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Patient Perspective

An integrated action plan to fund and support drug development for Dup15q syndrome: a patient organization perspective

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***Abstract*:** Maternal 15q11.2-13.1 duplication syndrome, or Dup15q syndrome (Dup15q), is a rare neurodevelopmental disorder affecting as many as 1 in 5000 to 1 in 20,000 children worldwide. Autism and seizures are two of the most commonly observed phenotypes in Dup15q, with intellectual disability, hypotonia, gastrointestinal distress, and substantial fine and gross motor deficits also commonly reported. The community that is now known as the Dup15q Alliance started in 1994 as a small group of families raising children with chromosome 15q duplications. Originally named IsoDicentric 15 Exchange, Advocacy and Support (IDEAS), the group received official nonprofit organization status 10 years later and rebranded to its current name, Dup15q Alliance, shortly thereafter. Today, there are over 2200 families affiliated with Dup15q Alliance, with an average intake of 10 new families each month. Historically, Dup15q Alliance has provided the community with access to family and caregiver resources in addition to serving as a repository for basic educational information about Dup15q and research developments. The recent installation of a dedicated director of scientific and clinical initiatives alongside other infrastructural changes has now primed the Dup15q Alliance to expand its scientific footprint by funding cutting-edge research, supporting clinical sites and trials, and investing in novel therapeutics that have the potential to change the reality of a Dup15q syndrome diagnosis. To do this, we have developed the *LEARN. TREAT. CURE.* program to align initiatives, fast-track progress, and bring hope and reality into coexistence. Briefly, we seek to *learn* as much as we can about the syndrome through cutting-edge research, natural history studies, and patient registry utilization, identify and develop methods to *treat* the symptoms of our patient community, with the ultimate goal of developing a *cure* for the disease-causing symptoms of the syndrome.

Plain language summary

A campaign to accelerate drug discovery in Dup15q Syndrome

Patient advocacy groups aid in raising awareness and funding for specific disorders. Nearly three decades ago, Dup15q Alliance was founded by parents of individuals with maternal Duplication 15q Syndrome. This group has grown significantly and is now focused on funding programs to advance research. To do this, they have revised their infrastructure to include a part-time Director of Scientific and Clinical Initiatives and developed a fundraising campaign dedicated to scientific and clinical programming. They also emphasize collaboration and community engagement as key elements of the campaign.

Keywords: collaboration, community, Dup15q syndrome, registry, scientific initiatives

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Biological basis of Dup15q syndrome

Duplications or multiplications of the maternal chromosome 15q11-q13.1 region are associated with an estimated 1–3% of all autism cases, making copy number variation (CNV) in this region one of the most frequent chromosome abnormalities associated with autism spectrum disorder (ASD).[1–4] In addition to autism, seizures of varying frequency and modality, intellectual disability, gastrointestinal distress, sleep disruption, and substantial fine and gross motor deficits are also commonly reported in Dup15q patients.[1,5–16] Dup15q syndrome 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 (int dup (15)) of the same region accounts for a smaller percentage of the population.[1,3,8,15–21] Clinical presentation, while historically reported as more severe in idic (15), is largely heterogeneous across the Dup15q population, with increased gene dosage, as opposed to the genetic mechanism, purportedly having the largest effect on phenotype.[15,16,22] 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, *ATP10A*, *NECDIN*, *SNORD*, and *UBE3A*.[1,2,23–25] Unraveling the interactions between these genes will be critical for developing therapies capable of changing the course of disease progression.

Constructing infrastructure to support scientific strategy

While Dup15q Alliance[26] has always had its hand on the pulse of progress, much of the effort has rested on the shoulders of parent volunteers. Early on, a Professional Advisory Board consisting of clinicians, scientists, and industry professionals was developed to promote communication and collaboration among the various contributors. More recently, to stay in tune with scientific progress and opportunities to acquire funding, the Alliance implemented a Science subcommittee co-chaired by board members and inclusive of other stakeholders within the family community and external stakeholders. This group focuses on summarizing advanced scientific publications for digestible dissemination to the community, overseeing the release and review of Dup15q-sponsored grant opportunities, identifying funding opportunities through partner organizations such as CURE epilepsy[27] and PCORI,[28] and preparing the community for clinical trials.

