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Short Communication

Does *FOXP2* gene polymorphism affect the duration of orogastric tube use in moderate to late preterm neonates? A cross-sectional study in Indonesia

Mauliza Mauliza[1], Herlina Dimiati[2*], Muslim Akmal[3] and Imran Imran[4]

[1]Doctoral Program in Medical Sciences, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [2]Department of Pediatrics, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [3]Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [4]Department of Neurology, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

*Corresponding author: herlinadimiati@usk.ac.id

Abstract

Premature and low birth weight neonates often struggle with oral intake due to immaturity or respiratory distress. Forkhead box protein 2 gene (*FOXP2*) is predicted to influence oral feeding ability in newborns, but studies assessing the role of this gene in influencing oral feeding ability are limited. The aim of this study was to investigate the role of *FOXP2* gene polymorphism, particularly single nucleotide polymorphism (SNP) rs17137124, on the duration of orogastric tube (OGT) use in moderate to late preterm neonates. A multi-center cross-sectional study was conducted in Lhokseumawe, Aceh, Indonesia, from September 2021 to August 2023, involving neonates with 32–36 weeks gestational age. The DNA samples were isolated from the saliva, amplified using polymerase chain reaction (PCR), and the *FOXP2* gene was sequenced. The associations between *FOXP2* gene polymorphisms and other plausible factors on the duration of OGT use were determined using Chi-squared test, Fisher's exact test or Pearson correlation as appropriate. Preterm neonates with the CC genotype had the longest OGT use, averaging 3 days (39.1%). TT genotype preterm neonates required OGT use for 4, 5, and 6 days (each 33.3%), while CT genotype neonates predominantly required it for 4 days (41.7%). No significant association was found between *FOXP2* genotypes and OGT use duration (p=0.233). Similarly, neonates with C allele required OGT use for 3 and 4 days, while those with T allele mostly required between 4 and 6 days, with no significant association (p=0.110). Analysis using dominant (p=0.109) and recessive models (p=0.481) also showed no significant associations with OGT use duration. However, the study found significant associations between delivery mode (p=0.002) and gestational age (p=0.001) with duration of OGT use in preterm neonates. This study highlights that *FOXP2* polymorphisms have limited association with the duration of OGT use among preterm neonates.

Keywords: Neonate, preterm, polymorphism, *FOXP2*, orogastric tube

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Introduction

Preterm neonates face challenges due to immature gastrointestinal system and delays of enteral nutrition initiation, which can result in poor feeding, nutritional deficits, and growth restrictions [1]. Development of gag and oral reflexes starts at 12–16 weeks of gestational age, with sucking and swallowing emerging at 28 weeks of gestational age, and coordinated suck-swallow-breathe at 32–34 weeks of gestational age [2]. Term neonates have better sucking abilities due to the

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development of nervous tissue by 28 weeks of gestational age, which is vital for meeting nutritional needs [3]. In contrast, preterm neonates may struggle with underdeveloped oromotor function, increasing the risk of malnutrition [4]. Therefore, mastering oral feeding is crucial for preterm neonates' hospital discharge [5]. Most preterm neonates require days or even weeks to develop oral feeding skills, with improper feeding leading to acute and long-term morbidity, prolonged hospital stays, and higher care costs [6]. Enteral feeding via orogastric tube (OGT) is therefore widely used clinically to support nutrition in preterm neonates [7].

A significant progress has been made in understanding molecular mechanisms regulating muscle and nerve interaction for speech and oral feeding [6,8]. Salivary protein expression of Forkhead box protein 2 (*FOXP2*) has been associated with successful oral feeding in preterm neonates [9]. *FOXP2*, a transcription factor, plays a role in developing motor control circuits; mutations in *FOXP2* gene are associated with severe speech and language disorders [10,11]. Feeding and sucking behaviors in preterm neonates involve neural pathways similar to language [12]. Single nucleotide polymorphism (SNP) rs17137124 in *FOXP2* is known to affect speech skills in preterm neonates [10]. However, studies assessing the impact of this SNP on oral feeding are limited. Therefore, further research is needed to understand the impact of *FOXP2* polymorphism on OGT use, especially in moderate to late preterm neonates. To the best of our knowledge, no studies have investigated the effect of *FOXP2* polymorphism on the duration of OGT use in preterm neonates. The aim of this study was to investigate the effect of *FOXP2* polymorphism, particularly SNP rs17137124, on OGT use duration in moderate to late preterm neonates.

