many additional clinical characteristics of the disorder. For example, patients with Dup15q experience altered gait and reduced gross and fine motor abilities, gastrointestinal distress, and respiratory difficulties. Understanding how duplication causes these characteristics or identifying novel interventions to mitigate hypotonia and the related deficits is of keen interest to the Alliance.

Drug repurposing

The ability to repurpose FDA-approved drugs for new indications is becoming increasingly important for rare diseases, such as Dup15q syndrome. Identifying and testing the efficacy of such drugs is a priority for the Alliance, making projects within this scope highly attractive.

Pubescence and disease trajectory

Pediatric patients affected by neurodevelopmental disabilities are 20 times more at risk of premature pubertal changes compared to the general population. Additionally, changes in symptomology at the onset of pubescence have been reported by clinicians and caregivers of Dup15q patients. Still, there is a paucity of information on how or why hormone fluctuation contributes to disease trajectory or if/how duplicated genes drive such changes. Studies focused on understanding this relationship may lead to improved treatments ahead of pubescence and prevent any puberty-related regression.

Application Instructions

The Dup15q Alliance seed grant program is open to research investigators affiliated with academic institutions, hospital systems, non-profit institutions, or other accredited research institutions based in the United States (U.S.) or internationally. Eligible applicants include post-doctoral fellows, clinical fellows, researchers, physicians, graduate students, or other associated research professionals with faculty appointments or research positions. The Alliance does not cover indirect costs for research grants. We are a small non-profit with limited funding, so every dollar allocated goes towards research.

All grant application material must be submitted directly to the Alliance through ryan.rogers-hammond@dup15q.org.

Application Components

Please include the following components in your research grant application. All forms can be found in the Appendix.

1. **Cover Page.** The *Dup15q Alliance Grant Application Cover Page* (form in the Appendix) should be completed and signed by the applicant/PI and the institution's Signing Official. Electronic signatures are acceptable.
2. **Key Personnel.** The *Dup15q Alliance Application Key Personnel Form* (Appendix) should be completed to include the requested information for the PI and all individuals who will contribute, in a substantive, meaningful way, to the scientific development or execution of the project, regardless if salaries are requested.
3. **CV/Biosketch for Key Personnel.** Attach a CV/Biosketch for each key personnel using either the *CV/Biographical Sketch Form* provided (Appendix A) or the NIH Biosketch format.
4. **Abstract and Lay Summary.** Provide a technical abstract and lay summary of the proposed work (1,500 characters maximum each). Please note that the lay summary may be shared publicly through our various communication channels if the application is selected for funding; therefore, it should not contain any proprietary information.
5. **Project Description.** Provide a description of the proposed project, with a 5-page maximum. Please include the following sections in the proposal, with figures embedded within corresponding sections. Work should be formatted in Arial or Times New Roman 11-point font with no less than ½ inch margins.
    a. Specific Aims (1 page max)
    b. Significance
    c. Preliminary Data
    d. Research Design, including methods.
    e. Translational Potential
6. **Literature References.** Include a list of references supporting the project description. This list is in addition to the 5-page project description. You may cite the references in-text using your preferred citation style.
7. **Timeline.** Please provide a detailed projection of the experimental timeline and key results. Gantt charts are preferred but not required.
8. **Resources & Environment:** This should describe the research facility, laboratory space, and major equipment needed for the study. Any procedures, materials, or situations that may be hazardous should be described along with the proposed precautions to be taken.
9. **Organizational Assurances.** Attach IRB and IACUC approvals, if applicable.
10. **Budget and Justification.** Please use the *Dup15q Alliance Budget* form (Excel sheet) and refer to the instructions below.

Budget Instructions

Please use the *Dup15q Alliance Budget* Excel workbook for your budget. The grant will not cover administrative overhead or indirect costs, so please do not include these line items in the budget. Dup15q Alliance does not cover institutional construction or renovation, purchase of capital equipment other than what is needed for the proposed research, office equipment or furniture, equipment service contracts, travel to medical meetings, tuition fees, journal subscriptions, dues or memberships, and publication fees.

All budget line items must be rounded to the nearest US Dollar amount ($0.50 is rounded to $1.00).

Personnel Costs

Name. Starting with the PI(s), list the names of all personnel involved in the project, regardless of whether a salary is requested. If no salary is requested, use $0.00 as the line item.

