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Chapter 3

Autism BrainNet

A network of postmortem brain banks established to facilitate autism research

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Abstract

Autism spectrum disorder (ASD or autism) is a neurodevelopmental condition that affects over 1% of the population worldwide. Developing effective preventions and treatments for autism will depend on understanding the genetic perturbations and underlying neuropathology of the disorder. While evidence from magnetic resonance imaging and other noninvasive techniques points to altered development and organization of the autistic brain, these tools lack the resolution for identifying the cellular and molecular underpinnings of the disorder. Postmortem studies of high-quality human brain tissue currently represent the only viable option to pursuing these types of studies. However, the availability of high-quality ASD brain tissue has been extremely limited. Here we describe the establishment of a privately funded tissue bank, Autism BrainNet, a network of brain collection sites that work in a coordinated fashion to develop an adequate library of human postmortem brain tissues. Autism BrainNet was initiated as a collaboration between the Simons Foundation and Autism Speaks, and is currently funded by the Simons Foundation Autism Research Initiative. Autism BrainNet has collection sites (nodes) in California, Texas, New York, and Massachusetts; an affiliated, international node is located in Oxford, England. All donations to this network become part of a consolidated pool of tissue that is distributed to qualified investigators worldwide to carry out autism research. An essential component of this program is a widespread outreach program that highlights the need for postmortem brain donations to families affected by autism, led by the Autism Science Foundation. Challenges include an outreach campaign that deals with a disorder beginning in early childhood, collecting an adequate number of donations to deal with the high level of biologic heterogeneity of autism, and preparing this limited resource for optimal distribution to the greatest number of investigators.

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INTRODUCTION

Autism spectrum disorder (ASD) is a behaviorally defined condition that is usually diagnosed in early childhood based on the occurrence of social communication impairments and the presence of repetitive behaviors or circumscribed interests. Its clinical description was initially published in the mid-1940s by Kanner (1943) and Asperger (1944). Its presentation is complicated by a large array of comorbid conditions that range from anxiety, to sleep and gastrointestinal disorders, to epilepsy. The severity of the core and co-occurring symptoms varies widely in different individuals and at least half of the affected individuals also have intellectual disability. There is currently no biologic marker for ASD and treatments generally consist of intensive behavioral intervention. While some individuals with autism may show such dramatic improvements that they no longer fit the criteria for a diagnosis, for most, it is a lifelong disorder. Recent studies indicate that individuals with autism have increased health problems and a shorter lifespan, although whether this is directly attributable to the biology underlying autism or is a correlate of living life with a neurodevelopmental disorder is currently unclear (Croen et al., 2015; Hirvikoski et al., 2016). Many children with autism are more prone to wandering or elopement (Rice et al., 2016) than typically developing children, often resulting in accidental injury or death. Other children with ASD have a fascination with water, increasing accidental deaths due to drowning (Franklin et al., 2017).

The behavioral manifestations of autism result from changes in brain function, but many questions remain concerning how, where, and when the brain is affected. There is, however, substantial evidence from magnetic resonance imaging studies that the brains of individuals with autism have undergone altered development (Amaral et al., 2008). Although substantial progress has resulted in identification of gene mutations and genomic microdeletions and duplication which confer high risk for autism (Iossifov et al., 2014), much less is known about alterations in the underlying molecular, cellular, and circuit mechanisms which result in autistic behavioral symptoms and neurologic comorbidities such as epilepsy. This situation is exacerbated by the recognition that ASD is a biologically heterogeneous disorder that has many genetic risk factors, both rare and common variants, as well as nongenetic factors. For example, about 15% of males with autism have a larger than expected brain size (Nordahl et al., 2011). However, whether the abnormal enlargement is due to the generation of more or larger neurons or glial cells or some other process is currently unclear.

