Observational cohort study of blood transcriptomics and proteomics information as biomarkers of traumatic encephalopathy syndrome

Version: 1.0

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Organization Committee

Tianjin Medical University General hospital

Information Sheet of Informed Consent Form

Dear potential research participants,

We sincerely invite you to participate in a study titled **Observational cohort study of blood transcriptomics and proteomics information as biomarkers of traumatic encephalopathy syndrome**. This research is supported by **the Department of Geriatrics, Neurosurgery, Medical Imaging and PET-CT of Tianjin Medical University**. The principal investigator is **Prof. Ping Lei** and **Dr. Xintong Ge**.

The ethics committee of Tianjin Medical University General Hospital has reviewed the research plan of this study, and agreed to conduct the clinical research program (Grant No. **IRB2021-YX-056-01**, Approved starts on: **05/01/2021**, Approval expires on: **11/01/2022**). The study has been registered at the global clinical research authority database, **ClinicalTrials.gov (Identifier: NCT04928534)**. The research program is funded by **the Natural Science Foundation of China (Grant No. 82071394, 82072166)**.

Please read the following text carefully as much as possible before deciding whether participate in this study. It can help you understand the purpose, content, procedures and duration of the study, and the possible benefits, risks and discomforts of being a participant. If you prefer, you can also discuss with your family and friends, or ask your doctor for explanations to help you make a decision.

P.S. Taking part in this study is entirely voluntary. You can refuse to participate, which will not affect your relationship with the doctor and the investigator. In addition, you will not be charged any additional fee.

1. Research Background and Objectives

Chronic traumatic encephalopathy (CTE) is a distinct neurodegenerative disease associated with traumatic brain injury (TBI). It is characterized by the clinical manifestations of progressive cognitive and neurological dysfunction, and the pathological changes of abnormal deposition of phosphorylated tau protein in neurons, astroglia and synapses around small blood vessels at the depths of cortical sulci. The occurrence of the disease is closely related to a history of repetitive mild TBI, concussion and sub-concussion, so that it is susceptible in boxers and other contact sports athletes, military veterans, elderly people with mobility impairments and victims of domestic violence.

The clinical symptoms of CTE mainly include cognitive decline, behavioral change, emotional

dysregulation and motor disturbance. The cognitive decline typically affects more than one domain of neurological deficits including executive, visuospatial, memory and language. Patients with mainly behavioral change may exhibit violence, poor impulse control, socially inappropriate behavior, avolition, apathy, change in personality and comorbid substance abuse. The emotional dysregulation includes depression, anxiety, agitation, aggression, paranoid ideation, deterioration of interpersonal relationships and suicidality, while the motor disturbance contains bradykinesia, tremor, rigidity, gait instability, dysarthria, dysphagia, ataxia and gaze disturbance. From this, CTE can seriously influence the quality of life. Consequently, early diagnosis and treatment for the disease has important clinical significance.

The traditional diagnostic criteria of CTE are based on neuropathology, which causes most patients to be diagnosed only by autopsy. In order to develop a clinical diagnostic criterion of CTE, so that the patients could receive effective treatment in time, the concept of Traumatic Encephalopathy Syndrome (TES) was proposed. Specifically, potential patients with CTE are divided into three categories: probable TES, possible TES and unlikely TES according to the likelihood of illness. The classification is based on the number of head traumas, clinical features and progressive courses. This diagnostic framework provides a practical approach for clinical evaluation of CTE.

However, the diagnostic criteria of CTE and TES that are based solely on clinical symptoms still lack sufficient specificity and sensitivity, while biomarkers could be an important tool to fill the deficiency and further improve diagnosis level of the disease. Blood biomarkers have always been a research hotspot in the field of neurotrauma due to their easy access to specimens and convenience for detection. Neverthless, there is still a lack of specific biomarkers for CTE/TES in clinical practice till now. In this study, we will use high-throughput screening and multi-omics (transcriptomics and proteomics) joint analysis technology to explore potential CTE/TES biomarkers (RNA and protein) in blood and its exosomes. We will also combine them with the reported TBI biomarkers to create a novel set of CTE/TES molecular diagnostic signatures, in order to open a new avenue of clinical diagnosis of the disease and future research on the therapeutic strategy.

