CORRELATION BETWEEN IQ, AUTISM SPECTRUM DISORDERS, AND FMRP LEVELS IN MALES WITH THE *FMR1* PREMUTATION

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Magister of Biomedical Sciences

Tanjung Ayu Sumekar
G4A009019

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USA

Principal Supervisor

Prof. Randi J. Hagerman, M.D[1]

Indonesia

Principal Supervisor

dr. Tri Indah Winarni, M Si.Med.
NIP. 19660510 199702 2 001

Supervisor

Prof. dr. Sultana MH Faradz, PhD
NIP. 1952 0202 1979 01 2 004

Recognition,

Head of Master's Degree Program in Biomedical Science

Diponegoro University Post Graduate Program

Dr. dr. Winarto, Sp.MK, Sp.M(K)
NIP. 1949 0617 1978 02 1 001

1) Medical Director of the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D) Institute, Professor of Pediatrics, Endowed chair of Fragile X Research

STATEMENT OF ORIGINALITY

I hereby declare that this thesis is my own work and that to the best of my knowledge and belief, it contains no materials previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where do acknowledgement is made in the text.

Semarang, February 2012

Tanjung Ayu Sumekar

CURRICULUM VITAE

Personal Data

Name	: Tanjung Ayu Sumekar, M.D.
Gender	: Female
Place/ Date of Birth	: Semarang/ October 25th, 1985
Address	: Bukit Agung Blok E No. 37 Semarang
E-mail address	: tanjungayusumekar@ymail.com
Parents	: Ir. Mohamad Affan & Dwi Bhakti Asih
Spouse	: Mahdi Yuda Anindita, S.E.

Educational Background

1. High School in SMU 3 Semarang, 2000-2003.
2. Diponegoro University, Faculty of Medicine, Indonesia (Medical Doctor), 2003-2009.
3. Diponegoro University, Post Graduate Program (Master in Biomedical Sciences, Genetic Counseling Concentration), 2010 – present.
4. Research fellow, Medical Investigation of Neurodevelopmental Disorder (M.I.N.D) Institute, University of California-Davis Health System, 2010-2011.

Award

1. Beasiswa Unggulan (Excellent Scholarship), Ministry of Education and Culture of Republic Indonesia for Joint degree on MSc genetic counseling at the M.I.N.D. Institute University of California , Davis, 2009-2011.

Working Experience

1. Faculty member at Department of Physiology Faculty of Medicine, Diponegoro University, Indonesia, 2009 – present.
2. Research fellow, Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute, University of California Davis, Sacramento, California, USA, 2010-2011.

Membership in scientific/professional societies

Indonesian Medical Association

Research Experiences

1. **Sumekar TA**, Subakir. Antifungal activity test of buah merah (*Pandanus conoideus*) extract in vitro to the growth of *Pityrosporum ovale* in dandruff in collaboration with Department of Microbiology and Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Indonesia. 2007 (unpublished).
2. Hessl D, Schneider A, **Sumekar TA**, Cheung K, Hagerman P, Roid G. Intelligence Measurement in X Linked Intellectual Disability: Limitations, Solutions, and Where Do We Go From Here? Presented at the 15th International Wokshop in Fragile X Syndrome and XLMR in Berlin, Germany, September 4-7, 2011.
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15th International Wokshop in Fragile X Syndrome and XLMR in Berlin, Germany, September 4-7, 2011.

Courses and Training

1. Training Management of Emergency Patient. Faculty of Medicine, Diponegoro University in collaboration with Indonesian Medical Association, Semarang, June 28th, 2007
2. Advanced Life Cardiac Life Support. Indonesian Heart Association, Semarang, November 20-22, 2009
3. Medical Genetic Course : From Basic to Clinic. Faculty of Medicine Diponegoro University in collaboration with Department of Human Genetics Radboud University Nijmegen Medical Centre, January 25-27, 2010
4. 2nd International Seminar and Workshop on fragile X, autism, and related disorders. August 7, 2010. Semarang, Indonesia.
5. The Summer Institute on Neurodevelopmental Disorders on Neuro Disorders Across the Lifespan : Research in Practice. August 5-8, 2011. Sacramento, California.

LIST OF PUBLICATIONS

1. **Sumekar TA**, Winarni TI, Ashrani AA, Hagerman RJ. Monoclonal Gammopathy of Undetermined Significance in a man with fragile X-associated tremor ataxia syndrome (FXTAS). Case Reports in Genetics, volume 2011 (2011), Article ID 143132, doi:10.1155/2011/143132.
2. **Sumekar TA,** Winarni TI, Chonchaiya W, Adams E, Nguyen DV, Tassone F, Iwahashi C, Cheung K, Faradz SMH, Hagerman PJ, Hagerman RJ. FMRP and mRNA Do Not Explain Autism in Fragile X Premutation Boys. In preparation for publication.