Genetic alterations in the brains of individuals with ASD are complex (Sanders et al., 2015; Werling et al., 2016). Recent studies have also demonstrated that the brain in autism may demonstrate somatic mutations present in only a fraction of cells within the brain (Jamuar and Walsh, 2014; Lodato et al., 2015). Thus, many mutations that elevate risk for autism may only be identified by studying brain tissue. By assessing when autism-associated genes are expressed across brain development, studies have inferred which brain regions and even which cortical layers may be most affected (Willsey et al., 2013). However, these studies have relied on bulk tissue analysis of only a few brain regions from a handful of brains, combined with in silico comparison with mouse and human gene expression datasets from unrelated samples, rather than direct analysis at cell type-specific resolution from genetically defined subgroups of ASD brains.

As current technologies lack the resolution to study the living human brain at the cellular and molecular levels, the only way to address questions of genetic and cellular neural alterations associated with ASD is to study postmortem brain tissue from individuals who had autism during life. Findings from the newer technologies of induced pluripotent stem cell differentiation are limited by the extent of differentiation and will require confirmation in the developing and mature human brain.

To uncover the genetic and neurobiologic underpinnings of autism, collaborative studies of brain tissue across disciplines such as neuropathology, neurochemistry, molecular biology, genetics, and proteomics will be necessary. However, research in these fields using postmortem autism brains is still very much in its infancy. Newcomers to autism research who are familiar with the pathology of other brain disorders, such as Alzheimer disease, are often surprised by how little is known about the brain in autism. A major reason for this is that tissue availability has been limited and the available tissue has often been poorly characterized, or the quality of the tissue has been compromised, making discovery difficult. Indeed, over the past three decades since the publication of the first substantive postmortem report in 1985 (Bauman and Kemper, 1985), only about 100 brain cases have been studied and only a fraction of these in a quantitative fashion. The mean sample size in published neuropathologic studies is still in single digits. Moreover, nearly all of the brains studied have been from adults with autism.

How can one hope to develop an adequate brain and tissue resource to fuel effective autism research? In the following sections, we briefly summarize early efforts of autism brain collection and then describe Autism BrainNet – a network strategy that, we believe, can optimize both the quantity and quality of brain donations for autism research.

EARLY EFFORTS AT AUTISM BRAIN COLLECTION

The Autism Tissue Program and the Maryland Brain Bank

Prior to the establishment of Autism BrainNet, postmortem autism brain donations were solicited by both private and public efforts. The foremost private effort, known as the Autism Tissue Program (ATP), was started in 1998 and was initially coordinated by the National Alliance for Autism Research. The ATP was visionary in many respects and ultimately became a component of the scientific program of Autism Speaks. For 15 years, the ATP carried out a nationwide campaign to increase the awareness of families of individuals with autism about the value of brain donations and tissue-based research. Brain donations collected through this initiative were stored at the Harvard Brain and Tissue Resource Center. The ATP relied on a tissue advisory committee to evaluate applications for tissue and maintained a web-based portal for dissemination of clinical information and an archive of scientific information gathered through analysis of its brain specimens. While not a brain bank per se, the ATP acted as a coordinator and facilitator of autism brain donations. By 2010, the ATP had acquired 92 brains from individuals with autism and their family members. An additional 16 brain donations came from individuals with 15q11.2-13.1 duplication syndrome (dup15q syndrome), one of the most frequently identified chromosomal alterations in individuals with autism. The ATP had also facilitated the donation of nine nonfamily member control brains. The ATP provided tissues to 103 research projects worldwide and, by 2010, 94 papers based on this resource had been published. The ATP also coordinated the production of a number of core resources such as a library of whole celloidin-embedded brains.

On the public side, autism brain donations, as well as valuable nonautism control cases, found their way to one of several national brain banks, most notably the National Institute of Child Health and Human Development-funded bank at the University of Maryland. Those brains were then made available through tissue dissemination procedures developed by each of the brain banks (see Chapter 6). The public and private acquisition processes maintained a highly collegial relationship and the ATP referred scientists to the Maryland Brain Bank and vice versa.

