

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

***HUBUNGAN ANTARA IQ, AUTISM SPECTRUM DISORDER,
DAN KADAR FMRP PADA LAKI-LAKI DENGAN PREMUTASI
GEN FMRI***



THESIS

**Submitted to fulfill the assignment and fit-out requisite in passing
Post-graduate Program Majoring Biomedical Science Genetic
Counseling Concentration Diponegoro University Semarang**

Magister of Biomedical Sciences

**Tanjung Ayu Sumekar
G4A009019**

**POST GRADUATE PROGRAM
DIPONEGORO UNIVERSITY
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**Tanjung Ayu Sumekar
G4A009019**

Has been defended on March 27, 2012 in front of Defend Committee

USA

Principal Supervisor



Prof. Randi J. Hagerman, M.D¹

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. Hessler 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 Workshop in Fragile X Syndrome and XLMR in Berlin, Germany, September 4-7, 2011.
3. Winarni TI, Chonchaiya C, **Sumekar TA**, Ashwood P, Morales GM, Tassone F, Nguyen D, Faradz SMH, Hagerman P, Hagerman R. Immune Mediated Disorders Among Female Carriers Of Fragile X. Presented at the

15th International Workshop 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.

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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
<i>FMR1</i>	: 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	: Phosphatase 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	: Wechsler 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

1. Informed consent to participate in research study
2. Institutional Review Board of UC Davis

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 $13.7 \pm SD 6.32$) 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 $13.7 \pm SD 6.32$) 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*

THESIS

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G4A009019**

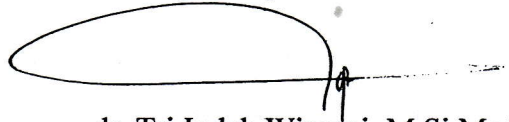

Has been defended on March 27, 2012 in front of Defend Committee

USA

Indonesia

Principal Supervisor

Principal Supervisor



Prof. Randi J. Hagerman, M.D.¹

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

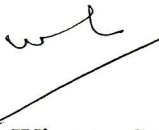
Supervisor



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



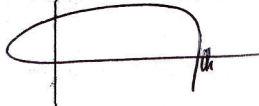
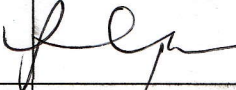


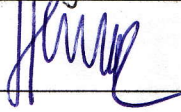



Dr. dr. Winarto, Sp.MK, Sp.M(K)
NIP. 1949 0617 1978 02 1 001

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

**DEVELOPMENT MONITORING SHEET
EXAMINATION OF THESIS**

I, who signed below stated that I agree with Correction of Thesis which was submitted on March 27th, 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		25/2012 5
2.	Prof. dr. Sultana MH Faradz, PhD	Co-supervisor		16/6 2012
3.	dr. Ismed Yusuf, Sp.KJ	Resource		23/6 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 FMRI PREMUTATION

Tanjung Ayu Sumekar, Tri Indah Winarni, Sultana MH Faradz

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, FMRI 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 FMRI premutation utilizing the new enzyme-linked immuno assay (ELISA) assessment of FMRP expression.

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

Key words : IQ, ASD, FMRP, FMRI premutation

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Tanjung Ayu Sumekar, Tri Indah Winarni, Sultana MH Faradz

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 $13.7 \pm SD 6.32$) 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 social ($p=0.731$), 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*