The current state of Dup15q exposure and inclusion in trials[29] is due in large part to active and engaged family-led advocacy. The voice of those with first-hand knowledge of the nuanced care needed for family members with Dup15q and enduring struggles faced in the absence of a cure has fostered relationships with preclinical drug programs and even moved the needle on trial inclusion. Still, this model is not entirely sustainable for the most actively engaged volunteers because this important work comes atop routine care and health management for affected family members, and in most cases is conducted in addition to full-time employment. To alleviate some of the constraints placed upon family volunteers without sacrificing the essential inclusion of the parent and caregiver perspective, the Alliance has recently hired a part-time Ph.D.-level Director of Scientific and Clinical Initiatives. This role is designed to be symbiotic with the Science committee and volunteers, providing a point person for ongoing initiatives to maintain a living history of progress, uphold and establish relationships with clinical, scientific, and industry partners, and serve as a voice for the community in the scientific and clinical space to realize change.

LADDER learning network

For the last three decades, Dup15q Alliance has been building a multifaceted community dedicated to advancing breakthrough research and life-changing treatments, supporting families affected by the disorder, and promoting advocacy.

The LADDER [Linking Angelman and Dup15q Data for Expanded Research (LADDER)] Learning Network (LLN) is a strategic collaboration between the Angelman Syndrome Foundation and Dup15q Alliance. The LLN was born to cultivate a community of clinics and providers to share knowledge, advocate for innovations in research, and drive therapeutic development. There are currently 14 multidisciplinary clinics

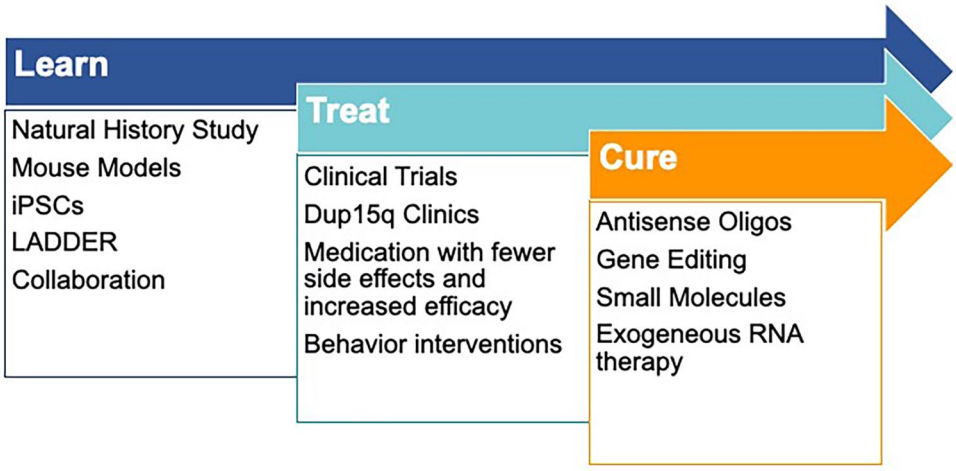

Figure 1. An Overview of Learn. Treat. Cure. The Dup15q Alliance has constructed a plan to raise awareness, funding, and participation in programs designed to expedite drug discovery and development.

specialized in the care of Dup15q syndrome across the United States in addition to a growing number of international sites specialized in the care of Dup15q syndrome.[30]

In collaboration with Research Triangle Institute (RTI) International, the LLN established the LADDER database, a centralized data repository to collect and manage the information provided by parents, caregivers, clinicians, and researchers about the disease trajectory and clinical needs of patients with Dup15q. The centralization of information has allowed for robust analysis of development, behavior, and how clinical needs may change over time. Currently, data in LADDER can be accessed by physicians and researchers, with the opportunity for pharmaceutical partners to engage following case reviews.

The utility of LADDER and LLN has highlighted both progress and pitfalls in our efforts to move the needle on a disease-modifying therapy for Dup15q patients. To manage the LLN, and enable progress, we have hired a full-time LLN director, who is shared between Dup15q Alliance and Angelman Syndrome Foundation (ASF).

LEARN. TREAT. CURE initiative

Dup15q Alliance has created a multi-year strategy that is tailored toward accelerating research that will lead to novel therapeutics for those affected by the syndrome. The Dup15q Alliance seeks to l*earn* as much as we can about the syndrome and identify and develop methods to *treat* the symptoms of our patient community, with the ultimate goal of a *cure* for the disease-causing symptoms of Dup15q so that patients may lead healthy and long lives. Our goal, which is described in detail below, relies on activating or supporting research grants, fundraising, clinical studies, patient registries, clinics, and industry partnerships.