While the efforts of the ATP and National Institutes of Health brain banks were essential to the work of many researchers, there were some inherent limitations with a centralized collection model:

1. advocacy for brain donations was carried out only at the national level and did not capitalize on the relationships of families affected by autism with medical centers where they participate in research or treatment;
2. training of affiliated medical examiners or coroners in optimal tissue preparation protocols for research was not carried out;
3. development of working relationships between autism scientists and medical examiners and coroners was limited or nonexistent;
4. the time between notification of death and brain extraction and processing was often longer than if a local collection center were available.

As the pace of autism research expanded at the turn of the century, the paucity of brain tissue increasingly became a roadblock to scientific advances. Exciting new strategies for genetic and neuroanatomic analyses were being developed but there was limited human brain tissue with which to deploy them. At meetings of special-interest groups established to discuss postmortem autism research, more words were dedicated to the lack of tissue than to new findings.

STEPS LEADING TO THE DEVELOPMENT OF AUTISM BRAINNET

Researchers studying other clinical disorders such as Parkinson disease, Alzheimer disease, and schizophrenia have demonstrated substantial success in collecting brain donations with a confederated model of regional collection sites distributed across the country. One of these, the Stanley Brain Collection (Torrey et al., 2000), was an inspiration for Autism BrainNet. At the time when the Stanley Brain Collection began, in 1994, there was a severe shortage of brain tissue available for research on schizophrenia and bipolar disorder. In a decade and a half, the Stanley Brain Collection successfully collected over 600 brains in their network, resulting in over 220 research publications employing a wide range of methodologies and examining a diverse array of brain regions (see Chapter 13). So much research has been generated that a web-based database was developed to integrate and further mine the data. The amount of research able to be conducted following the institution of this model for tissue collection has led to dramatic progress in understanding these disorders.

Success of the Stanley Brain Collection stemmed in part from its ability to create a large collection of brains from schizophrenia and bipolar disorder cases by first identifying several sites spread around the country to serve as regional collection centers. Personnel were trained at each regional site to carry out a standardized

optimal protocol of brain removal and initial processing; the brain was later sent to a long-term storage facility for further processing and distribution to investigators.

Inspired by the Stanley Foundation effort, David Amaral and Cynthia Schumann drafted a white paper in 2009 that proposed the implementation of a confederated network model for the optimal acquisition, preparation, and distribution of autism brain and other tissues. A key element of the model was that, although brain tissue would be collected regionally at several sites, all acquired tissue would contribute to a general pool for use by the autism research community.

At the same time that the white paper was being discussed, Dr. Schumann started a pilot program at the MIND Institute that was eventually called Brain Endowment for Autism Research Science or BEARS. BEARS was developed as a proof-of-principle effort that employed many of the strategies outlined in the white paper. The development of BEARS was based on the principle that the community needed to be engaged in the effort and families needed to feel comfortable with the institution to which they donated the brain of a loved one. Early successful donations to BEARS validated the need for a close relationship with the autism community. It also supported the premise that a collaborative, national effort was needed in order to increase the number of brain donations.

INITIAL STEPS, INSTITUTIONAL REVIEW BOARD (IRB), AND TRANSFER OF RESOURCES

The Simons Foundation and Autism Speaks made an initial 5-year commitment to the financial support of Autism BrainNet through the establishment of a new nonprofit limited liability company, Foundation Associates. Every effort was made to maintain continuity between the ATP and Autism BrainNet, which now includes and manages the distribution of the ATP resources.

To insure standardized regulatory management across all nodes, Foundation Associates engaged the services of Western Institutional Review Board (WIRB) to provide indepth expertise and capacity for multisite coordination. Prior to launching these operations, WIRB conducted an initial review of Autism BrainNet's standard operating procedures, including clinical processes (consenting and postmortem characterization of donated brain tissue). Upon satisfying WIRB's requirements, effective June 19, 2014, WIRB provided a certificate of approval for Autism BrainNet's national consent for postmortem tissue donation, consent for donor family clinical documentation, clinical questionnaire, and protocol.

Very soon after Foundation Associates was started, a process to transfer all of the resources of the ATP to Autism BrainNet was established and carried out by the scientific program officer.