Methods

Study setting and design

A multi-center cross-sectional study was conducted at the neonatal intensive care units (NICUs) of four hospitals in Lhokseumawe, Aceh, Indonesia—Cut Meutia Hospital, Abby Hospital, Metro Medical Center Hospital, and Prima Inti Medika Hospital—from September 2021 to August 2023. Preterm neonates were included in this study and saliva samples were collected for deoxyribonucleic acid (DNA) isolation. The DNA isolation was performed at the Laboratory of Integrated Research, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia. The DNA amplicons were then sent to 1st BASE Malaysia via PT. Genetic Science Jakarta, Indonesia, for further analysis. The polymerase chain reaction (PCR) amplification was conducted and subsequently analyzed through restriction fragment length polymorphism (RFLP) analysis. To identify *FOXP2* rs17137124 genotypes, agarose gel electrophoresis was performed. The sequences of the patients were compared with the reference human *FOXP2* sequences.

Sample and sampling method

The population proportion estimation formula was employed for sample size calculation [13]. Due to the absence of previous studies, a population proportion of p=0.5 was utilized. The margin of error (E) was set at 0.05, and a 95% confidence level was selected. Consequently, a minimum sample size of 50 preterm neonates was required. Consecutive sampling was used to select the neonates.

Patients and criteria

Preterm neonates were included as samples. Inclusion criteria for the present study were: (1) preterm neonates; (2) gestational age of 32–36 weeks; (3) normal vital signs; and (4) no congenital abnormalities in the mouth. All neonates that had congenital abnormalities such as intracranial hemorrhage, necrotizing enterocolitis, seizure, craniofacial malformation, cyanotic congenital heart disease, or omphalocele were excluded.

Saliva collection and storage

Saliva samples from the preterm neonates were collected using an oral swab, which was placed under the tongue or against the inner cheek. The swab was kept in place for 1–2 minutes to ensure it was moistened with saliva. After collection, the swab tip was inserted into a sterile tube containing 2 mL of DNA/RNA Shield (Zymo Research, Irvine, California, USA). The swab handle

was removed to avoid contamination. The tube was then stored at -20°C until it was used for further analysis.

DNA isolation

DNA isolation was performed at the Laboratory of Integrated Research, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia. DNA isolation from the saliva sample was performed using Quick DNA Miniprep Kit (Zymo Research, Irvine, California, USA), following the manufacturer's instructions. Briefly, the saliva sample was transferred to a microcentrifuge tube, and lysis buffer was added as specified in the manufacturer's protocol. The mixture was thoroughly mixed to lyse the cells. The lysed sample was then transferred to a DNA binding column placed in a collection tube. After centrifugation, wash buffer was added to remove impurities, and the column was centrifuged again. Elution buffer was added to release the purified DNA, which was then collected in a clean tube and stored at -20°C. The purified DNA was sent to 1st BASE Malaysia via PT. Genetic Science, Jakarta, Indonesia, for further analysis.

PCR amplification

The *FOXP2* amplification was performed using forward primer (5'→3') GGTTCCTACAGCAGTATCATGG and reverse primer (3'→5') TTATCTGCACCAATGGAAGG to achieve a final concentration of 50 pM [14]. A 25 µL PCR reaction mixture was prepared containing 1 µL of each primer, 12.5 µL of GoTaq Green PCR Master mix (Promega Corporation, Madison, Wisconsin, USA), and 120 ng of DNA template. The reaction was carried out using a Bio-Rad thermal cycler (Bio-Rad Laboratories Inc, Hercules, California, USA) with an initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 94°C for 45 s, annealing at 57°C for 45 s, and extension at 72°C for 45 s, with a final extension at 72°C for 10 min.

RFLP analysis

A total of 10 µL of PCR amplicon was combined with 2 µL of *BspTI* restriction enzyme (Thermo Scientific, Waltham, Massachusetts, USA) and 3 µL of NE-buffer in a PCR vial. The mixture was gently vortexed to ensure thorough mixing of the components. The reaction mixture was incubated at 37°C for 24 h for restriction enzyme digestion. Subsequently, the products were visualized by electrophoresis in a 2% agarose gel stained with ethidium bromide. DNA bands were visualized under ultraviolet (UV) light, captured, and compared to DNA ladders for analysis.

DNA sequencing

The results of PCR were also sequenced using an ABI 3730xl Genetic Analyzer (Applied Biosystems, Massachusetts, USA) to identify the *FOXP2* rs17137124 genotypes. The sequences were then compared with the reference human *FOXP2* sequence [15].

Study variables

The independent variable of the study was *FOXP2* polymorphism. The *FOXP2* rs17137124 polymorphism is a single nucleotide change, classified into two alleles: C and T; and three possible genotypes: CC, CT, and TT. The dependent variable was the duration of OGT use in preterm neonates. The duration of OGT use referred to the period during which the feeding tube was employed to provide nutrition until the neonates demonstrated the ability to maintain adequate nutrition through oral feeding. The duration of OGT use was presented in day.

In addition, plausible factors (mother characteristics and neonatal clinical characteristics) that might be associated with the duration of OGT use were also assessed. Mothers' data, including age, gravida status, parity status, and delivery mode, were documented. Age was recorded as the mother's age at the time of delivery. Gravida status referred to the number of pregnancies the mother had, including the current pregnancy, and was classified as primigravida for a mother who was pregnant for the first time, and multigravida for the mother who had been pregnant more than once. Parity status referred to the number of pregnancies resulting in live births, classified as 0–1 and >1. The delivery mode was classified based on the method of childbirth, vaginal delivery or cesarean section.

Preterm neonates' data, including sex, gestational age, first- and five-minute appearance, pulse, grimace, activity and respiration (APGAR) score, weight at birth, length at birth, and length

of stay, was documented. Sex was recorded based on observable physical characteristics. Gestational age was calculated using the Ballard score. APGAR score was obtained at the first and five-minute immediately after birth delivery. Weight at birth and length at birth were measured immediately after delivery. The length of stay was recorded as the total number of days from birth until discharge. The Ballard score was used to estimate newborn gestational age through assessments of physical and neuromuscular maturity. Physical maturity was evaluated based on skin texture, lanugo, plantar creases, breast tissue, eye/ear formation, and genital development, with each characteristic maturity being scored. The total score estimates the gestational age, with higher scores indicating greater maturity. Detailed descriptions of the scores for each component of physical maturity can be found elsewhere [16]. APGAR score assesses neonatal health immediately after birth using five criteria: appearance, pulse, grimace response, activity, and respiration. Each criterion is rated from 0 to 2, with 2 being the best score. Detailed descriptions of the scores for each component of APGAR component have been described elsewhere [17]. The total score ranges from 0 to 10, with scores between 7 and 10 indicating good health and below 7 suggesting the need for immediate medical attention.

Statistical analysis

Continuous data were presented as mean and standard deviation (for normally distributed data) and as median (minimum-maximum) for non-normally distributed data; categorical data were presented as frequency and percentages. The Shapiro-Wilk test was utilized to assess data normality. Chi-squared test or Fisher's exact test was employed to assess the associations between *FOXP2* polymorphism and duration of OGT use. The correlation between variables that had ratio scale (birth weight and length at birth) and duration of OGT use were assessed using Pearson correlation. SPSS version 25.0 software (IBM SPSS, Chicago, Illinois, USA) was employed for data analysis, with $p<0.05$ considered statistically significant.

Results

Mothers' and preterm neonates' characteristics

A total of 50 preterm neonates were included in this study and the characteristics of mothers and preterm neonates are presented in **Table 1**. The majority of mothers (78%) were aged between 20 and 35 years, with 74% having multigravida status. Cesarean section delivery was prevalent (96%), with preterm neonates had a mean birth weight of 2055 grams, length of 45 cm, and 5-day length of hospital stays. Over half of preterm neonates (60%) were female, and 36% were born at 35 weeks of gestational age. Most preterm neonates had APGAR scores of 7–10 at the fifth minute (72%) and 4–6 at the first minute (50%) after birth (**Table 1**).

Table 1. Mothers' and neonates' characteristics (n=50)

Variables	Frequency (%)
Mother age (year)	
<20	1 (2)
20–35	39 (78)
>35	10 (20)
Gravida status	
Primigravida	13 (26)
Multigravida	37 (74)
Parity status	
0–1	28 (56)
>1	22 (44)
Delivery mode	
Vaginal delivery	2 (4)
Cesarean section	48 (96)
Neonate sex	
Male	20 (40)
Female	30 (60)
Gestational age (week)	
32	3 (6)
33	7 (14)
34	6 (12)

Variables	Frequency (%)
35	18 (36)
36	16 (32)
First-minute APGAR score	
≤3	23 (46)
4–6	25 (50)
≥7	2 (4)
Five-minute APGAR score	
≤3	3 (6)
4–6	36 (72)
≥7	11 (22)
Weight at birth (gram), mean±SD	2055±271.47
Length at birth (cm), mean±SD	45.40±2.32
Duration of orogastric tube use (day), mean±SD	4.00±1.26
Length of stay (day), mean±SD	5.00±1.40

APGAR score: appearance, pulse, grimace, activity and respiration score

FOXP2 polymorphism frequency distribution

Sequencing results from 50 preterm neonates indicated that the sequenced samples had a 99.03% similarity with *FOXP2* gene reference sequences. Based on DNA sequencing results targeting *FOXP2* rs17137124, nearly half of the preterm neonates (48%) had CT genotype, 23 (46%) had CC genotype and 3 (6%) had TT genotype (**Table 2**).

Table 2. Distribution of genotypes and allele of FOXP2 rs17137124 polymorphism

FOXP2 polymorphism	Frequency (%)
FOXP2 genotypes	
CC	23 (46)
TT	3 (6)
CT	24 (48)
FOXP2 allele	
C	70 (70)
T	30 (30)
FOXP2 genotype dominant model	
CC	23 (46)
CT+TT	27 (54)
FOXP2 genotype recessive model	
CC+CT	47 (94)
TT	3 (6)

Factors associated with duration of OGT use

Our data indicated that age of the mother (p=0.795), gravida status (p=0.350), parity status (p=0.143), sex of neonates (p=0.149), the first-minute APGAR score (p=0.710), and five-minute APGAR score (p=0.251) were not associated with the duration of OGT use among preterm neonates (**Table 3**). However, delivery mode and gestational age of preterm neonate were associated with the duration of OGT use (**Table 3**).

Most of the preterm neonates included in this study were born with cesarean section that required OGT uses (**Table 3**). Only two neonates were delivered by vaginal delivery and both of them required six days OGT use. Fisher's exact test revealed a significant association between delivery mode and the duration of OGT use (p=0.002) (**Table 3**). At 33 weeks of gestational age, 42.9% of preterm neonates required OGT use for up to 5 days (**Table 3**). At 34 and 35 weeks, the duration predominantly spanned 4 days (33.3% and 50%, respectively). By 36 weeks, OGT use was mainly limited to 3 days (43.8%). A Chi-squared test revealed a significant association between gestational age and the duration of OGT use (p=0.001) (**Table 3**).

Table 3. Factors associated with duration of orogastric tube use

Variables	Total	Duration of orogastric tube use						*p*-value
		1 day	2 days	3 days	4 days	5 days	6 days	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Mother age (year)								0.795
<20	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	
20–35	39	1 (2.6)	7 (17.9)	11 (28.2)	11 (28.2)	6 (15.4)	3 (7.7)	
>35	10	0 (0.0)	2 (20)	2 (20)	4 (40)	0 (0.0)	2 (20)	

Variables	Total	Duration of orogastric tube use						*p*-value
		1 day	2 days	3 days	4 days	5 days	6 days	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gravida status								0.350
Primigravida	13	0 (0.0)	3 (23.1)	2 (15.4)	5 (38.5)	3 (23)	0 (0.0)	
Multigravida	37	1 (2.7)	6 (16.2)	12 (32.4)	10 (27)	3 (8.1)	5(13.5)	
Parity status								0.143
0–1	28	0 (0.0)	8 (28.6)	7 (25)	9 (32.1)	3 (10.7)	1 (3.6)	
>1	22	1 (4.5)	1 (4.5)	7 (31.8)	6 (27.3)	3 (13.6)	4 (18.3)	
Delivery mode								0.002*
Vaginal delivery	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	
Cesarean section	48	1 (2.1)	9 (18.8)	14 (29.2)	15 (31.3)	6 (12.5)	3 (6.3)	
Neonatal sex								0.149
Male	20	0 (0.0)	2 (10.0)	4 (20.0)	10 (50.0)	3 (15.0)	1 (5.0)	
Female	30	1 (3.3)	7 (23.3)	10 (33.3)	5 (16.7)	3 (10.0)	4 (13.3)	
Preterm neonate gestational age (week)								0.001*
32	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100)	
33	7	0 (0.0)	1 (14.3)	2 (28.6)	1 (14.3)	3 (42.9)	0 (0.0)	
34	6	0 (0.0)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	0 (0.0)	
35	18	0 (0.0)	3 (16.7)	3 (16.7)	9 (50.0)	2 (11.1)	1 (5.6)	
36	16	1 (6.3)	4 (25.0)	7 (43.8)	3 (18.8)	0 (0.0)	1 (6.3)	
First-minute APGAR score								0.710
≤3	23	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	
4–6	25	0 (0.0)	6 (16.7)	9 (25)	11 (30.6)	6 (16.7)	4 (11.1)	
≥7	2	1 (9.1)	3 (27.3)	3 (27.3)	4 (36.4)	0 (0.0)	0 (0.0)	
Five-minute APGAR score								0.251
≤3	3	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	
4–6	36	0 (0.0)	6 (16.7)	9 (25)	11 (30.6)	6 (16.7)	4 (11.1)	
≥7	11	1 (9.1)	3 (27.3)	3 (27.3)	4 (36.4)	0 (0.0)	0 (0.0)	

* Statistically significant at p=0.05

Plausible variables associated with the duration of OGT that had a ratio scale (birth weight and length at birth) were assessed using the Pearson correlation coefficient. The results found that a significant inverse correlation between birth weight and the duration of OGT use (r=-0.476; p=0.001), suggesting that OGT used duration decreased as birth weight increased (**Table 4**). Similarly, baby's birth length was inversely correlated with OGT duration (r=-0.345; p=0.014), suggesting that longer birth lengths were associated with shorter OGT use durations (**Table 4**).

Table 4. Correlation of birth weight and length at birth with duration orogastric tube use

Variable	Duration of orogastric tube use			
	Mean	Standard deviation	*r*	*p*-value
Birth weight (gram)	2055	271.47	-0.476	0.001
Length at birth (cm)	45.40	2.32	-0.345	0.014

Association between *FOXP2* polymorphism and the duration of OGT use

Among preterm neonates with CC genotype, 17.4%, 4.3% and 13.0% needed OGT for 4, 5, and 6 days, respectively, while 33.3% of those with TT genotype required OGT use for 4, 5, and 6 days (**Table 5**). The most prevalent of preterm neonates with CT genotype required OGT use for 4 days (41.7%), followed by 3 days (20.8%) and 5 days (16.7). A Chi-squared test showed no significant association between *FOXP2* gene polymorphism and duration of OGT use in preterm neonates (p=0.233).

Among preterm neonates with C allele, the most prevalent of them required OGT use for 3 and 4 days (29.8% each), whereas 33.3% of neonates with T allele required OGT use for 4, 5, and 6 days (**Table 5**). A Chi-squared test also revealed no significant association between allele type and duration of OGT use in preterm neonates (p=0.110). Both genotype dominant and recessive models of *FOXP2* polymorphism had no significant association with the duration of OGT use in preterm neonates (p=0.109 and 0.481, respectively) (**Table 5**).

Table 5. Effect of *FOXP2* rs17137124 polymorphism on the duration of OGT use

FOXP2 polymorphism	Total	Duration of orogastric tube use						*p*-value
		1 day	2 days	3 days	4 days	5 days	6 days	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
FOXP2 genotype								0.233
CC	23	0 (0.0)	6 (26.1)	9 (39.1)	4 (17.4)	1 (4.3)	3 (13.0)	
CT	24	1 (4.2)	3 (12.5)	5 (20.8)	10 (41.7)	4 (16.7)	1 (4.2)	
TT	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	
FOXP2 allele								0.110
C	94	2 (2.1)	18 (19.1)	28 (29.8)	28 (29.8)	10 (10.6)	8 (8.5)	
T	6	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (33.3)	2 (33.3)	
FOXP2 genotype dominant model								0.109
CC	23	0 (0.0)	6 (26.1)	9 (39.1)	4 (17.4)	1 (4.3)	3 (13.0)	
CT+TT	27	1 (3.7)	3 (11.1)	5 (18.5)	11 (40.7)	5 (18.5)	2 (7.4)	
FOXP2 genotype recessive model								0.481
TT	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	
CC+CT	47	1 (2.1)	9 (19.1)	14 (29.8)	14 (29.8)	5 (10.6)	4 (8.5)	

Discussion

Early feeding in preterm neonates typically involves orogastric or nasogastric tube feeding, although oral feeding is also used to stimulate stomatognathic system development [18,19]. The development of oral-motor skills also plays a role in determining the success of eating and speaking [20]. Babies who feed by sucking require complex oral-motor skills to coordinate adequate swallowing and breathing [21]. *FOXP2* is reported to have an important role in the success of oral feeding in neonates. Neurons expressing *FOXP2* are found in deep layers of the cortex, basal ganglia, parts of the thalamus and Purkinje cells of the cerebellum [22]. In mammals, this area included in network circuits involved in motor coordination, learning processes and the acquisition of sensorimotor skills, which are essential components in the development of oral feeding [22]. *FOXP2*, a transcription factor crucial for motor control circuitry development, is associated with severe speech and language disorders due to gene mutations [10,11]. Speech and oral feeding share neural pathways responsible for oral-motor coordination and cranial nerve innervation [23,24]. Early feeding and sucking behaviors in newborns demonstrate foundational motor control, highlighting neural links between feeding and language development [12].

The present study was conducted to investigate the role of *FOXP2* rs17137124 on the duration of OGT use in moderate to late preterm neonates. No significant association was found between distributions of *FOXP2* genotypes (p=0.233), alleles (p=0.110), or dominant (p=0.109) and recessive models (p=0.481) with duration of OGT use among preterm neonates. The role of *FOXP2* in several diseases have been mixed. Heterozygous *FOXP2* disorders are associated with altered gray matter density in cortical regions; however, their impact on neuronal function remains unclear [25]. Previous studies found that mutations in the *FOXP2* gene disrupt orofacial movement coordination, which is crucial for speech [26,27]. Another study found *FOXP2* gene polymorphism such as rs1456031 and rs17137124 were associated with verbal fluency tasks in patients with frontotemporal lobar degeneration [28]. However, the present study found a limited association between this gene and the duration of OGT use.

FOXP2 gene, expressed extensively in the fetal and adult brain, including regions such as the cerebral cortex, cerebellum, thalamus, basal ganglia, and inferior olivary nucleus, is crucial for motor control [29]. SNP rs17137124 is a genetic variation in *FOXP2* that affects language assessment [28]. This SNP, situated in its regulatory regions, can impact *FOXP2* expression in the basal ganglia, potentially leading to subtle oral dyskinesia, manifesting as cerebral palsy and myodystrophy, characterized by dysarthria, restricted mouth movements, and impaired tongue proprioception [29]. Genetic testing for *FOXP2* rs17137124 polymorphism in saliva can predict oral feeding ability in preterm neonates aged 30–34 weeks [30]. Nevertheless, our study did not find any association between this SNP and the duration of OGT use among neonates.