ACKNOWLEDGEMENTS

First I offer my sincerest gratitude to my supervisor Prof. dr. Sultana MH Faradz, PhD for her encouragement and effort, and without her, this thesis would not have been completed. I would also like to express my deepest gratitude to Prof. Randi Hagerman, M.D. for her guidance, encouragement, and all of the wonderful opportunities that have been given to me during this research at the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute, University of California Davis, California. I would like to give my immeasurable thanks to dr. Tri Indah Winarni, MSi.Med, who has supported me throughout my thesis with her patience and knowledge. One simply could not wish for a better or friendlier supervisor.

My deep and sincere thank to Prof. Paul Hagerman, M.D., PhD for giving me the opportunity to learn in his laboratory and for all his guidance and also to Flora Tassone, PhD for providing me the chance to learn in her laboratory. I thank Paul's laboratory assistants especially Katherine Cheung and Christine Iwahashi, and Flora's laboratory assistants especially Joyce Lo, Nimrah Choudhary, and Kirin Basuta for sharing knowledge and skills in laboratory technique. I gratefully acknowledge the wonderful encouragement and loving of Louise Gane, M.S. which open my mind to keep the hope for the patients. I also thanks David Hessl, PhD for sharing his knowledge, advice and experience.

I wish to thank Mary Jae, M.D, Lulu Wang, M.D., and Lily Ngotran, M.D. for helping me taking medical history and physical examination of the patients. I acknowledge David Hessl, PhD, Andrea Schneider, PhD, and Susan Harris for

doing the IQ tests and assessing the autism diagnosis of the patients. We also thank Antoniya Boyd, Kylee Cook, and Floridette Abucayan for their contribution with data processing. To all Fragile X Team member at the M.I.N.D. Institute especially Michele Ono,M.S., Kylee Cook, Antonia Dobrinova, Emma Hare, Floridette Abucayan, Tasleem Chechi, Jacky Au, Cindy Johnston, Julie Morcillo, Patrick Adams, Jonathan Polussa, Jessica Famula, and Andrew Ligsay for their kind help regarding my research, introducing me to the American culture, and for such a great friendship throughout the year.

This work would have been imposible without the generous help and support of my colleagues in Indonesia. My acknowledge goes particularly to the head of Department of Physiology Faculty of Medicine Diponegoro University (FMDU) Prof. dr. Zainal Muttaqin, PhD, SpBS, the former dean of FMDU dr. Soejoto, SpKK (K) and the dean of FMDU dr. Endang Ambarwati, SpKFR, the head of Biomedical Science Post Graduate Program of Diponegoro University Dr. dr. Winarto, Sp.MK, SpM(K), and the director of Center for Biomedical Research (Cebior) FMDU, Prof dr. Sultana MH Faradz, PhD. I gratefully acknowledge dr. Hardian for his helps, suggestions especially in statistical part and support from the early stage of this research. I wish to thanks Dr. dr. Andrew Johan, MSi, dr. Ismed Yusuf, SpKJ, dr. Agustini Utari, MSi.Med, Sp.A, and Dr.drg. Henry Setyawan S, MSc, for the suggestion and advices to improve my thesis.

I thank the M.I.N.D. Institute, University of California Davis and the Cebior FMDU for providing me the best place to study and do the research. This work has been funded by Beasiswa Unggulan BPKLN Ministry of National Education and Culture Republic of Indonesia. Many thanks to the staffs of Beasiswa Unggulan project especially Dr. Abe Susanto. I acknowledge the

support from National Institute of Health Grants HD036071, HD02274, DE019583, DA024854, AG032119, AG032115, MH77554; National Center for Resources UL1RR024146; Health and Human Services Administration of Developmental Disabilities Grant 90DD05969.

To all the staffs of Division of Human Genetics Cebior Faculty of Medicine Diponegoro University in Semarang Indonesia for your cooperation and friendship you have shared over the years dr. Farmaditya EP Mundhofir, MSi.Med, dr. Muflihatul Muniroh, MSi.Med, dr. Nani Maharani, MSi.Med, Dina Ardiana, S.Sos, Wiwik Lestari, Rita Indiarti, Lusi Suwarsi, Dwi Kustiyani, and Inthus Apriasa, A.Md. I would give my special thanks to my friends especially batch 4 members of S2 Genetic Counseling drg. Bremmy Laksono, dr. Fanti Saktini, dr. Ferdy Kurniawan Cayami, dr. Galuh Dyah Nur Astuti, dr. Gana Adyaksa, dr. Puspita Kusuma Dewi, dr. Rahajeng Nareswari Tunjungputri, dr. Tuntas Dhanardhono, and dr. Siti Nurhajjah that always give me an endless support during this research.

