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TITLE: The Prenatal Origins of Autism Spectrum Disorder

PRINCIPAL INVESTIGATOR: Dr. Jennifer Straughen

CONTRACTING ORGANIZATION: Henry Ford Health System

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6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Henry Ford Health System
1 Ford Place
Detroit, MI 48202-3450

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study seeks to examine the interrelationships of placental histopathology, placental and neonatal angiogenesis, and ASD severity. In doing so, it addresses two critical gaps in ASD knowledge: (1) why the majority of ASD cases are male and (2) mechanisms underlying the heterogeneity of ASD symptoms. In addition, it will open the door to non-invasive placenta-based diagnosis at the time of birth, well before onset of red-flag symptoms. This study is leveraging existing data, resources, and biologic samples as well as physician partnerships to conduct a study of 177 ASD cases (62 with archived placental tissue) and 62 frequency matched controls born in Michigan between 2012 and 2017. ASD cases are extensively evaluated by a team of experts at the Henry Ford Health System Center for Autism and Developmental Disabilities and have detailed diagnostic information including severity level in their electronic medical record. Neonatal angiogenic profile will be measured in archived dried blood spots from Michigan's Newborn Screening Program. Placental histopathology and angiogenic markers will be assessed in archived placental tissue from 62 cases and 62 typically developing controls frequency matched on year of birth, preterm status, and sex. At present, all administrative tasks related to preparing for participant recruitment have been addressed and study protocols, databases and recruitment tools are ready. Final IRB and HRPO approvals remain pending and participant recruitment will commence as soon as all IRB and HRPO approvals are in place.

15. SUBJECT TERMS

Autism spectrum disorder, placenta, angiogenesis, neurodevelopment, neonatal dried blood spots

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1. INTRODUCTION

This study seeks to examine the interrelationships of placental histopathology, placental and neonatal angiogenesis, and ASD severity. In doing so, it addresses two critical gaps in ASD knowledge: (1) why the majority of ASD cases are male and (2) mechanisms underlying the heterogeneity of ASD symptoms. In addition, it will open the door to non-invasive placenta-based diagnosis at the time of birth, well before onset of red-flag symptoms. This study is leveraging existing data, resources, and biologic samples as well as physician partnerships to conduct a study of 177 ASD cases (62 with archived placental tissue) and 62 frequency matched controls born in Michigan between 2012 and 2017. ASD cases are extensively evaluated by a team of experts at the Henry Ford Health System Center for Autism and Developmental Disabilities and have detailed diagnostic information including severity level in their electronic medical record. Neonatal angiogenic profile will be measured in archived dried blood spots from Michigan's Newborn Screening Program. Placental histopathology and angiogenic markers will be assessed in archived placental tissue from 62 cases and 62 typically developing controls frequency matched on year of birth, preterm status, and sex.

2. KEYWORDS

Autism spectrum disorder, placenta, angiogenesis, neurodevelopment, neonatal dried blood spots

3. ACCOMPLISHMENTS

What were the major goals of the project? The major tasks for this project as defined in the scope of work are outlined below.

Major Task 1: Administrative tasks related to preparing to recruit study participants. Projected completion of task 1 was April 31st, 2020. All these tasks have been completed, but final HRPO approval is still pending (details below). Overall, this task is 90% complete.

- Develop study protocols, recruitment documents, questionnaire, obtain data use agreements
- Develop and test study database
- Prepare and submit IRB documents

Major Task 2: Identification and enrollment of study participants and biologic sample acquisition. Projected completion of this task is February, 28 2022. This is 5% complete.

- Identify potentially eligible study participants from the Henry Ford Health System (HFHS) electronic medical record (on-going)
- Contact potentially eligible study participants, obtain informed consent, and administer questionnaire (on-going)
- Retrieval of electronic medical record data from HFHS and external facilities; this is on-going and will occur concurrently with enrollment of study participants
- Review cases with unclear ASD classification and severity ratings (on-going)
- Request and obtain archived dried blood spot samples from the Michigan Neonatal Biobank
- Retrieve archived placental specimens

Major Task 3: Analysis of archived dried blood spots. Projected completion of task 3 is the end of November 2021. This is 0% complete.

- Measure angiogenic markers in dried blood spot samples

Major Task 4: Digitization and analysis of archived placental samples. Projected completion of task 4 is January 31, 2022. This is 0% complete.

- Slide digitization
- Placental pathologist review of archived placental slides
- Immunohistochemical staining for angiogenic markers in archived placenta samples

Major Task 5: Prepare manuscript to address Specific Aim 1 - Determine whether type and duration of exposure to placental histopathology is associated with ASD severity. Projected completion of task 5 is the end of July 2022. This is 0% complete.

