

**ASSOCIATION OF *PDGFRA* GENE POLYMORPHISM AND
EARLY-ONSET MYOPIA IN SOUTH SUMATERA**

**HUBUNGAN ANTARA POLIMORFISME GEN *PDGFRA*
DENGAN MIOPIA USIA DINI DI SUMATERA SELATAN**



Thesis

**Submitted to fulfill the assignment and fit-out requisite
in passing Post-graduate Program**

Master of Biomedical Sciences

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PREFACE

One of the biggest eye diseases is nearsightedness (myopia). As a multifactorial disease, myopia can be caused by genetic or environmental factors. There are some risk factors for having early-onset myopia, such as sex, family history, corneal curvature, and genetic susceptibility. There is a need for information about these two risk factors that leads the author to write “**Association of *PDGFRA* gene polymorphism and early-onset myopia in South Sumatera**”.

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Author realised that this manuscript is not perfect. But, author hope this manuscript can provides more information about genetics in Indonesia especially in ophthalmology.

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ABBREVIATIONS

ARMS PCR	: Amplification Refractory Mutation System Polymerase Chain Reaction
CD140A	: Cluster Designation 140A, Clusters of Differentiation 140A
CEBIOR	: Center of Biomedical Research
cM	: CentiMorgan
COL1A1	: Collagen, Type I, Alpha 1
COL2A1	: Collagen, Type II, Alpha 1
D	: Dioptri
DNA	: Deoxyribose Nucleic Acid
EDTA	: Ethylenediaminetetraacetic Acid
FRAP1	: FK506 binding protein 12-Rapamycin Associated Protein 1
GEPIS	: Gene Expression Profiling In Silico
GWAS	: Genome Wide Association Study
HRM	: High Resolution Melting
HRMA	: High Resolution Melting Analysis
MYP3	: Myopia 3
MYP17	: Myopia 17
NCBI	: National Center for Biotechnology Information
NIH	: National Institutes of Health
NLM	: National Library of Medicine
PC	: Personal Computer
PCR	: Polymerase Chain Reaction
PDGF	: Platelet-derived Growth Factor
PDGFRA	: Platelet-derived Growth Factor Receptor, Alpha polypeptide
PDGFR2	: Platelet-derived Growth Factor Receptor 2
PI3	: Phosphatidil Inositol 3
qPCR	: Qualitative Polymerase Chain Reaction
RTK	: Receptor Tyrosine Kinase

SCORM	: Singapore Cohort study of the Risk factors for Myopia
SiMES	: Singapore Malay Eye Study
SINDI	: Singapore Indian Eye Study
SNP	: Single Nucleotide Polymorphism
SP2	: Singapore Prospective Study Program
SPSS	: Statistical Package for the Social Sciences
WHO	: World Health Organisation

GLOSSARY

- ARMS PC : PCR technique that used a pair universal primer and 1 allele specific primer. This technique will produced 1 control band and 1 inner band specific for 1 allele.
- Cataract : Partial or complete opacity on or in the lens or capsule of one or both eyes.
- Collagen : The principle protein of connective tissue.
- Conjunctivitis : Inflammation of conjunctiva.
- Cornea : The transparent part of the eye that covers the iris and the pupil and allows light to enter the inside.
- Corneal curvature : Radius of horizontal and vertical meridian of cornea.
- Fibroblast : Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules.
- GWAS : An analysis comparing the allele frequencies of all available polymorphic markers in unrelated patients with a specific symptom or disease condition, and those of healthy controls to identify markers associated with a specific disease or condition.
- HRMA : A simple and fast post-PCR analysis method used for identifying genetic variation in nucleic acid sequences based on PCR melting curve techniques.
- Hyperopia : A condition in which visual images come to a focus

behind the retina of the eye and vision is better for distant than for near objects, called also farsightedness.

- Keratitis : Inflammation of the cornea.
- Keratoconus : A non-inflammatory, usually bilateral protrusion of the cornea, the apex being displaced downward and nasally.
- Myopia : A condition in which the visual images come to a focus in front of the retina of the eye resulting in defective vision of distant objects--called also nearsightedness.
- Polymorphism : A common variation in the sequence of DNA among individuals, occurring in more than 1% of the population.
- Presbyopia : Defective accommodation and inability to focus for near vision because of loss of lens elasticity.
- Receptor : A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell.
- SNP : Common variations that occur in human DNA at a frequency of 1 every 1,000 bases.
- Steep cornea : Corneal refractive power of ≥ 48 diopters.

Association of *PDGFRA* Gene Polymorphisms and Early-onset Myopia in South Sumatera

ABSTRACT

Background: Myopia is a refractive error that may be caused by corneal curvature (CC) anomaly. The purpose of this study was to identify platelet-derived growth factor receptor alpha (*PDGFRA*) gene and to find a correlation between sex, family history, near work, lighting, outdoor activity, CC, *PDGFRA* gene polymorphisms, and early-onset myopia in South Sumatera tribes.