Role on Project. Identify the role of everyone listed on the project.

Effort. Enter the percent effort devoted to the project. A 100 percent effort equals 12 months/year, 40 hours/week. All listed personnel must have a % Effort > 0.00% regardless of whether a salary is requested.

Institutional Base Salary. This is the annual compensation issued by the employer for an employee's appointment, regardless of whether that individual's time is spent on research, teaching, patient care, or other activities. Base salary excludes any income earned outside of duties for the applicant/grantee organization.

Fringe Rate. The fringe rate is a percentage of an hourly wage or salary representing the employer's additional costs of employee benefits. The institution usually sets this rate. The separate *Budget Justification* document must explain different fringe rates for different individuals.

Salary Requested. This is the salary requested for the individual. *This amount cannot be greater than the institutional base salary multiplied by the % effort*; however, it can be less.

Fringe Requested. This is calculated by multiplying the requested salary by the fringe rate.

Total Personnel Cost. Totals are calculated as the sum of the salary requested and fringe requested.

Non-Personnel Costs

Equipment. List each item of equipment with the amount requested separately and justify each purchase under *Justification*.

Supplies. Itemize supplies in separate categories, such as glassware, chemicals, radioisotopes, disposables, etc. *Animal purchases are considered supplies.* If animals are to be purchased, state the species and the number to be used.

Patient Care Cost. If inpatient and/or outpatient costs are requested for research with human subjects, briefly describe the costs. Provide the names of hospitals and/or clinics and the amounts requested in the *Budget Justification*. If both inpatient and outpatient costs are requested, provide information for each separately. If multiple sites are to be used, provide detailed information by site.

Other Direct Costs. Itemize any other expenses by category and unit cost. These might include *animal maintenance and handling* (unit care costs and number of care days), patient travel, core facility costs, etc. Be sure to describe any other costs clearly in the *Budget Justification.*

Total Costs

This value is automatically calculated from the sum of all Subtotal Direct Costs.
The total costs must be within the budget limit set by Dup15q Alliance.

Budget Justification

Please attach a separate document with the file named *JUSTIFICATION+NAME_YEAR.* All line items in the budget Excel workbook must be easily linked to the items discussed in this file.

Awardee Expectations

Grant Period

Research grant awards made by Dup15q Alliance are usually approved for a 12-month grant period.

Grant Payment

The funding approval letter will outline grant payment terms under "Payment Schedule." It must be signed and returned before payments are issued.

Grant Reporting

The awardee shall provide two progress reports (6-month and final report) during the grant period. Progress reports will include, at a minimum, (i) a summary of all research performed during the reporting period, (ii) the results of such research, (iii) an assessment of progress toward achieving the specific aims, and (iv) full disclosure of any project IP or publications generated. The six-month report should be, at most, three pages long, excluding references. The final report should be a maximum of six pages, excluding references, and accompanied by a financial report. Report due dates will be included in the notice of award.

Sixty (60) days following the end date of the grant, the awardee shall provide a final project report that will include the following:

- A technical summary of all research performed during the grant period.
- A one-paragraph lay summary of the work and key findings written for a non-scientific audience
- Detailed results of the research.
- Immediate and future impacts of the work, including future directions suggested by the research.
- Any grant proposals submitted or to be submitted because of the work conducted under the Alliance's seed grant.
- A listing of any project IP, publications, and/or conference presentations in preparation, submitted, in press, or published from the research conducted under the Alliance's seed grant.
- A financial report of expenditures, signed by the appropriate institutional official. Please note that any unexpected funds will be refunded to the Alliance unless the awardee and Alliance have entered into a No Cost Extension agreement.

Dup15q Alliance Scientific Meeting

Awardees must attend and present at the annual Scientific Meeting during the calendar year funded.

Publication Policy

The results of research supported by the Dup15q Alliance are expected to be published as soon as practical, as conference abstracts and/or in relevant peer-reviewed journals. Acknowledgment of funding support, either in whole or in part, from the Dup15q Alliance is required. The responsibility for publication lies exclusively with the awardee and does not require prior review by the Dup15q Alliance. Electronic copies of presented conference posters, conference presentations, and published manuscripts (whether during the grant term or after it has ended) should be promptly forwarded to the Dup15q Alliance.