- Data analysis
- Manuscript writing

Major Task 6: Prepare manuscript to address Specific Aim 2 - Determine whether placental histopathology is associated with angiogenic markers or multi-marker profiles in the placenta and neonatal blood. Projected completion of task 6 is the end of July 2022. This is 0% complete.

- Data analysis
- Manuscript writing

Major Task 7: Prepare manuscript to address Specific Aim 3 - Determine whether angiogenic markers or multi-marker profiles in the placenta and neonatal blood are associated with ASD severity. Projected completion of task 7 is the end of July 2022. This is 0% complete.

- Data analysis
- Manuscript writing

What was accomplished under these goals?

The following activities under Major Task 1 have been completed:

(1) Develop study protocols, recruitment documents, questionnaires, obtain data use agreements;
(2) Develop and test study databases and;
(3) Prepare and submit IRB documents.

At present all recruitment tools including consent forms, questionnaires, tracking databases, and databases for collection of questionnaire data have been developed, tested and refined and are ready to be used. Whenever possible questionnaires will be completed online and data will be collected in REDCap (Research Electronic Data Capture) which is a secure web-based tool for collecting and managing research data. Questionnaires can also be administered over the phone or in person (and data still entered into the REDCap database) if needed.

In addition, we have submitted IRB documents to the Henry Ford Health System IRB and the State of Michigan IRB (required for use of neonatal dried blood spots) and have obtained initial approvals. The Henry Ford Health System IRB was initially approved 8/28/19. The initial IRB approval from the State of Michigan was obtained 3/9/20. We submitted human subjects documents to the DOD HRPO in December 2019 and revised documents March 31, 2020 and

again on June 8, 2020. The most recent comments from the DOD HRPO were received August 11, 2020. Approvals from the HRPO are pending receipt of local IRB approvals. We are currently re-submitting the Henry Ford Health System IRB and the State of Michigan IRB with the changes that were requested by the DOD HRPO. We do not expect any challenges in obtaining approvals as the changes requested by the DOD HRPO did not significantly alter participant risk and should be considered minor revisions. However, there may be delays related to COVID-19 staffing limits and re-prioritizations at the State of Michigan IRB. The Henry Ford Health System IRB has been working remotely and should be able to expeditiously review the required changes.

We did not plan to accomplish Major tasks 2-7 until years 2 and 3 of the project. However, we had initially anticipated starting recruitment at the very end of year 1. COVID-19 related closures, protocols, and responses likely delayed approval and processing of IRB/HRPO documents. As such recruitment has not yet started. Nonetheless, we fully anticipate recovering from this slight delay during the next reporting period. While waiting for IRB and HRPO approvals, our strategy for identification for participants has been developed (related to Major task 2). This involves how we will identify potentially eligible participants using queries in our electronic medical record system. Because this has been completed, we can begin implementing this strategy and contacting potential participants as soon as all IRB and HRPO approvals are obtained. Notably because we expect the vast majority of study participants to complete the study protocols online, we do not anticipate having to halt the project for COVID-19 related closures.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish these goals?

In the next reporting period our efforts will largely focus on Major task 2, Identification and enrollment of study participants and biologic specimen acquisition. In order to accomplish this task, we will implement our strategy for identification of study participants in the epic electronic medical record. This will be done programmatically via a series of queries that specifically identify participants that meet eligibility criteria. Eligible participants will contacted via email, regular mail, and phone as needed and invited to participate. Data collection will occur on an on-going basis and will include electronic medical record abstraction and query, questionnaires and biologic specimen acquisition from the biorepositories.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change
There were no significant changes in approach. However, we did have to identify a new study co-investigator and pathologist to take on the duties of Dr. Kristen Adams. Dr. Adams left her institution and had not yet identified a new place of employment. Dr. Ghassan Allo at Henry Ford Health System was identified to take her place. This request was submitted to Shui-Lin (Stan) Niu, Science Officer on April 30, 2020.

Actual or anticipated problems or delays and actions or plans to resolve them

Changes that had a significant impact on expenditures
There were no significant changes that impacted expenditures. Dr. Allo replaced Dr. Adams, but the salary structure is similar and did not significantly impact expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards and/or select agents

Significant changes in use or care of human subjects
All protocols, consents, data collection tools, recruitment documents and other human subjects related materials were submitted to the Henry Ford Health System IRB as well as the State of Michigan IRB. Approval dates are detailed below:

Henry Ford Health System IRB: initial approval was obtained August 28, 2020.

