

**ANTINUCLEAR ANTIBODIES IN FRAGILE X SYNDROME  
PATIENTS TREATED WITH AND WITHOUT  
MINOCYCLINE**

*ANTINUKLEAR ANTIBODI PADA PASIEN SINDROM FRAGIL X  
DENGAN DAN TANPA PENGobatan MINOCYCLINE*



**Thesis**

**Submitted in Fulfillment of the Assignment and Fit-Out Requisite  
For the Degree of Biomedical Science  
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**Nuva Rafika  
22010110400093**

**POSTGRADUATE PROGRAM ON BIOMEDICAL SCIENCE  
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## **DECLARATION**

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material 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 education.

Semarang, 19 January 2013

Nuva Rafika

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Nuva Rafika

## LIST OF ABBREVIATIONS

FXS	: Fragile X syndrome
ID	: Intellectual disability
<i>FMRI</i>	: Fragile X mental retardation 1 (for human)
DNA	: Deoxyribonucleic acid
FMRP	: Fragile X mental retardation protein (for human)
MMP-9	: Matrix metalloproteinase-9
ALS	: Amyotrophic lateral sclerosis
<i>Fmr1</i>	: Fragile X mental retardation 1 (for animal)
<i>dFMRI</i>	: Drosophila fragile X gene (for animal)
ANA	: Antinuclear antibody
MIA	: Minocycline induced autoimmunity
DIL	: Drug-induced lupus
SLE	: Systemic lupus erythematosus
IQ	: Intelligence quotient
UTR	: Untranslated region
ASD	: Autism spectrum disorder
PDD-NOS	: Pervasive developmental disorder not otherwise specified
FXTAS	: Fragile X-associated tremor/ataxia syndrome
FXPOI	: Fragile X primary ovarian insufficiency
PCR	: Polymerase chain reaction
CVS	: Chorionic villus sampling
ADHD	: Attention deficit hyperactivity disorders
SSRI	: Serotonin reuptake inhibitors
mGlur	: Metabotropic glutamate receptors
mGlur5	: Metabotropic glutamate receptors5
CNS	: Central nervous system
GABA	: Gamma-aminobutyric acid
HSR	: Hypersensitivity syndrome reaction

SSLR	: Serum sickness like reaction
SOD	: Single organ dysfunction
LFT	: Liver functioning test
SSc	: Systemic sclerosis
SS	: Sjogren's syndrome
IFA	: Indirect fluorescent assay
FITC	: Fluorescein isothiocyanate
MCTD	: Mixed connective tissue disease
ADOS	: Autism diagnostic observation schedule
ADI-R	: Autism diagnostic interview- revised
DSM-IV	: Diagnostic and statistical manual of mental disorders-fourth edition
WPPSI-III	: Wechsler preschool and primary scale of intelligence-third edition
WISC-III	: Wechsler intelligence scale for children-third edition
WISC-IV	: Wechsler intelligence scale for children-fourth edition
WASI	: Wechsler abbreviated scale of intelligence
WAIS-III	: Wechsler adult intelligence scale-third edition
LFT	: Liver functioning test



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## CURRICULUM VITAE

### **Personal Data**

Name : Nuva Rafika, S. Psi  
Address : Jl. Sabut Blok E. 10 No. 10 Pondok Kelapa, Jakarta 13450  
Cell phone : 081318183106  
Place & Date of Birth : Pekalongan/ June 29<sup>th</sup>, 1987  
Sex/ Marital Status : Female/ Single

### **Educational Background**

2011 – Present Post Graduate Program of Diponegoro University, Master in Biomedical Science Majoring Genetic Counseling, Semarang (Joint Program with University of California Davis, USA)  
2005-2009 Bachelor Degree of Psychology at Paramadina University, Jakarta  
2003-2005 High School at Cambridge High School, Abu Dhabi, UAE

### **Academic achievements:**

#### **Scholarships**

2011-Present Excellence Scholarship (*Beasiswa Unggulan*) from Ministry of National Education Republic Indonesia  
2008-2009 Paramadina University Education Aid Scholarship (*Bantuan Pendidikan Universitas Paramadina*) from PT. Djarum Bakti Pendidikan  
2007-2008 Scholarship for High Academic Achievement (*Peningkatan Prestasi Akademik*) from Directorate General for Higher Education, Ministry of National Education, Indonesia  
2006-2007 Scholarship for Student Aid (*Bantuan Belajar Mahasiswa*) from Directorate General for Higher Education, Ministry of National Education Republic Indonesia

#### **Publications**

2009 Rafika, N. ALEXITHYMIA: A descriptive study among a sample of nurses at a hospital in Jakarta. 2009. *Jurnal Inquiry: Jurnal Ilmiah Psikologi Vol 2, No. 1, ISSN: 1979-7273 pp. 12-25.*  
26<sup>th</sup> July 2012 Presented preliminary research on ‘Antinuclear antibodies in Fragile X Syndrome Patients Treated with Minocycline’

at 13<sup>th</sup> International Fragile X Conference in Miami, Florida hosted by National Fragile X Foundation.