I am deeply indebted to my parents, Mohamad Affan and Dwi Bhakti Asih, also my parents in law, Bambang Sudibyo and Budi Rahayu for always supporting me. I most thankful my husband, Mahdi Yuda Anindita, my sister Arum Sekarrini and my brother Riando Adi Nagara for unconditional love, understanding and tolerance during my study. Without their support, I do not think that I could overcome the difficulties during these years.

Finally, I would like to thank all of the patients and their families who participated in this research, this research would not be possible without their involvement and cooperation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADHD : Attention Deficit Hyperactivity Disorder

ADOS : Autism Diagnostic Observation Schedule

AMPA : α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid

ARC : Activity-regulated Cytoskeleton-associated protein

ASD : Autism Spectrum Disorder

CGG : Cytosine Guanine Guanine

CNS : Central Nervous System

CYFIP1 : Cytoplasmic FMR1 Interacting Protein 1

ELISA : Enzyme-Linked Immunosorbent Assay

FMR1 : Fragile X Mental Retardation 1

FMRP : Fragile X Mental Retardation Protein

FXPOI : Fragile X-associated Primary Ovarian Syndrome

FXS : Fragile X Syndrome

FXTAS : Fragile X-associated Tremor Ataxia Syndrome

GABA : Gamma Amino Butyric Acid

HERC : Hect domain and RLD

HPA : Hypothalamus-Pituitary-Adrenal

ID : Intellectual Disabilities

KO : Knock-Out

LTD : Long-Term Depression

MAPK : Mitogen-activated Protein Kinase

mGluR1 : metabotropic Glutamate Receptor 1

mGluR5 : metabotropic Glutamate Receptor 5

MMP-9 : Matrix Metalloproteinase-9

mRNA : messenger Ribonucleic Acid

mTOR : mammalian Target of Rapamcin

PBS : Phosphate Buffer Saline

PBS-T : Phosphate Buffer Saline containing 0.05% polyoxyethylene sorbitan monolaurate

PDDNOS : Pervasive Developmental Disorder Not Otherwise Specified

PCR : Polymerase Chain Reaction

PNS : Peripheral Nervous System

POI : Primary Ovarian Insufficiency

PSD-95 : Post Synaptic Density Protein-95

PTEN : Phospatase and Tensin Homolog

RNA : Ribonucleic Acid

SD : Standard Deviation

SHANK3 : SH3 and multiple ankyrin repeat domains

UTR : Untranslated Region

WAIS-III : Wechsler Adult Intelligence Scale, Third Edition

WASI : Weschler Abbreviated Scale of Intelligence

WISC-III : Wechsler Intelligence Scale for Children, Third Edition

WISC-IV : Wechsler Intelligence Scale for Children, Fourth Edition

WPPSI : Wechsler Preschool and Primary Scales of Intelligence

LIST OF APPENDICES

ABSTRACT

Introduction: Clinical manifestation of autism spectrum disorders (ASD) and cognitive deficits have been reported to be associated with fragile X premutation. These may be related to variations in CGG repeat lengths, *FMR1* protein (FMRP) levels, background genetics effects and/or environmental toxins. FMRP is an RNA-binding protein that regulates the translation of a number of other genes that are important for synaptic developments and plasticity.

Objective: This study was done to identify the correlation between cognitive, social deficits, FMRP levels and CGG repeats in males with the *FMR1* premutation utilizing the new enzyme-linked immuno assay (ELISA) assessment of FMRP expression.

Methods: This study included 31 males with the *FMR1* premutation ranging from age 2.96 to 27.36 (mean 13.7 ± SD 6.32) years old participated in Fragile X Families research project at the UC Davis M.I.N.D. Institute between 2006 and 2011. All subjects were confirmed to carry the *FMR1* premutation. They undergone a full medical history and physical examination. Assesment of cognitive ability and specific measures for ASD were completed. ELISA technique was used to measure the level of FMRP.

Results: FMRP levels were measured from the lymphocytes with mean level was 1.5 ± 0.55 with mean level of CGG repeats was 101.5 ± 41.10. FMRP levels were not correlated with ADOS communication score (p=0.420), ADOS social interaction score (p=0.641), ADOS total score (p=0.517), nor FSIQ (p=0.125). CGG repeats were also not correlated with ADOS communication score (p=0.454). ADOS social interaction score (p=0.731). ADOS total score (p=0.660), nor FSIQ (p=0.571).