State of Michigan IRB: Initial approval was obtained March 9, 2020.

In addition, all documents were submitted to the DOD HRPO in December 2019. We submitted human subjects documents to the DOD HRPO in December 2019 and revised documents on March 31, 2020 and again on June 8, 2020. The most recent comments from the DOD HRPO were received August 11, 2020. We were asked to resubmit our IRB documents with the changes requested by the DOD HRPO to the local IRBs (the Henry Ford Health System and the State of Michigan). This is in progress. As soon as approvals are received, they will be sent the DOD HRPO. Approvals from the HRPO are pending receipt of local IRB approvals.

Significant changes in use or care of vertebrate animals
Nothing to report. Vertebrate animals are not used in this project.

Significant changes in use or care of biohazards and/or select agents
Nothing to report. Biohazards and/or select agents are not used in this project.

6. PRODUCTS

Publications, conference papers, and presentations

Journal publications

Under Review:
Jennifer K. Straughen, Alexandra R. Sitarik, Christine Cole Johnson, Ganesa Wegienka, Dennis R. Ownby, Tisa M. Johnson-Hooper, Ghassan Allo, Albert M. Levin, Andrea E. Cassidy-Bushrow. *Prenatal IgE as a risk factor for the development of childhood neurodevelopmental disorder*. Frontiers Pediatrics 2020. Under Review.

Books or other non-periodical, one-time publications
Nothing to report.

Other publications, conference papers, and presentations
Nothing to report.

Websites or other internet sites
Nothing to report.

Technology or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other products
Nothing to report.

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Jennifer Straughen, PhD*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3.6*
Contribution to Project:	*Dr. Straughen is responsible for the organization and direction of all research activities carried out by this multidisciplinary research program. Dr. Straughen leads the research team, she oversees the collection, analysis, interpretation, and dissemination of study data and laboratory results. Dr. Straughen will also ensure that systems are in place to guarantee institutional compliance with US laws, and DOD policies, including biosafety (human research, data, and facilities).*
Funding Support:	*DoD; NIH; The Fund for Henry Ford*

Name:	*Albert M. Levin, PhD*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Levin will participate in the conduct and interpretation of analyses, including the identification of key covariates. Dr. Levin has extensive experience collaborating on epidemiologic study design, analyzing complex data, and communicating those results to a study team. In addition, he will contribute to preparation of abstracts, presentations, and manuscripts. He also will supervise statistical analyses done by the data analyst.*
Funding Support:	*DoD; NIH; The Fund for Henry Ford*

Name:	*Tisa Hooper-Johnson, MD*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Hooper-Johnson will review cases where the diagnosis or severity level are ambiguous. Dr. Hooper-Johnson contribute to preparation of abstracts, presentations and manuscripts.*
Funding Support:	*DoD; The Fund for Henry Ford*

Name:	*Ghassan Allo, MD*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Ghassan Allo, a pathologist, will review the digitized placental slides and contribute to other aspects of this study including manuscripts, abstracts, and presentations. Dr. Allo is replacing Dr. Kristen Adams from the University of Mississippi Medical Center.*
Funding Support:	*DoD; The Fund for Henry Ford*

Name:	*Kristen Adams, MD (UMMC)*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Allo replaced Dr. Kristen Adams and she is no longer part of this project. While part of the project, she worked on processing of start-up regulatory documents required for the study (including those needed for prime institution) and IRB preparation.*
Funding Support:	DoD; University of Mississippi Medical Center

Name:	*Chad Coleman*
Project Role:	*Project Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2.4*
Contribution to Project:	*Mr. Coleman assisted Dr. Straughen in coordinating communications and meetings among staff and preparing IRB submissions, and managing IRB protocols. He will also support manuscript preparation and other dissemination activities. He will receive ongoing training in compliance with research ethics and HIPAA regulations. Lisa King will be replacing Chad Coleman.*
Funding Support:	*DoD; NIH; Pharmaceutical;* *The Fund for Henry Ford*

Has there been a change in the active or other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Adams left her institution and had not yet identified a new place of employment. Dr. Ghassan Allo at Henry Ford Health System was identified to take her place as described in the above sections. The UMMC subcontract was terminated.

What other organizations were involved as partners?

Organization Name:	University of Mississippi Medical Center
Location of Organization:	2500 North state Street, Jackson, MS 39216
Partner's contribution to the project:	Dr. Kristen Adams will no longer be on this project and the University of Mississippi Medical Center is no longer involved due to Dr. Adams departure from the institution.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

Nothing to report.