Patent Policy

Discoveries and related regulatory approvals made under the Alliance's sponsorship are the property of the Sponsoring Institution or Principal Investigator conducting the research; provided, however, that the Alliance shall have the right of royalty-free use for non-commercial purposes of such discoveries. The Sponsoring Institution and Principal Investigator ensure that prompt public disclosure of all commercially usable information is made as soon as possible. The Principal Investigator and Sponsoring Institution are also responsible for notifying the Alliance of the filing of any letters patent for any discovery made on research funded by the Foundation.

Publicity

The Dup15q Alliance shall be permitted to use the name, image, and likeness of the Principal Investigator and Co-Investigators, as well as the affiliated Institution/s, in connection with all statements, printed materials, or electronic media related to a grant.

Sharing Policy

The Dup15q Alliance encourages data sharing and collaboration among its awardees and the Dup15q research community. Materials produced from research supported by the Foundation (e.g. data, animal models, expression plasmids, antibodies, permanent cell lines, and detailed protocols for their use) may be made available, upon request, to qualified scientists for non-commercial research purposes. Such protocols for request and use may be included on the Dup15q Alliance website. Requestors will be expected to bear shipping costs and acknowledge the source of the materials in resulting publications. The Foundation may decide to require awardees to upload data to a data-sharing site of the Foundation's choosing. Data would be embargoed from the public until the data are either published by the PI or as specified in the applicable funding agreement. Access to and use of data and images would be for non-commercial research or educational purposes in the Dup15q field.

Termination of the Award

This Award may be terminated or canceled by the Alliance upon 30 days written notice to the Principal Investigator and Responsible Administrative Official at the Sponsoring Institution if, at the sole discretion of the Foundation, (a) the Principal Investigator is unable to carry out, promptly, the research for any reason, (b) the Principal Investigator or any member of his/her research team is found by an institutional investigation to have committed scientific misconduct or fraud, (c) the Principal Investigator has failed to comply with any of the terms and conditions of this Award or (d) institution concludes that the Principal Investigator has received overlap funding for the Award or that the funds are not being used for the purposes originally outlined in the Research Proposal.

In the event of cancellation or termination, all unexpended and uncommitted funds as of the termination/cancellation date must be returned to the Foundation within 45 days of such written notice. The Principal Investigator and Sponsoring Institution are responsible for notifying the Foundation immediately and in writing of any institutional investigation into the conduct of the Principal Investigator or any member of his/her research team and for keeping the Foundation informed on a timely basis of the progress and outcome of the investigation. The Sponsoring Institution may also terminate the Award upon 30 days written notice.

Transfer or Retirement of the Principal Investigator

If the named principal investigator changes affiliations, the award will follow only after approval of the transfer from Dup15q Alliance. If the named principal investigator ceases work on the project for which the award was made, the award will terminate, and the remaining balance will be returned to the Alliance.

Ownership of Equipment

Title to all equipment purchased with the Alliance Seed Grant funds shall vest in the Alliance for the duration of the Award and for a period not to exceed sixty days from the termination date of the Award. During this time, the Alliance may, at its option, direct the transfer of title to the equipment to the Sponsoring Institution, Principal Investigator, or a third party. After such time, title to the equipment shall revert to the Sponsoring Institution.

Responsibilities and Liabilities

The Sponsoring Institution and Principal Investigator agree that they shall be responsible for all actions and activities of the Sponsoring Institution, its directors, officers, and employees, and of the Principal Investigator. The Sponsoring Institution and Principal Investigator further agree that the Alliance shall

not be liable for (a) any injury or loss to persons or property sustained for whatever reason whatsoever by the Sponsoring Institution, Principal Investigator or its or their officers, employees, agents, subcontractors, patients, visitors or other individuals who may be involved in the research outlined in the Research Application, or (b) any injury or loss to persons or property sustained for any reason whatsoever by any person caused by or otherwise attributable to acts of omission or commission of persons performing work pursuant to the research project, unless such liability is imposed by law.

Human Subjects

For research involving human subjects, the Sponsoring Institution shall ensure that the research proposal is reviewed and approved in writing by an Institutional Review Board in accordance with current regulations promulgated by the United States Department of Health and Human Services and approved by the Department. Legally acceptable consent must be secured for all human subjects taking part in any research funded in whole or in part by the Foundation. IRB approval forms from an Institutional Review Board must be submitted for the life of the grant (whether granted for its entirety from the outset or renewed during the grant).