2. Estimated Number of Subjects

120 subjects are expected to take part in this study, including 50 athletes from the Weightlifting, Wrestling, Judo, Boxing and Taekwondo Sports Management Center of Tianjin Sports Bureau, 50

patients with multiple (≥2 times) exposure to brain trauma attending Tianjin Medical Insurance designated hospitals such as Tianjin Medical University General Hospital, and 20 healthy volunteers.

3. Screening, Inclusion and Exclusion Criteria

3.1 Athletes and Patients with TBI

Screening Criteria:

1) Age ≥ 18 and ≤ 80 years old with independent behavior ability or authorized legal representative.

2) Have a clear history of repetitive mild TBI, concussion or subconcussion.

3) The most recent head injury occurred 3 months ago.

Inclusion Criteria:

On the basis of meeting the screening criteria, the participants need to fully understand the nature of the study, and voluntarily participate in the study and sign the informed consent form.

Exclusion Criteria:

1) Pregnant or lactating women.

2) History of other neurological diseases.

3) History of tumors, hematological diseases, severe cardiopulmonary diseases, hepatic failure or renal failure.

4) Have participated in clinical trials in the past four weeks.

5) The investigator believe that not appropriate for inclusion.

3.2 Healthy Volunteers

Screening Criteria:

1) Age ≥ 18 and ≤ 80 years old with independent behavior ability.

2) No history of repetitive mild TBI, concussion or subconcussion.

3) Fully understands the nature of the study, and voluntarily participates and signs the informed consent.

Inclusion Criteria:

On the basis of meeting the screening criteria, the healthy volunteers need to fully understand the nature of the study, and sign the informed consent form.

Exclusion Criteria:

1) Pregnant or lactating women.

2) History of TBI or other neurological diseases.

3) History of tumors, hematological diseases, severe cardiopulmonary diseases, hepatic failure or renal failure.

4) Have participated in clinical trials in the past four weeks.

5) The investigator believes that not appropriate for inclusion.

4. Study Procedures

4.1 Before you enroll in the study, the doctor will record your past medical history, and conduct a basic physical examination.

If you are a qualified subject, you could voluntarily participate in the study, and sign the informed consent form.

If you do not meet the inclusion criteria, we will suspend your participation in this study.

4.2 If you agree to participate in the study, you will undergo blood tests (30-ml venous blood) for the following items.

1) Transcriptomics and proteomics high-throughput detection and quantitative verification;

2) Exosomal transcriptomics and proteomics high-throughput detection and quantitative verification;

3) Quantitative detection for classical biomarkers of traumatic brain injury, including S100B, GFAP, UCH-L1, NFL, T-Tau and p-Tau181.

4.3 If you agree to participate in the study, you will receive cognitive function tests, including RPQ, MMSE, MoCA and LOTCA.

4.4 If you agree to participate in the study and meet the diagnostic criteria for probable TES or possible TES, you will be eligible to apply for head MRI (plain scan and DTI) examination and head PET (FDG-PET, Tau-PET and Amyloid-PET) examination. We will randomly select part of the applicants (about 20 cases) to accept the above examinations. You will be monitored for possible adverse events during the PET examination, and will be called 24 hours later and 2 weeks later to assess for any potential adverse events.

The collected blood samples and image data will only be used in this study.

5. Benefits

All participants will be given a physical examination (Package C, valued at ¥ 1,500) at the Health Management Center of Tianjin Medical University General Hospital.

6. Risks, Discomforts and Inconveniences

During the research, you will need to go to Tianjin Medical University General Hospital for personal information and past medical history collection. The doctor will also conduct cognitive function tests and blood tests for you. Some participants will also accept neuro-imaging examinations. The above work will take up some time, and may cause some inconvenience.

For the subject undergoing the PET examination, a very small number of them would have adverse events such as contrast allergy due to the use of contrast agents (see the Informed Consent Form for PET Examination at Tianjin Medical University General Hospital for details). Otherwise, this study will not bring you any risks or discomforts.

7. Financial Information

You will not be charged for participating in this study.

8. Privacy

Your research records and medical files will be kept by Tianjin Medical University General Hospital. The investigator and the ethics committee will be permitted to assess your records. Any public report on the results of this study will not reveal your personal information. We will make every reasonable effort to protect the privacy of your personal research records to the extent permitted by law.

According to medical research ethics, the research data will be available for public inquiry and sharing, except for the personal privacy information. The query and sharing will be limited to web-based electronic databases, ensuring that no personal privacy information will be disclosed.

9. How to obtain more information about the study?

You can ask any questions about this research at any time and get answers.

We will keep you informed if there is any critical new information during the research course that may affect your willingness to continue participating in the study.

10. Voluntary Participation and Withdrawal

Participating in this study is completely voluntary. You may refuse to take part in this research, or stop participating in the research at any time that you wish without losing any of your rights.

For your best interests, the doctor or the investigator may your participation at any time during the study.

11. What need to do now?

Thank for reading the materials. Before making a decision on whether to participate in this study, please ask the doctor or the investigator about the research as much as possible.

If you decide to take part in this study, please tell your research coordinator, she will arrange everything for your participation and following tests.

Please keep this form properly.

12. Sharing the Results

Your physical examination report and FDG-PET examination report will be mailed to your home within 1 month after the examination. The research findings will be sent to you by mail by the end of this study. In addition, the results of this study will be published and shared through academic papers, professional academic conferences, internet, Wechat, etc., so that the patients and practitioners in the medical field and pharmaceutical industry can learn.

13. Who can I contact about this study?

Principal Investigator: Dr. Xintong Ge

E-mail: gexintongbob@163.com Telephone: 022-60364359

Research Coordinator: Prof. Fanglian Chen

E-mail: chenfanglian1976@163.com Telephone: 022-60362237

Program Assignment No. IRB2021-YX-056-01

Certificate of Informed Consent Form

Study Title: Observational cohort study of blood transcriptomics and proteomics information as biomarkers of traumatic encephalopathy syndrome

Name of Organization: Tianjin Medical University General Hospital

Consent Statement:

I have read the above introduction to this study, and have the opportunity to discuss it with **Dr. Xintong Ge**, the principal investigator of the research program. All the questions I asked have been satisfactorily answered.

I know that participating in this study is completely voluntary. I understand the risks and benefits that may arise from taking part in this study. I confirm that I have enough time to consider, and realize that:

- I can ask the doctor and the investigator for more information about the study at any time.
- I can withdraw from the study at any time without discrimination or retaliation, and my rights will not suffer any loss.
- If I have more questions or concerns about this research, I can contact with **Dr. Xintong Ge**.

I agree that the investigator and the ethics committee could review my research materials.

I will receive a copy of this form with my signature and the date.

Finally, I decide to agree to participate in this study, and promise to do my best to follow the instructions from the doctor and the investigator.

Name of participant: _____ Telephone: _____ Date: _____

(If applicable) **The informed consent form of _____ (participant) can not be signed in person due to his/her illness. _____ is granted as the legal representative to represent the patient's informed consent and all of his/her rights in the study.**

_____ (representative) agree with _____ (participant) on participating in the study.

Name of representative: _____ Telephone: _____ Date: _____

Relationship between the participant and representative: _____

(If applicable) I have witnessed the authorization of the participant to the legal representative, and the participant volunteering to participate in this study.

Name of witness: _____ Telephone: _____ Date: _____

I confirm that the details of this study have been stated to the participant, including his/her power, potential benefits and risks. The participant has been given opportunities to put questions about the study, and all the questions have been answered accurately. I confirm that the participant was not coerced into giving consent, and a copy of this form has been provided to him/her.

Name of Doctor: _____ Date: _____