Learn

Although there have been many advances in understanding Dup15q syndrome, further exploration is needed to fully unravel the biological basis of the disorder. To do so, we have identified several areas where there is a stark absence of information. To account for this and to advance progress, the first pillar of our program, 'learn', relies on building our knowledge base to inform ideas that will advance progress (Figure 1). Given the complexity of Dup15q and the heterogeneity of the population, launching a natural history study to better define the genetic subgroups and natural progression of the disease in each population is essential. While LADDER and former data repository platforms have served as a foundation for identifying trends, the rate and key characteristics of disease progression remain unknown, with even less data available for adults living with the condition. In addition to natural history data, we also seek to improve our understanding of the mechanistic underpinnings of the

disorder, including genetic interactions between duplicated genes, mapping downstream pathways of each affected gene and/or product, and elucidating traceable biomarkers to predict severity and responsivity to drugs. All of the targeted learning outcomes in this initiative, in addition to those that have yet to be revealed, will provide valuable data for families, researchers, and clinicians to bring the community closer to novel and life-changing interventions that eliminate disease signatures.

In addition to learning from a research-based or clinical lens, we also aim to continue ongoing efforts to learn from our patients and families. By distributing surveys to parents and caregivers tailored toward understanding the priorities of families living with Dup15q, we will be able to align our strategies and initiatives to best support the community. For example, we recently released a short survey (one question) to determine the prevalence of Lennox-Gastaut syndrome (LGS) within the Dup15q population. From this survey, using caregiver-reported data, we learned that 23% of individuals with a confirmed Dup15q diagnosis are also confirmed for LGS. Armed with this information, we have unearthed a criterion for our patients that may increase the likelihood of inclusion in future clinical trials.

Treat

Except for individuals with mosaic Dup15q, all cells in the body contain duplications or multiplications of genetic material within the 11.2–13.1 regions of chromosome 15. Of the affected cells, neurons are most sensitive to these duplications, which may explain why epilepsy, autism, behavioral challenges, and cognitive disabilities are key hallmarks of the disorder. Because of this, Dup15q is traditionally characterized as a neurodevelopmental disorder, but other common symptoms include GI problems, hypotonia, sleep disturbance, and anxiety across the affected population. To 'treat' the disorder, Dup15 Alliance will promote and support research that informs strategies to improve patient quality of life through symptom management and elimination (Figure 1). Since the population of Dup15q is heterogeneous, there is no magic bullet to treat all symptoms simultaneously. For this reason, Dup15q patients require a variety of medical treatments based on their symptoms that often include a variety of anti-epilepsy drugs, mitigation and management of various aspects of autism and behavior challenges, and treatments to facilitate GI health and function. In addition to the aforementioned goals, Dup15q Alliance actively leverages patient-reported data to collaborate with top physicians in the Dup15q syndrome clinics to develop treatment guidelines and advisories for physicians. We are mindful to include caregiver expertise so that treatment plans and trial design are feasible for this particular patient population.

Cure

Learning the genetic underpinnings of Dup15q syndrome will identify druggable targets to eliminate symptoms of the disease. Such disease-modifying therapeutics are already in development for UBE3A, with efforts to target other duplicated genes, such as those encoding GABA receptor subunits and HERC2, in the preclinical research phase. Because neurons are the cells most affected by misexpression of duplicated genes, it will be critical for these drugs to reach the brain and restore normal function. While this poses an added challenge, we will also embrace devices and modalities that improve the blood–brain barrier crossing. The heterogeneous nature of Dup15q syndrome means that a 'cure' may look different for each patient (Figure 1). For this reason, we aim to be as transparent as possible when communicating with our community, and use the term as a synonym for 'disease-modifying therapeutics'.

Leveraging the unprecedented interest from the biopharmaceutical industry to expedite disease-modifying treatments for rare diseases, we have been actively seeking out industry partners with preclinical programs in disorders affecting the same region of Chromosome 15, such as Angelman syndrome. In doing so, we have not only helped inform clinical endpoints but also incited further interest in drug development for Dup15q patients. Specifically, we are proactive in contacting companies that have antisense oligonucleotides in development, providing education on our patient community, and showcasing our ability to mobilize and organize when the time comes for trial enrollment.