SELECTING NODES

As noted above, the intent in selecting sites for the Autism BrainNet nodes was based on a set of criteria including the following:

1. Each node director must have familiarity with the scientific study of human brain tissue or have experience with postmortem brain collection.
2. The node university must have an active autism research program to capitalize on existing clinical expertise to carry out postmortem ascertainment of the clinical condition of the donor.
3. The node should be in a city with a large population to enable the largest numbers of donations from within 300 miles surrounding the node site.

By adopting these criteria, the premise was that the postmortem interval could be kept to a minimum and that interaction with the autism community would motivate the greatest number of autism donations.

Using these criteria, Autism BrainNet nodes were established at the UC Davis MIND Institute in Sacramento under the leadership of Dr. Cyndi Schumann, at UT Southwestern in Dallas, under the leadership of Dr. Carol Tamminga, at Harvard Medical School/Beth Israel Deaconess Medical Center in Boston under the leadership of Dr. Matthew P. Anderson, and at the Icahn School of Medicine at Mount Sinai in New York City, under the leadership of Dr. Patrick Hof. As a boarded, practicing clinical neuropathologist, Dr. Anderson was designated the clinical neuropathologist for Autism BrainNet to provide clinical reports for physicians, medical examiners, and pathologists when necessary. Based on a relationship that the ATP had established with the Oxford Brain Bank, an international node of Autism BrainNet has been established at Oxford under the leadership of Drs. Olaf Ansorge and Steven Chance.

AUTISM BRAINNET IS LAUNCHED

Once the transfer of resources between the ATP and Autism BrainNet had been negotiated, the node sites selected, and IRB oversight established, Autism BrainNet was formally launched at the International Meeting for Autism Research in May of 2014. The overall structure of Autism BrainNet is illustrated in Figure 3.1. As indicated in Figure 3.1, the oversight of Autism BrainNet is provided by a board of managers of a nonprofit organization, Foundation Associates.

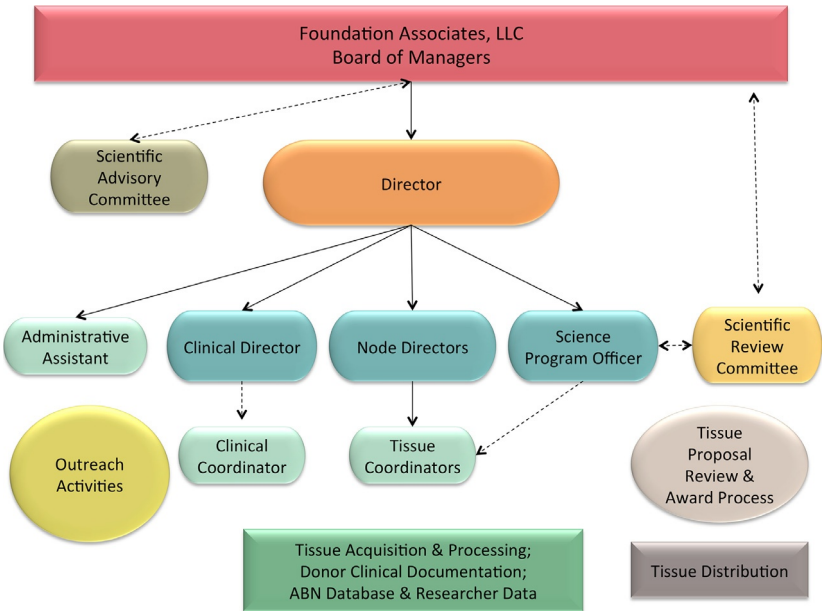

Fig. 3.1. Overall organizational structure of Autism BrainNet (*ABN*). *LLC*, limited liability company.

ORGANIZATION OF AUTISM BRAINNET

A director is the interface between Foundation Associates and the directors of the four US and single international nodes. The scientific program officer is supervised by the director. The scientific program officer is the primary interface with the research community and insures that applications for tissue resources are appropriate and that data acquired through use of Autism BrainNet tissue are ultimately returned to the Autism BrainNet database. An administrative assistant supports the activities of the director and scientific program officer. Foundation Associates has two employees (clinical director and clinical coordinator) and they handle all IRB issues and are also in charge of processes related to gathering clinical information on donors, including conducting a postmortem Autism Diagnostic Interview-Revised with next of kin to insure an accurate diagnosis of autism for the donor.