Conclusion: There were no correlation between FMRP levels, ADOS scores, and FSIQ nor CGG repeats, ADOS scores, and FSIQ in males with the *FMR1* premutation.

Key words : IQ, ASD, FMRP, *FMR1* premutation

ABSTRAK

Latar Belakang: Manifestasi klinis yang terdiri atas *autism spectrum disorders* (ASD), dan defisit kognitif dilaporkan berhubungan dengan fragile X premutasi. Hal tersebut mungkin disebabkan karena variasi jumlah CGG *repeat*, kadar FMRP, pengaruh genetik, dan/atau faktor lingkungan. FMRP merupakan suatu protein pengikat RNA yang mengatur translasi gen-gen yang penting untuk perkembangan dan plastisitas sinaps.

Tujuan : Penelitian ini dilakukan untuk mengidentifikasi hubungan antara manifestasi klinik antara lain defisit kognitif dan sosial dengan kadar FMRP dan CGG *repeat* pada laki-laki dengan premutasi gen *FMR1* menggunakan teknik baru *enzyme-linked immuno assay* (ELISA) untuk mengukur kadar FMRP.

Metode : Penelitian ini mencakup 31 laki-laki dengan premutasi gen *FMR1* dengan rentang usia 2.96 sampai 27.36 tahun (rata-rata 13.7 ± SD 6.32) yang berpartisipasi dalam proyek penelitian Fragile X Families di UC Davis M.I.N.D. Institute pada tahun 2006 sampai 2011. Semua subjek telah dikonfirmasi membawa premutasi gen *FMR1*. Riwayat medik lengkap dan pemeriksaan fisik dilakukan oleh klinisi. Penentuan kemampuan kognitif dan penilaian spesifik untuk ASD dilakukan selama evaluasi klinik. Teknik ELISA untuk mengukur kadar FMRP .

Hasil: Kadar FMRP diukur dari limfosit dengan kadar rata-rata 1.5±0.55 dan nilai rata-rata CGG repeat adalah 101.5 ± 41.10. Kadar FMRP tidak berhubungan dengan skor komunikasi pada ADOS (p=0.420), skor interaksi sosial (p=0.641), Skor total (p=0.517), maupun skor total IQ (p=0.125). CGG *repeat* juga tidak berhubungan dengan skor komunikasi pada ADOS (p=0.454), skor interaksi sosial (p=0.731), Skor total (p=0.660), maupun skor total IQ (p=0.571).

Kesimpulan: Tidak terdapat hubungan antara kadar FMRP dengan skor ADOS dan skor total IQ serta tidak terdapat hubungan antara CGG *repeat* dengan skor ADOS dan skor total IQ pada laki-laki dengan premutasi gen *FMR1*.

Kata Kunci : IQ, ASD, FMRP, premutasi gen *FMR1*

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Tanjung Ayu Sumekar
G4A009019

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Head of Master's Degree Program in Biomedical Science

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Dr. dr. Winarto, Sp.MK, Sp.M(K)
NIP. 1949 0617 1978 02 1 001

1) Medical Director of the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D) Institute, Professor of Pediatrics, Endowed chair of Fragile X Research

DEVELOPMENT MONITORING SHEET
EXAMINATION OF THESIS

I, who signed below stated that I agree with **Correction of Thesis** which was submitted on March 27 th, 2012 from :

Name of student : dr. Tanjung Ayu Sumekar
Student Identification Number : G4A009019
Title : *Correlation Between IQ, Autism Spectrum Disorders and FMRP Levels In Males With The FMR1 Premutation*

NO	NAME	RESOURCE	SIGNATURE	DATE
1.	dr. Tri Indah Winarni, M.Si.Med, PA	Supervisor		26/5/2012
2.	Prof. dr. Sultana MH Faradz, PhD	Co-supervisor		16/6 2012
3.	dr. Ismed Yusuf, Sp.KJ	Resource		29/6 2012
4.	dr. Agustini, Sp.A, M.Si.Med	Resource		1/6 2012
5.	Dr.drg. Henry Setiawan S, M.Sc	Biostatistic		24/5 2012
6.	Dr.dr. Winarto, DMM,Sp.MK, Sp.M (K)	Resource		22 May 2012
7.	Dr.dr. Andrew Johan, M.Si	Resource		15 May 2012
8.	dr. Neni Susilaningsih, M.Si	Resource		14 May 2012

CORRELATION BETWEEN IQ, AUTISM SPECTRUM DISORDERS, AND FMRP LEVELS IN MALES WITH THE FMR1 PREMUTATION

Tanjung Ayu Sumekar, Tri Indah Winarni, Sultana MH Faradz

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Kata Kunci : IQ, ASD, FMRP, premutasi gen *FMR1*