Community engagement and inclusion

The rollout of the Learn. Treat. Cure. initiative is contingent upon community inclusion and

Figure 2. Overview of the 'Learn. Treat. Cure'. execution plan.

support (Figure 2). To ensure that the collective viewpoint is incorporated into the fabric of the program, we developed a high-level implementation strategy, led by the newly installed Director of Scientific and Clinical Initiatives. The plan was developed and refined alongside Dup15q Alliance staff, and Science and Fundraising committee chairs, which all include Dup15q patient caregivers. From these early conversations, it became clear that messaging and delivery would require nuanced and frequent communication across multiple platforms. To actualize this aim effectively, a letter was distributed to all Dup15q community members, donors, and researchers describing the education plan and including an invitation to a later Town Hall. Each recipient was encouraged to provide questions to drive the conversation during the meeting. The letter now lives on the Dup15q page, which will be updated with monthly roundups on scientific and clinical progress as they align with each of the Learn. Treat. Cure. (LTC) categories. Ahead of the Town Hall meeting, social media posts, crafted and curated by caregivers on the Science committee, are strategically deployed on a weekly basis to educate the community on basics and associated progress as they relate to each of the buckets. Our goal is to have a dedicated and all-encompassing network to launch and maintain the initiative.

Partnerships and collaboration

Establishing and preserving partnerships with other patient advocacy groups (PAGs) in the rare epilepsy space has been critical to the growth and success of Dup15q Alliance. Specifically, we have fostered deep-rooted relationships with other rare epilepsy PAGs, including the Rare Epilepsy Network, Epilepsy Leadership Council, and were a founding third of The Commission on Novel Technologies for Neurodevelopmental CNVs (CNV Commission).[31] From these relationships, we have gained a tremendous sense of community, often leaning on the experiences of these groups to inform decision-making in the context of scientific strategy and infrastructure. The scientific and clinical initiative's role was borne out of conversations with more established PAGs, leveraging their experiences to derive the posting and seeking guidance for optimal candidate selection. Now that Dup15q Alliance has a part-time person serving in this role, they have access to a network of Scientific Directors working in the rare epilepsy space, who connect on a semi-regular basis to collaborate on strategy and identify areas in need of improvement. As a whole, these interactions across the greater rare epilepsy community have afforded Dup15q Alliance opportunities to participate in shared projects focused on policymaking, data access and sharing, clinical trial enrolment, and preparedness in addition to eligibility for funding designed to understand commonalities and variation across the rare epilepsy space. By uniting in this way, Dup15q Alliance has been able to leverage the experiences of others while providing insight for newer PAGs.

In addition to the greater rare epilepsy community, Dup15q Alliance actively collaborates with ASF on a variety of platforms. First, as described above, Dup15q and ASF have partnered to make significant investments in the search for therapeutics and

treatment by developing LADDER. From the data, we have already identified several areas of interest related to seizures, behavior, and developmental interventions. LADDER data have also provided insight into the patient and clinical needs, which has informed clinic design and evaluation. In addition to LADDER, Dup15q and ASF co-sponsor a scientific conference each year, with each group hosting a family conference ahead of the meeting on an alternating schedule. These meetings not only give families access to unpublished and cutting-edge developments in Dup15q and Angelman syndrome research, drug development, and clinical practices, but they also allow a diverse group of experts, parents included, to gather and share perspectives, expertise, and ideas that will ultimately drive the field forward in terms of therapeutic development.

Conclusion

The mission of Dup15q Alliance is to empower individuals living with Dup15q syndrome and other related rare diseases to reach their full potential by advancing breakthrough research and life-changing treatments in addition to supporting families affected by Dup15q and promoting advocacy. To realize this mission, the group has implemented infrastructural processes and personnel to aid in the execution of the Learn. Treat. Cure. initiative and continues to collaborate with PAGs in the rare epilepsy space. Dup15q is a complex disorder, but through advanced research, creative collaboration, community support, and persistence, we believe that the hope for disease-altering therapeutics is becoming increasingly closer to a reality.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Ryan Rogers-Hammond: Conceptualization; Project administration; Writing – original draft; Writing – review & editing.

Carrie Howell: Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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