Each of the nodes is staffed with personnel who are highly trained in the preparation and storage of donated brains. Using standard operating procedures that are consistent across all nodes, the goal is for these staff to prepare one hemisphere as unfixed, frozen coronal slabs while the contralateral hemisphere is fixed whole. A number of meetings took place, with the assistance of several knowledgeable consultants, to establish the standard operating procedures for preparation of the brain tissue. This is an ongoing process. It has as its goal the establishment of procedures that will allow distribution of samples from each brain to as many researchers as possible. It is hoped that, by collating the experimental results from these defined samples into a central data repository, the value of each case will grow with time. For example, each case is currently being defined by its genetic mutations and neuropathologic changes in order to reduce the heterogeneity for future experimental studies with those samples. Such data would, for example, allow one to identify parallel changes in the brains of genetically engineered mouse models of specific genetic autisms and the human brain tissues, a critical step in translational research.

OUTREACH EFFORTS THROUGH THE AUTISM SCIENCE FOUNDATION

The It Takes Brains To Solve Autism campaign

Early in the establishment of Autism BrainNet it was appreciated that an outreach effort aimed at conveying the need for postmortem brain tissue would be an essential component of a successful operation. Capitalizing on an awareness campaign launched by the Autism Science Foundation (ASF) prior to the establishment of Autism BrainNet, ASF was selected to lead the outreach effort for Autism BrainNet. ASF receives supervision of its program by the director and members of the Foundation Associates board of managers. ASF designed the outreach campaign with the theme that families that make a donation are superheroes. The campaign was developed after convening several focus groups with selected members of the autism community. Family members and individuals with autism were asked to provide their thoughts on brain tissue donation, why they would or would not register, why they would or would not donate tissue, and any important messages they would like to see.

Fig. 3.2. Home page of the It Takes Brains website.

Two important factors were revealed by these focus groups concerning local outreach and community involvement: (1) families wanted the ads to include photos of people with autism who benefited from research, rather than photos of people who had died and donated brain tissue; and (2) they wanted the ads to include photos of families who lived near by. After reviewing all the data, the ASF launched the It Takes Brains campaign in print and on the internet (www.takesbrains.org). More information concerning the It Takes Brains campaign can be viewed at the website (Fig. 3.2).

As many organizations and projects have struggled to reach a widespread community, it was important for Autism BrainNet to take a multipronged approach to communications and insure that as many autism research and advocacy groups were mentioned in materials as possible. The goal of having a presence at multiple events or methods of engagement is to keep Autism BrainNet on the minds of autism families, and to destigmatize postmortem brain tissue donation. Information about the program is distributed through: in-person communications at outreach events and fundraisers; social media channels; partnerships with other national research studies and programs (i.e., the Simons Simplex Collection, the Autism Treatment Network, the Interactive Autism Network); localized outreach to hospitals, clinics, and research projects near the node areas (staff training, providing hardcopy and electronic Autism BrainNet materials); and presence in local and national media, including television, newspaper, and magazines. Registration in the program is voluntary and is not a binding consent.

The main message of all outreach materials is the importance of understanding the donation process as well as how research utilizing Autism BrainNet donations has made an impact on families affected by autism. While many brain banks use a binding registration and consent process, this did not prove to be feasible with Autism BrainNet. In early focus group and feedback sessions, families indicated that they did not want to think about the death of their child or family member with autism and thus "signing them up" for brain donation was a real turnoff for participation in the program. We thus aimed the program at providing information to families in the hope that if they were intending to make a donation, the knowledge of Autism BrainNet (knowing who to call) would facilitate the process.