**Working experiences:**

March 2011 – June 2011

Part-time as assessor for psychological testings at Lembaga Psikologi Terapan (LPT), Jl. Karigarang No. 58, Semarang

November 2009 – November 2010

Corporate secretary and purchasing (import division) for PT. TRABAUD AROMATIC LABORATORIES, Cipendawa, Naragong Km 7, Bekasi

June 2009 – September 2009

Staff of human resources (HR) and secretary of president director for PT. BOLEH NET INDONESIA, Cyber Building 10<sup>th</sup> Floor, Kuningan, Jakarta

2009

Intelligence quotient (IQ) assessor using Standford Binet Test for children with special needs in SDN Meruya Selatan 06 Pagi, Jakarta

2004

Librarian assistant of the Cambridge High School, Abu Dhabi, UAE

2004

Kindergarten assistant of the Cambridge High School, Abu Dhabi, UAE

**Organizational experiences:**

2008-2009

Mentor and facilitator for the student orientation *Graha Mahardika Paramadina* (GMP) at Paramadina University, Jakarta

2007-2008

Vice President, Treasurer and Secretary of the Paramadina Debating House, Paramadina University, Jakarta

2007-2008

Chief coordinator and admin for Information Technology Relations of *Himpunan Mahasiswa Psikologi* (HIMA Psi) Paramadina University, Jakarta

2007

Facilitator of Paramadina Leader's Camp III at Situ Gunung, Sukabumi

2006-2007

Staff of internal research for Executive Student Body – *Badan Eksekutif Mahasiswa* (BEM) Paramadina University, Jakarta

## ABSTRACT

**Background:** Minocycline is a targeted treatment for fragile X syndrome (FXS) as it inhibits matrix metalloproteinase-9 (MMP-9) that is upregulated in FXS. Minocycline side effects may also cause autoimmune symptoms that may be detected with positive antinuclear antibodies (ANA) titers. The study investigates the prevalence of positive ANA titers in individuals with FXS who have been treated with and without minocycline.

**Methods:** ANA titers of patient with FXS who are on minocycline and without minocycline were collected. ANA positivity was compared to variables including age, sex (male and female), full scale IQ, autism diagnosis (autism, ASD and no autism), molecular data (full and mosaic), and concomitant medications (may cause DIL or not causing DIL) in patients with and without minocycline. Duration and dosage in patients with minocycline were also examined. Titers and patterns commonly seen in this population are observed.

**Results:** From a total of 48 patients on minocycline, 27.08% had ANA positivity (titers  $\geq$  1:80). While 23 patients without minocycline had ANA positivity of 26.08%. There was no correlation between ANA in FXS patients with and without minocycline ( $p=0.318$ ). ANA positivity was also not correlated with the variables examined. Percentage of ANA positivity was seen higher in females treated with minocycline (5 out of 9 patients). The most common titer in ANA positivity was 1:160 for both with and without minocycline. A negative titer of 1:40 was also seen high in patients with minocycline. Homogeneous-speckled was the most common ANA pattern.

**Conclusions:** ANA positivity was not associated with minocycline treatment in FXS. However, the prevalence of ANA positivity in patients with and/or without minocycline is higher than reported in children with autism and general population. No patients were symptomatic for autoimmune diseases, however clinicians should still continue to monitor for any possible side effects including autoimmune symptoms in patients on minocycline.

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Keywords: Fragile X syndrome; minocycline; antinuclear antibodies; ANA profile.

## ABSTRAK

**Latar Belakang:** Minocycline merupakan terapi target untuk pengobatan penderita sindrom fragil X (FXS) yang dapat memperlambat pembentukan *matrix metalloproteinase-9* (MMP-9) yang tinggi di FXS. Efek samping minocycline juga dapat mengakibatkan gejala autoimun yang dapat dideteksi dengan titer antinuklear antibody (ANA) yang positif. Penelitian ini menginvestigasi tingkat kejadian titer ANA pada individu dengan FXS dengan dan tanpa pengobatan minocycline.

**Metode:** Pemeriksaan ANA dilakukan pada individu dengan FXS dengan dan tanpa pengobatan minocycline. Positif ANA telah dibandingkan dengan variabel-variabel termasuk usia, jenis kelamin (laki-laki dan perempuan), IQ, diagnosis autisme (autisme, ASD dan tidak autisme), data molekuler (full dan mosaik), obat-obatan yang digunakan (yang dapat menyebabkan DIL dan yang tidak) pada pasien dengan dan tanpa minocycline. Durasi serta dosis minocycline juga diteliti. Titer dan pola yang umum pada studi direkam.

**Hasil:** Dari sejumlah 48 pasien dengan minocycline memiliki ANA positif (titer  $\geq$  1:80) sebesar 27,08% dan pada 23 pasien tanpa pengobatan minocycline menunjukkan ANA positif sebesar 26,08%. ANA tidak ditemukan perbedaan yang signifikan dengan seluruh variabel yang diteliti. Persentase ANA positif terlihat lebih banyak pada pasien perempuan yang menggunakan pengobatan minocycline (5 dari 9 pasien). Titer 1:160 merupakan titer paling umum pada ANA positif pada pasien dengan dan tanpa minocycline. Titer negative sebesar 1:40 juga terlihat tinggi pada pasien dengan minocycline. Pola *homogeneous-speckled* merupakan pola ANA paling umum terlihat pada penelitian.

**Kesimpulan:** ANA positif tidak ditentukan oleh pengobatan minocycline pada pasien FXS. Prevalensi positif ANA pada pasien dengan ataupun tanpa minocycline lebih tinggi dari yang dilaporkan pada anak-anak dengan autisme dan populasi umum. Tidak ada pasien yang tercatat memiliki gangguan autoimun, tetapi klinisi disarankan agar tetap memantau gejala-gejala autoimun yang kemungkinan dapat terjadi.

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Kata kunci: Fragile X syndrome; antinuklear antibody; minocycline; profil ANA.