Method: Using a random sampling method, population-based, cross-sectional study included 100 subjects aged 18-40 years from Palembang, South Sumatera, Indonesia. Visual acuity was measured by Snellen Chart and CC was measured by manual keratometer. DNA sample from buccal swab was investigated with Amplification Refractory Mutation System PCR and visualized in agarose gel.

Result: Females were 4.21 times more likely to have early-onset myopia than male. Subjects with parental, sibling, and paternal grandparent history of myopia were 6.64, 3.55 and 3.58 times more likely to have early-onset myopia, respectively. Reading ≥ 6 times/week, reading > 2 hours/day and television viewing distance ≤ 60 cm were 2.95, 2.85 and 19.13 times more likely to have early-onset myopia, respectively. Median of corneal curvature for right eye was 7.73 (7.07-8.63) mm and left eye was 7.73 (7.04-8.69) mm. There was no difference between CC in myopic and normal subjects. Distribution of mutant allele in rs17084051, rs7677751, rs7682912, and rs2114039 were bigger in myopic subjects compared to normal subjects. Significant *p* value for association between *PDGFRA* gene polymorphism and early-onset myopia was found only in rs17084051 (*p* = 0.009) and rs7677751 (*p* = 0.001).

Conclusion: Mutant type allele A of rs17084051 and mutant type allele T of rs7677751 *PDGFRA* gene polymorphism, female sex, parental history of myopia, paternal grandparent history of myopia, sibling history of myopia, frequency of reading ≥ 6 times per week, duration of reading > 2 hours per day, and television viewing distance ≤ 60 cm are associated with early-onset myopia in South Sumatera tribes.

Keywords: myopia, early-onset myopia, polymorphism, SNP, *PDGFRA*, corneal curvature, myopia risk factor, Indonesia, South Sumatera

Hubungan Antara Polimorfisme Gen *PDGFRA* dan Miopia Usia Dini di Sumatera Selatan

ABSTRAK

Latar Belakang: Miopia adalah suatu kelainan refraksi yang dapat disebabkan oleh anomali kelengkungan kornea mata. Tujuan penelitian ini adalah untuk mengidentifikasi polimorfisme pada gen *platelet-derived growth factor receptor alpha (PDGFRA)* dan untuk mencari hubungan antara faktor risiko miopia, kelengkungan kornea, polimorfisme gen *PDGFRA* dengan miopia usia dini di Sumatera Selatan.

Metode: Sampel diambil secara acak dengan desain studi potong lintang yang melibatkan 100 subjek berusia 18-40 tahun dari kota Palembang, Sumatera Selatan. Ketajaman penglihatan diukur dengan Snellen *Chart* dan kelengkungan kornea diukur dengan keratometer manual. Sampel DNA diambil dari apus mukosa pipi dan diperiksa dengan *Amplification Refractory Mutation System PCR* lalu dibaca dengan gel agarosa.

Hasil: Perempuan memiliki kemungkinan terkena miopia usia dini 4,21 kali lebih besar dibandingkan laki-laki. Subjek dengan orang tua, saudara kandung, serta kakek nenek dari pihak ayah dengan riwayat miopia memiliki kemungkinan 6,64 kali, 3,55 kali, dan 3,58 kali lebih besar menderita miopia usia dini dibandingkan yang tidak. Subjek yang membaca ≥ 6 kali/minggu dan > 2 jam/hari kemungkinan menderita miopia usia dini 2,95 kali lebih besar daripada yang tidak. Subjek yang menonton televisi dengan jarak ≤ 60 cm memiliki kecenderungan menderita miopia usia dini 19,13 kali lebih besar dibandingkan yang tidak. Median nilai kelengkungan kornea pada mata kanan adalah 7,73 (7,07-8,63) mm dan mata kiri 7,73 (7,04-8,69) mm. Tidak ada perbedaan kelengkungan kornea antara subjek miopia dengan subjek normal. Distribusi alel mutan pada rs17084051, rs7677751, rs7682912, dan rs2114039 lebih besar pada kelompok miopia dibandingkan normal. Asosiasi antara polimorfisme gen *PDGFRA* dan miopia usia dini hanya ditemukan pada rs17084051 ($p = 0.009$) dan rs7677751 ($p = 0.001$).

Kesimpulan: Alel mutan A pada rs17084051 dan alel mutan T pada rs7677751 polimorfisme gen *PDGFRA*, perempuan, riwayat orang tua dan saudara kandung dengan miopia, riwayat kakek nenek dari pihak ayah dengan miopia, membaca ≥ 6 kali/minggu dan > 2 jam/hari, menonton televisi dengan jarak ≤ 60 cm berasosiasi dengan miopia usia dini pada suku Sumatera Selatan, Indonesia.

Kata kunci: miopia, miopia usia dini, polimorfisme, SNP, *PDGFRA*, kelengkungan kornea, faktor risiko miopia, Indonesia, Sumatera Selatan.