THE DONATION PROCESS

Brain tissue recovery is coordinated nationally by Autism BrainNet. In the event of a death, we ask that next of kin or medical caretaker contact Autism BrainNet as soon as possible on a 24-hour hotline number (+1-877-333-0999). Typically, a family member will call this number when the death of a family member has occurred or is imminent. When this number is called, the Autism BrainNet staff walk the family through the donation process. The process involves insuring that the donor meets the inclusion and exclusion criteria for Autism BrainNet and, if so, the consent process is undertaken to authorize research uses, including genetic analyses, of the donor tissue and the acquisition of medical records and

additional clinical information from the next of kin. The clinical director then contacts the closest node and personnel at the node begin preparations for obtaining the brain donation in the shortest possible time. Autism BrainNet employs a number of strategies in obtaining the brains, including using local staff or contracting with a professional network of autopsy consultants that have been identified across the country. Autism BrainNet assumes all costs related to tissue recovery.

The clinical director or clinical coordinator will also follow up after an appropriate grieving period, to schedule a visit with the donor's family. The purpose of this visit is to collect essential documentation about the donor and to learn more about the donor's background. It is often the case that the autism diagnosis is suspected but has not yet been clinically confirmed. This is particularly true for older individuals who may live at home or in an institutional setting because of their behavioral disabilities associated with presumed autism but they may have never received a formal diagnosis from a clinician. Because autism continues to be a behavioral diagnosis that is subject to interpretation, community diagnoses are occasionally proven to be incorrect when the individual is evaluated more comprehensively using research-proven indices. Because an inaccurate clinical diagnosis would further cloud any potential neuropathologic findings, Autism BrainNet takes all possible measures to insure that the diagnosis is accurate. This is done principally through the administration of a questionnaire called the Autism Diagnostic Index – Revised to the next of kin. The entire process of obtaining clinical information on the donor subject is illustrated in Figure 3.3.

RESEARCHERS' APPLICATION FOR BRAIN TISSUE

Allocation of tissue to researchers is through an independent peer review process. This is outlined in Figure 3.4. The researcher can apply for tissue through an online application process that is overseen by the scientific program officer.

Once the application is received, it is reviewed by an independent scientific review committee that provides advice to the Foundation Associates board of managers regarding the quality and priority of the proposed research. In addition to an evaluation of the scientific merit of the project, the investigator must also demonstrate that there is adequate funding to carry out the proposed research. If the application is approved, the investigator's home institution must sign a research distribution agreement that indicates that, after primary publication, the data that arise from use of the tissue must be submitted to Autism BrainNet for incorporation into its database, preferably returned as individual case data to enrich the understanding of each case for future research.

ALLIANCE AND PARTNERSHIP STRATEGY

Autism BrainNet is a collaborative network designed to facilitate research into the biologic bases of ASD. Collaborations are important not only within the network but also with advocacy groups and other brain-banking initiatives. It is for this reason that Autism BrainNet established a memorandum of understanding with the

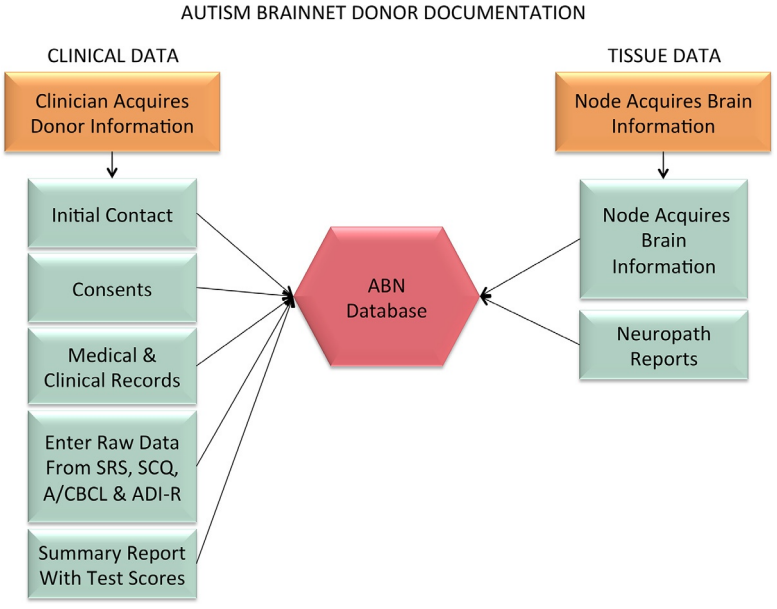

Fig. 3.3. Clinical and brain information stored in the Autism BrainNet (*ABN*) database. *ADI-R*, Autism Diagnostic Index – Revised.