Use of Experimental Animals

For research involving animals, the Sponsoring Institution shall ensure compliance with applicable chapters of the Public Health Service Animal Welfare Policy, the NIH Manual for Grants and Contracts, and all requirements of the Sponsoring Institution concerning animal welfare. Approval forms from the Sponsoring Institution's Animal Welfare Committee must be submitted for the life of the grant (whether granted for its entirety from the outset or renewed during the grant).

Overlap Funding

The Principal Investigator and the Sponsoring Institution are responsible for ensuring that the research described in the Research Proposal is not sponsored or funded by any other entity or organization. If support for the project is obtained elsewhere, the Principal Investigator agrees to notify the Alliance immediately. Any funds awarded by the Alliance may be withdrawn should funding be received for the same purposes from other sources.

Laboratory Visits

As a condition of support, the Principal Investigator agrees that a representative of the Alliance may visit the laboratory where the grant is being funded upon reasonable prior notification.

Review Mechanism

All proposals will undergo rigorous peer review by the Dup15q Alliance, composed of experts in Dup15q syndrome and related research areas as appropriate. Applications will be scored according to the following criteria:

- Significance of the research to Dup15q syndrome
- Innovation of the project
- Feasibility of the proposed methods
- Investigators and environment
- Impact of the project on Dup15q syndrome
- Translational potential

The Alliance will provide a summary statement of reviewer critiques to applicants. Depending on peer review and current priorities, the Alliance may work with applicants to revise the submitted work plan for future submission to federal or large funding bodies.

Appendix:
Application Forms

Dup15q Alliance Grant Application Cover Page

Date submitted:		
TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*		
PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR		
NAME (Last, first, middle) POSITION TITLE DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT MAJOR SUBDIVISION TELEPHONE AND FAX *(Area code, number, and extension)* TEL FAX:		DEGREE(S) MAILING ADDRESS *(Street, city, state, zip code)* E-MAIL ADDRESS:
HUMAN SUBJECTS RESEARCH ☐ No ☐ Yes	HUMAN SUBJECTS ASSUARNCE No.	IRB STATUS/DATE
VERTEBRATE ANIMALS ☐ No ☐ Yes	ANIMAL WELFARE ASSURANCE No.	IACUC STATUS/DATE.
DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year)* From / Through		COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT Direct Costs ($) / Total Costs ($)
APPLICANT ORGANIZATION Name Address		TYPE OF ORGANIZATION Public: ☐ Federal ☐ State ☐ Local Private: ☐ Private ☐ Nonprofit For-profit: ☐ General ☐ Small Business
ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS Name Title Address Tel: FAX E-Mail:		OFFICIAL SIGNING FOR APPLICANT ORGANIZATION Name Title Address Tel: FAX: E-Mail:
APPLICANT ASSURANCE: I certify that the statements herein are true, complete, and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded because of this application.	SIGNATURE OF APPLICANTE *(Electronic signature acceptable.)*	DATE
SIGNING OFFICIAL ASSURANCE: I certify that the statements herein are true, complete, and accurate to the best of my knowledge, and accept the obligation to comply with the grantor's terms and conditions if a grant is awarded because of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.	SIGNATURE OF SIGNING OFFICIAL *(Electronic signature acceptable.)*	DATE

Dup15q Grant Application Key Personnel Form

Principal Investigator (Last, First, Middle):	
ROLE:	
NAME (Last, first, middle)	DEGREE(S)
POSITION TITLE	MAILING ADDRESS *(Street, city, state, zip code)*
DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
MAJOR SUBDIVISION	
TELEPHONE AND FAX *(Area code, number and extension)* TEL . FAX:	E-MAIL ADDRESS:
ROLE:	
NAME (Last, first, middle)	DEGREE(S)
POSITION TITLE	MAILING ADDRESS *(Street, city, state, zip code)*
DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
MAJOR SUBDIVISION	
TELEPHONE AND FAX *(Area code, number and extension)* TEL . FAX:	E-MAIL ADDRESS:
ROLE	
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ROLE	
NAME (Last, first, middle)	DEGREE(S)
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DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
MAJOR SUBDIVISION	
TELEPHONE AND FAX *(Area code, number and extension)* TEL . FAX:	E-MAIL ADDRESS: