The Uniqueness of Biobanks for Neurological and Psychiatric Diseases: Potentials and Pitfalls

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Key Words

Brain/tissue/biobanks · Central nervous system disorders · Autopsy · Donors · Quality control · Ethical-legal-social issues

Abstract

Objectives: Central nervous system (CNS) biobanks are facing difficult and specific challenges due to the sensitive issue of collecting specimens of the CNS, and especially the brain. At present, there is no global network/central database to serve researchers, clinicians and pharma companies, or to supply the special specimens and the accompanying data in sufficient numbers and detail, respectively. The main challenge/objective is to standardize and harmonize all the facets involved in CNS biobanking in order to maximize efficient sample collection. **Methods:** Since the number of CNS biospecimens stored in existing biobanks is relatively limited and the accompanying data are not always readily available and hard to identify, we propose using optimal procedures for handling and storage of these specimens, and the global standardization of the cliniconeuropathological diagnostic criteria. **Results:** One of the prominent achievements of the current global activity in brain tissue biobanks (BTB-banks) is the development of an inventory of international standards, available specimens and concomitant data, and national registries. **Conclusions:** Taking into consideration the huge vari-

ety of the specimens stored in different repositories and the enormous differences in medicolegal systems and ethics regulations in different countries, we strongly recommend that healthcare systems and institutions who host BTB-banks make efforts to secure adequate funding for the infrastructure and daily activities. BTB-banks will refine standard operating procedures and their internal guides of best practices/codes of conduct. This in turn will enable the BTB-banks to share the collected specimens and data with the largest possible number of researchers, aiming at maximal scientific spin-off and advance of public health research.

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Introduction

The use of human biological specimens in scientific research is the focus of current international public and professional concern and a major issue in bioethics in general. Brain tissue biobanks (BTB-banks) are a rapidly developing sector, and such banks act locally as steering units for the establishment of the local standard operating procedures (SOPs) according to local, national and international legal regulations and ethical guidelines to be followed in the procurement and dissemination of research specimens. An appropriate guide of best practices/code of conduct is also mandatory for the successful operation of

BTB-banks and the research applications they handle. What is currently still missing? Major needs include: (1) adequate funding for research BTB-banks, (2) standard evaluation protocols for auditing BTB-bank performance, (3) internationally accepted SOPs which will facilitate exchange and sharing of specimens and data with the scientific community and (4) an internationally accepted guide of best practices/code of conduct.

BTB-Bank Cost Model

BTB-banks are not only expensive to establish, but also expensive to maintain; running costs may vary from EUR 10,000–15,000 per brain collected in the Brain Net Europe (BNE) Consortium to USD 10,000–30,000 in the United States. Only through a balanced and effective cost-recovery policy can long-term sustainability of BTB-banks be guaranteed. Currently, there is much confusion with regard to this policy as funding of biobanks is extremely variable. In this regard, peer-reviewed projects of high scientific quality should have high priority and commercial interests should be minimized or even disregarded, so that the BTB-banks will abide by the scientific quality and the ethical code of conduct. Adequate funding for BTB-banks can be achieved either by working under the auspices of an academic institution or a hospital in conjunction with the neuropathology units. In another model, BTB-banks can also get funded by an established foundation which will support the exclusive needs/expenses of the bank; this can be achieved via external sponsors, donors and subsidies from patient's associations and local/national governmental bodies. All funding should aim at creating a cost-recovery model for individual BTB-banks, where internal and external auditing of the BTB-bank activities and expenses should be a must.

Harmonization of Procedures and Nomenclature

The final diagnosis of central nervous system (CNS) disorders is severely hampered by the difficulty in accessing the CNS tissues together with the absence of specimens obtained from donors and the lack of reliable and accurate biomarkers that can be measured in body fluids such as blood, urine and cerebrospinal fluid (CSF). In this regard, the search for biomarkers is a difficult process due to the huge genetic diversity and variability among different individuals, distinct laboratories and techniques in the absence of parallel information about the tissues (e.g. CNS) primarily involved by the disease. Biospecimens from living donors (mostly restricted to patient tissues) have already contributed to a vast amount of data, whereas obtaining specimens at postmortem autopsy from pa-

tients and controls still remains very difficult. Furthermore, autopsy specimens show significant data fluctuation due to fast and difficult-to-control postmortem changes in brain and body fluids [1–3]. Specimens collected for biomarker identification are very heterogeneous in terms of sampling methods, size, storage conditions and availability of adequate/relevant associated clinical data. Specimen origin is also heterogeneous as it may originate from the general population, surgical procedures, biopsy samples or autopsy materials [4–10].

The Unique Nature, Structure and Role of BTB-Banks

Despite all the above, BTB-banks are unique and play a major role in identifying the pathological hallmarks of dementing and mental disorders. In this regard, the biospecimens available in a BTB-bank form an essential bridge between the clinics, basic science, biobanks, and biotech and pharma companies, which results in increased research and knowledge, and higher levels of clinical translation (fig. 1).

It is clear from the scheme illustrated in figure 1 that each BTB-bank is the center of a web of numerous participants. Thus, all BTB-bank contributors are involved in the flow of biological specimens from donors to scientists and industry, and back to routine clinical practice. The local healthcare system, policy makers, clinicians and pathologists are the supporting elements, and it is obvious that the main core of the banks is adherence to local regulations, ethics review committee recommendations and a solid internal guide of best practices/code of conduct.

Animal and cellular models of CNS disorders are not sufficient to highlight and explain human disease mechanisms and pathology; therefore, the availability of specimens from deceased donors and normal controls, whether fresh, frozen or fixed, facilitates and catalyzes the development of methodologies for studying the neuropathology of CNS diseases [11, 12].

Objectives

In this paper, we strongly plead for the need for quick global action to change the current status/situation by the following steps:

- To harmonize the recruiting methods, as well as the storage and handling procedures applied on specimens derived from patients with CNS disorders and controls

Fig. 1. Flowchart of BTB-bank interfaces. This scheme illustrates BTB-banks as intermediaries to facilitate the availability of specimens for research. The middle line shows the main parties who make this combination a success: the donors on the one hand, the BTB-banks and the global scientific research community on the other.

- To enhance and facilitate the exchange/collaboration and the establishment of consensus guidelines among those groups who have access to large cohorts of subjects with CNS disorders

Numerous European and international initiatives have been taken in the last years to bring in the global component in biobanking in general, and in brain banking in particular. Such efforts started in 1993 with the European Network of Brain Banking (ENBB), followed by the BrainNet Europe (BNE), European Society of BioBanks (ESBB), International Society of Biorepositories (ISBER), and Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) initiatives.

Methods

To achieve the two major goals stated above, seven basic measures which represent unique golden standards of brain banking should be implemented:

- A well-established local donor system in which consent is obtained for tissue usage for scientific research purposes and for access to the medical records
- Fast autopsies with a very short postmortem delay and fresh dissection; these are prerequisites for optimal application on the tissues obtained by an increasingly higher range of technical procedures and systems, including neuronal cell culture
- Compatibility of the protocols used for tissue procurement, management, preparation and storage with the most up-to-date diagnostics and scientific research technologies
- Generally accepted consensus on clinical and neuropathological diagnostic criteria

- Quality control and assurance of the disseminated samples (pH/agonal state).
- Abiding by internationally accepted guidelines while conforming to the ethical and legal aspects of the local medico-legal system
- Monitoring of proper safety procedures

Results of BTB-Bank Networking and Collaborations

A good example of successful biobanking of CNS disorders is in the Netherlands, where numerous collaborative studies have been performed by neurologists, neuropathologists, geneticists, brain bankers and basic researchers. Such collaborative studies, which have been ongoing for more than 15 years, include research studies on Alzheimer's disease (AD) [13–27], Parkinson's disease [13, 28–32], frontotemporal dementia (FTD) [37–47], multiple sclerosis [37–47], amyotrophic lateral sclerosis, motor neuron disease and psychiatric disorders, including depression and schizophrenia [48–51].

The above studies, many of which use *ex vivo* CNS specimens, as well as specimens obtained at (fast) post-mortem autopsies, have led to an enormous amount of data which have contributed to a better understanding of the pathophysiology and the etiology of many CNS disorders, from which FTD and AD are two clear examples.

FTD and AD are both cortical dementias presenting with common clinical symptoms and pathological findings, i.e. tau pathology. Thus, it is often difficult to distin-

guish between them on clinical grounds, whereas the genetic identification of tau mutations in familial forms of FTD enables correct diagnosis during life. There are still familial forms of AD-like dementia and FTD with unknown predisposing/determining genetic factors; therefore, it is essential to obtain more insight into the underlying causes, mechanisms and pathophysiology of both groups of diseases, and this is where autopsy validation by BTB-banks plays a major role. Autopsy validation provides a better insight into disease etiology, which in turn, enables identification of targets for drug development and eventually slow down and contribute to prevent disease progress. Another critical issue in biobanking and BTB-banking is the collection of sufficient amounts of specimens from both 'normal' and 'disease-associated' controls, so as to be able to highlight the changes in the brain and CNS which are specific for the investigated disease (fig. 2).

FTD is a neurodegenerative disorder with presenile onset, and is currently more often diagnosed during life. Pathogenic mutations in the Tau gene on chromosome 17q21–22 have been identified in several, but not all, families with hereditary FTD or Pick's disease. Numerous tau mutations have been identified in familial cases of FTD from Europe, USA, Japan and Australia. In the Netherlands, there has been an intensive collaboration and research in the past 15 years between neurologists and clinical geneticists on both the epidemiological and molecular genetics of FTD. The main purpose has been to identify as many familial cases as possible, and to eventually validate the clinical diagnosis by postmortem studies at The Netherlands Brain Bank. Thus, The Netherlands Brain Bank has played a critical role in this research network and project on FTD. In more detail, all hospital-based neurological, psychiatric practices and physicians in nursing homes and psychogeriatric hospitals in the Netherlands were surveyed by a questionnaire about patients who were suspected of familial FTD; FTD patients were then requested to visit the neurology out-patient clinic. Afterward, data on dementia and other neurodegenerative disorders in first-degree relatives of FTD patients were collected for genealogical studies and medical records. Hard copies of neuroimaging from patients and affected family members were searched whenever possible and allowed by the participating individuals and their legal representatives. At this step, blood for DNA studies was obtained from all patients after informed consent to be processed and stored at The Netherlands Brain Bank. Patients and their families were informed about the possibility of genetic counseling and tau screening. Based on

Fig. 2. Brains obtained at autopsy; note the significant differences between the 2 brains; the top one has been obtained from a control donor, without any neurological or psychiatric disorders and the bottom one has been obtained from a donor with AD.

their decision, mutation screening for the tau gene was carried out either in the genetic counseling settings or for scientific purposes only. Various missense (G272V, Dk280, P301L, R406W, L315R, S320F) and splice donor site mutations of exon 10 in the (MAP) tau gene were identified in several families with an autosomal dominant form of FTD. The discovery of TDP-43 within cellular inclusion bodies found in FTD has resulted in a better understanding of transcription in the human brain [36].

The transactive response DNA-binding protein TDP-43 has been discovered to be a major ubiquitinated protein in frontotemporal lobar degeneration with ubiquitinated tau-negative inclusions (FTLD-U), which consequently has been renamed FTLD-TDP. TDP-43 is present in AD and dementia with Lewy bodies, but is often confined to the limbic region rather than the more wide-

spread pattern seen in FTLT-TDP. Previous work has suggested some relationship between hippocampal sclerosis and TDP-43 expression. The presence of abnormal TDP-43 confined to the limbic regions in the moderate stages, whereas occasionally, cases in the high stages also showed neocortical positivity. No relationship could be established between abnormal TDP-43 expression and the degree of hippocampal sclerosis either in the surgical or autopsy cases. Altogether, these results highlight the potential of tissue collected by brain banks to advance our understanding of major scientific and clinical issues.

Regarding daily routine work of BTB-biobanks, at present a major concern exists about the global decline in autopsy rates [3, 4], which is due to several reasons/factors. Firstly, many neurologists/healthcare professionals assume that applying modern neuroimaging diagnostic techniques on the patient during life and searching for valid biomarkers for AD are sufficient and accurate enough for reliable diagnostics in AD and other related disorders. Some neurologists even consider postmortem validation studies to be redundant. Without their collaboration, it is very difficult in practice to convince patients about the benefits of brain donation to BTB-banks. Secondly, the legal and ethical framework needed to run brain banks still remains a matter of debate and will determine the future and continuity of research on neurological and psychiatric disorders of the nervous system. In addition, getting signed informed consent from the donors and their next of kin, prior to death, is a tedious and difficult process. Furthermore, in many religions, the body should stay whole after death, which may block the donation process in specific cases, particularly in specific regions and countries around the world. In turn, setting up a fast and efficient autopsy system and a well-operating BTB-bank is a time-consuming and expensive process which requires a dedicated team operating 24 h a day, 7 days a week. The consent-donation process is also complex due to the delay between the consent and the donation processes, together with the unpredictable nature of the exact place and time of such donation.

The notion that autopsy validation of a clinical-biological diagnosis is redundant is a huge misunderstanding. In fact, currently the one and only concise and correct way to validate the final diagnosis of the clinical conditions in AD and other related neurological disorders, relies on performing a detailed neuropathological examination, including histopathological, immunophenotypic and molecular testing. In many cases of mixed clinical diagnoses, it is essential to look into the neuropathological changes in the brain at the end stage of life.

Due to the large variability of the collected material, multiple patient-related factors, as well as systematic and random errors, also introduce a huge variation in the results. Therefore, collecting and providing postmortem human brain samples for research should include accurate matching for ante- and postmortem factors. Each area dissected from the brain of a diseased patient needs to be matched with an identical area from a control subject. Tissues must be matched for age, sex, agonal state, lateralization, seasonal variations, clock time of death and medication prior to death, among other factors. In addition, postmortem factors should be taken into account such as postmortem delay, fixation and storage time. In many instances, various neuroscientists who work on AD require specimens from patients who suffered from other neurological disorders in addition to the nondemented controls, so as to be able to control for disease-specific and nonspecific findings (fig. 2). Therefore, standardization and harmonization of the BTB-bank procedures is also crucial. Such standardization/harmonization efforts are directly linked to the need for adequate control assurance procedures, involving both the quality of samples and their components and the quality of the data associated with them. Thus, quality control in BTB-banking is critical for the efficient use of the collected specimens and the guarantee for high-quality research.

Concluding Remarks

Standardization and harmonization of current SOPs in biobanking of CNS diseases is of utmost importance and relevance to basic researchers, clinicians, neuropathologists and biobank managers. All of these groups of professionals share a common interest concerning biobanking of patient samples and clinical data, and sharing information about the availability of such specimens and data for research, especially pertaining to access to specimens and information that is difficult to acquire. In addition, BTB-banking also represents a challenge to medico-legal professionals and ethics experts, as the regulations for handling specimens and the genetic testing in CNS diseases have yet to be finalized in an ethical code of conduct at the international level.

The absence of objective measures to track disease progression or to allow early diagnosis strongly affects the costs that biotech and pharma companies will sustain in order to develop disease-modifying therapies that can effectively extend a patient's life and/or quality of life. Thereby, at present, many diagnostic and pharmaceutical

Fig. 3. Standardized dissection protocol for the human hippocampus. **a** Making the hippocampus ready during fresh dissection at autopsy. **b** The 5 areas of the hippocampus dissected for research.

companies are looking for protein biomarkers in neurological diseases. For this purpose, new genomic and proteomic platforms may have a great potential in the development of new (clinical) diagnostic tools. Their acceptance in clinical practice would depend on changes in general misperception of their costs and technical complexity, whereas their fast implementation relies on the availability of neurological tissues and other body fluid samples from patients with distinct neurological disorders and control subjects for biomarker discovery and validation [52, 53]. In this regard, availability of postmortem samples for both diagnostic and research purposes remains a challenge [54]. For example, AD is characterized by decreased CSF concentrations of $A\beta_{42}$ and increased concentrations of tau. Investigating the prevalence and prognostic value of CSF biomarkers in patients with mild/subjective cognitive impairment will be crucial in the near future to decide whether CSF analysis is to become routine in people with memory complaints for the diagnosis of disorders such as AD [55–57].

One common drawback is that BTB-banks, as well as other tissue banks and blood biobanks, are all driven by local legislation, ethical codes of conduct and motivation. Harmonization of the ethical-legal-social issues framework at the regional, national and even international levels is most welcome.

As autopsy rates are quickly declining worldwide, it is also of crucial importance to enhance the interoperability between brain banks and brain bank networks in different countries. At the same time there is an urgent need to increase the number of autopsies that are performed, especially those with short postmortem delays, even though many biomarkers are quite stable for a long time after death. In this regard, a large amount of work has already

been performed on the harmonization of procedures for collecting and assessing brains, setting of targets, and audit of performance through EBBN, BNE, the MRC UK Brain Bank Network, BBMRI, ISBER, ESSB and Brains for Dementia Research. Ongoing efforts are also being performed by large-scale initiatives such as the UK Biobank and the UK Dementia Platform, which include multiple large longitudinal cohorts with a large amount of clinical data and rigorous standardized protocols for dissection, sample collection, specimen analysis and storage (fig. 3). Such SOPs should also be followed by parallel implementation of adequate internal and external quality assurance protocols and programs. Setting up international, multicenter collections based on large patient cohorts, combined with population-based cohorts, in the setting of clinical trials, will provide the crucial tools needed to enhance the likelihood of success in getting deeper insight into the human brain and human brain genomics. This will pave the way to enable definition of both the intra- and interspecific variation in human and primate gene expression patterns [58], make clear where the potentials and pitfalls are present or hidden, and enable the identification of long-awaited valid biomarkers for specific neurological and psychiatric disorders [3, 60–62].

The need for control tissues in neuroscience research cannot be emphasized enough. Recruitment of control cases is difficult and can be best done within the framework of a national donor program promoted by the BTB-banks. The ‘control’ groups should be clearly defined for each study, as the matching factors are variable between CNS diseases. For example, mild cognitive impairment with a low Braak stage (stage I–II) is a good control for various CNS disorders, except AD [62].

The issue of quality control in brain banking and biobanking is a central issue for the use of collected specimens and the guarantee for high-quality research. Two of the most commonly used markers of tissue quality are RNA integrity and tissue/CSF pH [1, 63–66]. RNA integrity is quantified digitally by assessing the ratio of the 28S and 18S ribosomal RNA species to produce an RNA integrity number which ranges from 1 to 10. A higher RNA integrity number indicates greater RNA integrity.

RNA integrity is positively correlated with the pH of the CNS. Unlike pH, RNA integrity may vary in different

regions of the brain. Both antemortem and postmortem factors may reduce tissue quality. Antemortem factors which lead to a prolonged agonal state such as seizures, coma, respiratory illness and hypoglycemia are often excluded by the brain banks. The other factors, mainly postmortem, should be carefully monitored and registered to be able to perform the optimal matching of samples when used in both clinical and basic research. This will avoid and prevent bias and inaccurate conclusions about disease-specific CNS processes.

References

- 1 Ravid R: Standard operating procedures, ethical and legal regulations in BTB (brain/tissue/bio) banking: what is still missing? *Cell Tissue Bank* 2008;9:121–137.
- 2 Ravid R: Biobanks for biomarkers in neurological disorders: the Da Vinci bridge for optimal clinico-pathological connection. *J Neurol Sci* 2009;283:119–126.
- 3 Ravid R, Fasano M: The importance of harmonizing and standardizing CNS biomarkers and clinical trials in neurological disorders. *Future Neurol* 2012;7:663–666.
- 4 Ravid R, Ferrer I: Brain banks as key part of biochemical and molecular studies on cerebral cortex involvement in Parkinson's disease. *FEBS J* 2012;279:1167–1176.
- 5 Ravid R: The pitfalls and procedures in research on psychiatric and neurological disorders. *Proceedings of the 1st Brain Bank Symposium in Fukushima, Japan*. Blackwell Scientific 2008, pp 8–13.
- 6 Anderson R, Balls M, Burke MD, et al: The establishment of human research tissue banking in the UK and several Western European countries: the report and recommendations of ECVAM Workshop 44. *Altern Lab Anim* 2001;29:125–134.
- 7 Cruz-Sánchez FF, Ravid R, Cuzner ML: The European Brain Bank Network (EBBN) and the need of standardized neuropathological criteria for brain tissue cataloguing; in: Cruz-Sánchez FF, Cuzner ML, Ravid R (eds): *Neuropathological Diagnostic Criteria for Brain Banking*, European Union Biomedical and Health Research. Amsterdam, IOS Press, 1995, vol 10, pp 1–3.
- 8 Orr S, Alexandre E, Clark BJ, et al: Fourth meeting of the European Network of Research Tissue Banks – future strategy to increase collaborations in the supply of human tissue for biomedical research. *Cell Tissue Bank* 2005;6:131–138.
- 9 Schmitt A, Bauer M, Heinsen H, et al: Consortium of Brain Net Europe II: How a neuropsychiatric brain bank should be run: a consensus paper of Brain Net Europe II. *J Neural Transm* 2007;114:527–537.
- 10 Ravid R, Ikemoto K: Pitfalls and practicalities in collecting and banking human brain tissues for research on psychiatric and neurological disorders. *Fukushima J Med Sci* 2012;58:82–87.
- 11 Cao Y, Xiao Y, Ravid R, Guan ZZ: Changed clathrin regulatory proteins in the brains of Alzheimer's disease patients and animal models. *J Alzheimers Dis* 2010;22:329–342.
- 12 O'Callaghan P, Sandwall E, Li JP, et al: Heparan sulfate accumulation with Aβ deposits in Alzheimer's disease and Tg2576 mice is contributed by glial cells. *Brain Pathol* 2008;18:548–561.
- 13 Quinn JG, Coulson DT, Brockbank S, et al: α-Synuclein mRNA and soluble α-synuclein protein levels in post-mortem brain from patients with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. *Brain Res* 2012;1459:71–80.
- 14 Beyer N, Coulson DT, Heggarty S, et al: Zinc transporter mRNA levels in Alzheimer's disease postmortem brain. *J Alzheimers Dis* 2012;29:863–873.
- 15 Coulson DT, Beyer N, Quinn JG, et al: BACE1 mRNA expression in Alzheimer's disease postmortem brain tissue. *J Alzheimers Dis* 2010;22:1111–1122.
- 16 Berson A, Knobloch M, Hanan M, et al: Changes in readthrough acetylcholinesterase expression modulate amyloid-beta pathology. *Brain* 2008;131:109–119.
- 17 Webster JA, Myers AJ, Pearson JV, et al: Sorl1 as an Alzheimer's disease predisposition gene? *Neurodegener Dis* 2008;5:60–64.
- 18 Reiman EM, Webster JA, Myers AJ, et al: GAB2 alleles modify Alzheimer's risk in APOE ε4 carriers. *Neuron* 2007;54:713–720.
- 19 Coon KD, Myers AJ, Craig DW, et al: A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. *J Clin Psychiatry* 2007;68:613–618.
- 20 Brunner P, Sözer-Topcular N, Jockers R, et al: Pineal and cortical melatonin receptors MT1 and MT2 are decreased in Alzheimer's disease. *Eur J Histochem* 2006;50:311–316.
- 21 Papassotiropoulos A, Lambert JC, Wavrant-De Vrièze F, et al: Cholesterol 25-hydroxylase on chromosome 10q is a susceptibility gene for sporadic Alzheimer's disease. *Neurodegener Dis* 2005;2:233–241.
- 22 Webster J, Reiman EM, Zismann VL, et al: Whole genome association analysis shows that ACE is a risk factor for Alzheimer's disease and fails to replicate most candidates from meta-analysis. *Int J Mol Epidemiol Genet* 2010;1:19–30.
- 23 Hellström-Lindahl E, Ravid R, Nordberg A: Age-dependent decline of neprilysin in Alzheimer's disease and normal brain: inverse correlation with Aβ levels. *Neurobiol Aging* 2008;29:210–221.
- 24 Beyer N, Coulson DT, Heggarty S, et al: ZnT3 mRNA levels are reduced in Alzheimer's disease post-mortem brain. *Mol Neurodegener* 2009;4:53.
- 25 Corneveaux JJ, Liang WS, Reiman EM, et al: Evidence for an association between KIBRA and late-onset Alzheimer's disease. *Neurobiol Aging* 2010;31:901–909.
- 26 Moloney AM, Griffin RJ, Timmons S, et al: Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol Aging* 2010;31:224–243.
- 27 Coulson DT, Brockbank S, Quinn JG, et al: Identification of valid reference genes for the normalization of RT qPCR gene expression data in human brain tissue. *BMC Mol Biol* 2009;9:46.
- 28 Fasano M, Alberio T: Biomarkers of Parkinson's disease; in: *Advances in Parkinson's Disease Management*. London, Future Medicine Ltd., 2012, pp 18–25.
- 29 Fasano M: Biochemistry of Parkinson's disease – insights from cellular models, animal models and human tissue specimens obtained by autopsy. *FEBS J* 2012;279:1145.

- 30 Natale M, Bonino D, Consoli P, et al: A meta-analysis of two-dimensional electrophoresis pattern of the Parkinson's disease-related protein DJ-1. *Bioinformatics* 2010;26:946–952.
- 31 Grünblatt E, Zander N, Bartl J, et al: Comparison analysis of gene expression patterns between sporadic Alzheimer's and Parkinson's disease. *J Alzheimers Dis* 2007;12:291–311.
- 32 Donker Kaat L, Boon AJ, Kamphorst W, et al: Frontal presentation in progressive supranuclear palsy. *Neurology* 2007;69:723–729.
- 33 Van Herpen E, Rosso SM, Severijnen LA, et al: Variable phenotypic expression and extensive tau pathology in two families with the novel tau mutation L315R. *Ann Neurol* 2003;54:573–581.
- 34 Bronner IF, ter Meulen BC, Azmani A, et al: Hereditary Pick's disease with the G272V tau mutation shows predominant three-repeat tau pathology. *Brain* 2005;128:2645–2653.
- 35 Bronner IF, Bochdanovits Z, Rizzu P, et al: Comprehensive mRNA expression profiling distinguishes tauopathies and identifies shared molecular pathways. *PLoS One* 2009;4:14–19.
- 36 Neumann M, Sampathu DM, Kwong LK, et al: Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314:130–133.
- 37 Van Veen T, Nielsen J, Berkhof J, et al: CCL5 and CCR5 genotypes modify clinical, radiological and pathological features of multiple sclerosis. *J Neuroimmunol* 2007;190:157–164.
- 38 Matute C, Torre I, Pérez-Cerdá F, et al: P2X(7) receptor blockade prevents ATP excitotoxicity in oligodendrocytes and ameliorates experimental autoimmune encephalomyelitis. *J Neurosci* 2007;27:9525–9533.
- 39 Bsibsi M, Bajramovic JJ, Van Duijvenvoorden E, et al: Identification of soluble CD14 as an endogenous agonist for Toll-like receptor 2 on human astrocytes by genome-scale functional screening of glial cell derived proteins. *Glia* 2007;55:473–482.
- 40 Mahad D, Callahan MK, Williams KA, et al: Modulating CCR2 and CCL2 at the blood-brain barrier: relevance for multiple sclerosis pathogenesis. *Brains* 2006;129:212–223.
- 41 Shiarli A-M, Jennings R, Shi J, et al: Comparison of extent of tau pathology in patients with frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration with Pick bodies and early onset Alzheimer's disease. *Neuropathol Appl Neurobiol* 2006;32:374–387.
- 42 Vallejo-Illarramendi A, Domercq M, Pérez-Cerdá F, et al: Increased expression of glutamate transporters EAAT1 and EAAT2 in multiple sclerosis. *Neurobiol Dis* 2006;21:154–164.
- 43 Bö L, Geurts JJ, Ravid R, Barkhof F: Magnetic resonance imaging as a tool to examine the neuropathology of multiple sclerosis. *Neuropathol Appl Neurobiol* 2004;30:106–117.
- 44 Bot JC, Blezer EL, Kamphorst W, et al: The spinal cord in multiple sclerosis: relationship of high-spatial-resolution quantitative MR imaging findings to histopathologic results. *Radiology* 2004;233:531–540.
- 45 Van Waesberghe JH, Kamphorst W, De Groot CJ, et al: Axonal loss in multiple sclerosis lesions: magnetic resonance insights into substrates of disability. *Ann Neurol* 1999;46:747–754.
- 46 Nijeholt GJ, Bergers E, Kamphorst W, et al: Post-mortem high-resolution MRI of the spinal cord in multiple sclerosis: correlative study with conventional MRI, histopathology and clinical phenotype. *Brain* 2001;124:154–166.
- 47 Lycklama à Nijeholt GJ, Bergers E, Kamphorst W, et al: Postmortem MR imaging of the spinal cord in MS at 4.7T: correlative study with conventional MR imaging, histopathology and clinical phenotype. *Brain* 2001;124:154–166.
- 48 Ravid R: Methodological considerations of the establishment of a brain bank for psychiatric research; the Amsterdam and European experience; in Agam G, Belmaker RH, Everall I (eds): *The Post-Mortem Brain in Psychiatric Research*. Norwell, Kluwer Academic Publishers, 2002, pp 8–13.
- 49 Matsumoto I, Niwa SI, Ravid R: Psychiatric brain banks: situation in Europe and Asia; in Agam G, Belmaker RH, Everall I (eds): *The Post-Mortem Brain in Psychiatric Research*. Norwell, Kluwer Academic Publishers, 2002, pp 3–10.
- 50 Kromkamp M, Vermetten E, Ravid R, et al: The initiation of a postmortem research programme in schizophrenia in The Netherlands. Donor-registration and diagnosis of schizophrenia patients and their parents. *Dutch Med J* 2001;55:105–108.
- 51 Ravid R: The pitfalls and practicalities in collecting and banking human brain tissues for research on psychiatric and neurological disorders. *Proceedings of the 1st Fukushima Brain Bank symposium*. *Psych Clin Neurosci*, Blackwell-Synergy 2007;61:S19–S23.
- 52 Alberio T, Fasano M: Proteomics in Parkinson's disease: an unbiased approach towards peripheral biomarkers and new therapies. *J Biotechnol* 2010;156:325–337.
- 53 Kwon KH, Kim JY, Kim SY, et al: Chromosome 11-centric human proteome analysis of human brain hippocampus tissue. *J Proteome Res* 2013;12:97–105.
- 54 Fagan AM, Shaw LM, Xiong C, et al: Comparison of analytical platforms for cerebrospinal fluid measures of Aβ1–42, total tau and p-tau181 for identifying Alzheimer's disease amyloid plaque pathology. *Arch Neurol* 2011;68:1137–1144.
- 55 Mattsson N, Rosén E, Hansson O, et al: Age and diagnostic performance of Alzheimer disease CSF biomarkers. *Neurology* 2012;78:468–476.
- 56 Vos S, van Rossum I, Burns L, et al: Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI. *Neurobiol Aging* 2012;33:2272–2281.
- 57 Schoonenboom NS, Reesink FE, Verwey NA, et al: Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology* 2012;78:47–54.
- 58 Enard W, Khaitovich P, Klose J, et al: Intra- and interspecific variation in primate gene expression patterns. *Science* 2002;296:340–343.
- 59 Ferrer I, Armstrong J, Capellari S, et al: Effects of formalin fixation, paraffin embedding, and time of storage on DNA preservation in brain tissue: a BrainNet Europe study. *Brain Pathol* 2007;17:297–303.
- 60 Alafuzoff I, Pikkarainen M, Al-Sarraj S, et al: Interlaboratory comparison of assessments of Alzheimer disease and related lesions: a study of the BrainNet Europe Consortium. *J Neuropathol Exp Neurol* 2006;65:740–757.
- 61 Watson PH, Ravid R, Eng CB, et al: What are the main roadblocks to transnational biobank collaboration, and how can we overcome them? *Biopreserv Biobank* 2011;9:213–216.
- 62 Ravid R, Swaab DF, Van Zwieten EJ, Salehi A: Controls are what makes a brain bank go round; in Cruz-Sanchez FF, Ravid R, Cuzner ML (eds): *Neuropathological Diagnostic Criteria for Brain Banking*. Amsterdam, IOS Press, 1995, pp 4–13.
- 63 Ravid R, van Zwieten EJ, Swaab DF: Brain banking and the human hypothalamus-factors to match for, pitfalls and potentials; in Swaab DF, Hofman MA, Mirmiran M, et al (eds): *The Human Hypothalamus in Health and Disease*. Amsterdam, Elsevier, 1992, vol 93, pp 83–95.
- 64 Kingsbury AE, Foster OJ, Nisbet AP, et al: Tissue pH as an indicator of mRNA preservation in human post-mortem brain. *Mol Brain Res* 1995;28:311–318.
- 65 Stan AD, Ghose S, Gao XM, et al: Human postmortem tissue: what quality markers matter? *Brain Res* 2006;1123:1–11.
- 66 Tomita H, Vawter MP, Walsh DM, et al: Effect of agonal and postmortem factors on gene expression profile: quality control in microarray analyses of postmortem human brain. *Biol Psychiatry* 2004;55:346–352.