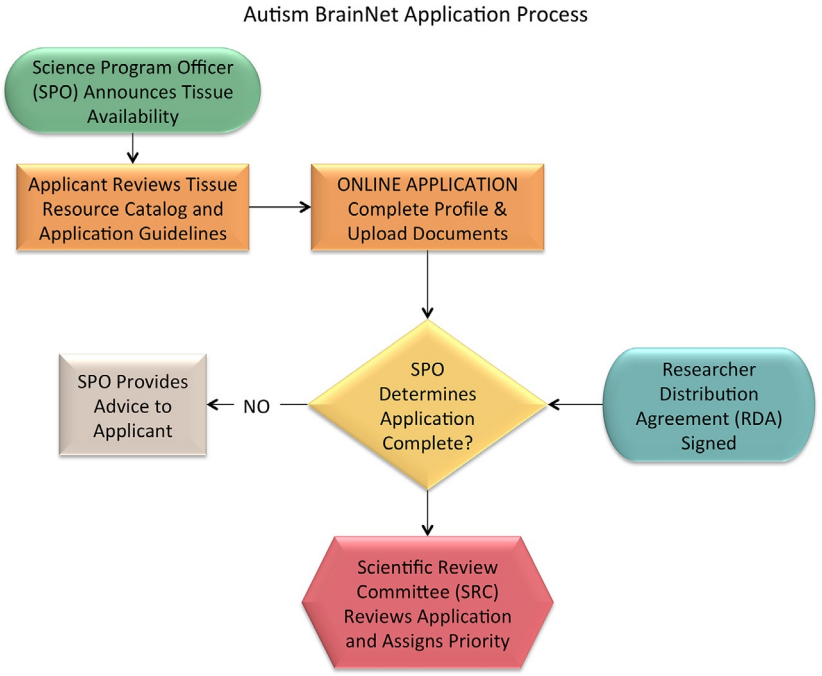

Fig. 3.4. Application and review process.

National Institutes of Health NeuroBioBank, which also collects donations of autism brains primarily through the Maryland Brain Bank, to collaborate on collection and distribution of brain tissue. Details on the logistics of this collaboration include referral of donations to the closest collection site, efforts to use similar standard operating procedures for brain preparation, and communication between the two online catalogs of available tissue. In addition, formal agreements have also been established with the Dup15q Alliance and the Phelan-McDermid Syndrome Foundation, to collect brains for these two genetically defined forms of autism. Families associated with these organizations who are interested in making a donation can work through the systems set up by Autism BrainNet. These organizations will have additional input on which investigators receive donations through these organizations.

CHALLENGES

The infrastructure for Autism BrainNet is now fully established and can support a donation from any part of the United States and United Kingdom. The major challenge is to get the word out that brain donations are a critical part of the process of understanding autism so that the autism research field can move towards more effective treatments and improvements in the quality of life of affected individuals. Because a donation needs to be made quickly to allow the highest-quality research, it is important that families and individuals affected by autism discuss the possibility of brain donation during life.

From a logistics point of view, the biggest challenge is to determine standard operating procedures for the processing of brain donations that allow tissue distribution to the largest number of investigators. Rather than distributing large blocks of tissue to individual investigators, Autism BrainNet will distribute the minimal amount of tissue necessary for the proposed project. For the fixed hemisphere of the brain, this will require sectioning the tissue and distributing series of sections through the area of interest. Of course, there is no sectioning procedure that is optimal for all studies, so substantial discussion has gone into the best possible procedure to carry out. Similarly, for the frozen side of the brain, whether it makes sense in some cases to distribute blocks of tissue rather than extracted DNA or other forms of genetic material is currently under debate and will be guided by scientific requirements.

CURRENT STATUS

Autism BrainNet collected 10 brains in 2014, 23 brains in 2015, and 42 in 2016; 27 donations have been made in the first half of 2017. Thus, Autism BrainNet has, to date, collected 102 donations. Of these, 41 are from individuals with autism, 51 are from age-matched controls, and 10 are characterized as “other.” The last category are cases that may have a genetic mutation that is associated with autism but the individual did not receive a diagnosis of autism during life. We are hopeful that this

number will continue to grow as our outreach campaign matures. From a funding perspective, it has been important that the Simons Foundation understands and supports the long-term process needed to establish the infrastructure essential for creating a brain bank that is able to meet the diversity of demands of scientists who are committed to enhancing our scientific understanding of autism.

CONCLUSIONS

There is widespread appreciation that a complete understanding of the biology of ASD will necessitate, among other things, intensive analysis of postmortem brain material. This perspective has been endorsed by parent advocacy groups such as the National Alliance for Autism Research, Cure Autism Now, and the Autism Society of America. Initial efforts by these groups and NIH grant support (1999–2006) were sustained by Autism Speaks and now by the Simons Foundation. Autism BrainNet has established a collaborative network of university-based sites that share the common goal of generating a library of postmortem brain material that is sufficiently large to support modern genetic and neuropathologic studies. All of the authors of this paper have contributed to the establishment of Autism BrainNet and continue to participate in ongoing discussions to chart an efficient, effective, and family-friendly campaign to solicit donations to achieve this goal. We are extremely thankful to the many families who have helped to shape our strategy or made a donation to this program thus far and to those who are considering making a donation in the future.

References

Amaral DG, Schumann CM, Nordahl CW (2008). Neuroanatomy of autism. Trends Neurosci 31: 137–145.

Asperger H (1944). Die 'Autistischen Psychopathan' in Kindesalter. Archive fur Psychiatrie und Nervenkrankheiten 117: 76–136.

Bauman M, Kemper TL (1985). Histoanatomic observations of the brain in early infantile autism. Neurology 35: 866–874.

Croen LA, Zerbo O, Qian Y (2015). The health status of adults on the autism spectrum. Autism 19: 814–823.

Franklin RC, Pearn JH, Peden AE (2017). Drowning fatalities in childhood: the role of pre-existing medical conditions. Arch Dis Child. https://doi.org/10.1136/archdischild-2017-312684.

Hirvikoski T, Mittendorfer-Rutz E, Boman M et al. (2016). Premature mortality in autism spectrum disorder. In: Premature mortality in autism spectrum disorder, Br J Psychiatry, 208: pp. 232–238.

Iossifov I, O'Roak BJ, Sanders SJ et al. (2014). The contribution of de novo coding mutations to autism spectrum disorder. Nature 515: 216–221.

Jamuar SS, Walsh CA (2014). Somatic mutations in cerebral cortical malformations. N Engl J Med 371 (2038).

Kanner L (1943). Autistic disturbances of affective contact. Nervous Child 2: 217–250.

Lodato MA, Woodworth MB, Lee S et al. (2015). Somatic mutation in single human neurons tracks developmental and transcriptional history. Science 350: 94–98.

Nordahl CW, Lange N, Li DD et al. (2011). Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders. Proc Natl Acad Sci U S A 108: 20195–20200.

Rice CE, Zablotsky B, Avila RM et al. (2016). Reported wandering behavior among children with autism spectrum disorder and/or intellectual disability. J Pediatr 174 (232–239): e232.

Sanders SJ, He X, Willsey AJ et al. (2015). Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. Neuron 87: 1215–1233.

Torrey EF, Webster M, Knable M et al. (2000). The Stanley Foundation brain collection and neuropathology consortium. Schizophr Res 44: 151–155.

Werling DM, Parikshak NN, Geschwind DH (2016). Gene expression in human brain implicates sexually dimorphic pathways in autism spectrum disorders. Nat Commun 7: 10717.

Willsey AJ, Sanders SJ, Li M et al. (2013). Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell 155: 997–1007.