The present study had some limitations, including the absence of a control group consisting of term neonates and preterm neonates under 32 weeks, which limited the evaluation of *FOXP2* polymorphism role. Additionally, laboratory findings, such as for sepsis and other conditions that

might be associated with the duration of OGT use, were also not assessed. Future research should include a larger sample size with term and preterm neonates under 32 weeks and assess laboratory results for more robust findings.

Conclusion

Our data suggested no significant association between the genotype and allele of *FOXP2* rs17137124 polymorphism and the duration of OGT use. Therefore, clinical strategies to reduce OGT use duration should focus on managing factors associated with prematurity, such as delivery mode and gestational age, rather than genetic factors.

Ethics approval

The protocol of the present study was reviewed and approved by Ethical Committee of Health Research, Dr. Zainoel Abidin Hospital, Banda Aceh, Aceh, Indonesia (approval number: 101/EA/FK-RSUDZA/2022).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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References

1. Rohsiswatmo R, Amandito R. Optimalisasi pertumbuhan bayi prematur dan pasca prematur di Indonesia; Mengacu pada pedoman nutrisi bayi prematur di RSCM. Sari Pediatri 2020;21(4):262.
2. Liu YL, Chen YL, Cheng I, *et al.* Early oral-motor management on feeding performance in premature neonates. J Formos Med Assoc 2013;112(3):161-164.
3. Shandley S, Capilouto G, Tamilia E, *et al.* Abnormal nutritive sucking as an indicator of neonatal brain injury. Front Pediatr 2021;8(1):1-13.
4. Ikatan Dokter Anak Indonesia. Konsensus asuhan nutrisi pada bayi prematur. Available from: https://pediatricfkuns.ac.id/data/ebook/Konsensus-Asuhan-Nutrisi-Prematur.pdf. Accessed: 3 March 2024.
5. Lau C. Oral Feeding in the Preterm Infant. NeoReviews 2006;7(1):e19-e27.
6. Khanna P, Maron JL, Walt DR. Development of a rapid salivary proteomic platform for oral feeding readiness in the Preterm Newborn. Front Pediatr 2017;5(12):1-6.
7. Dawson JA, Summan R, Badawi N, *et al.* Push versus gravity for intermittent bolus gavage tube feeding of preterm and low birth weight infants. Cochrane Database Syst Rev 2021;8(8):CD005249.
8. Maron JL. Insights into Neonatal Oral Feeding through the Salivary Transcriptome. Int J Pediatr 2012;2012:1-7.
9. Zimmerman E, Maron JL. *FOXP2* gene deletion and infant feeding difficulties: A case report. Mol Case Stud 2016;2(1):a000547.

10. Padovani A, Cosseddu M, Premi E, *et al.* The speech and language *FOXP2* gene modulates the phenotype of frontotemporal lobar degeneration. J Alzheimers Dis 2010;22:923-931.
11. Zeesman S, Nowaczyk M, Teshima I, *et al.* Speech and language impairment and oromotor dyspraxia due to deletion of 7q31 that involves *FOXP2*. Am J Hum Genet 2006;140A:509-514.
12. Adams-Chapman I, Bann CM, Vaucher YE, *et al.* Association between feeding difficulties and language delay in preterm infants using bayley scales of infant development-third edition. J Pediatr 2013;163(3):680-5.e53.
13. Sastroasmoro S. Dasar-dasar metodologi penelitian klinis. Edisi ke-4. Jakarta: Sagung Seto; 2011.
14. Tolosa A, Sanjuán J, Dagnall AM, *et al. FOXP2* gene and language impairment in schizophrenia: Association and epigenetic studies. BMC Med Genet 2010;11(1).
15. Zhao Y, Ma H, Wang Y, *et al.* Association between *FOXP2* gene and speech sound disorder in Chinese population. Psychiatry Clin Neurosci 2010;64(5):565-573.
16. Arshpreet D. Validity of modified ballard score after 7 days of life. Int J Med Res Health Sci 2017;6(7):79-83.
17. Watterberg KL, Aucott S, Benitz WE, *et al.* The APGAR score. Pediatrics 2015;136(4):819-822.
18. Mauliza M, Herlina D, Akmal M, *et al.* Role of forkhead box protein 2 (*FOXP2*) in oral-motor abilities of preterm infants: A brief literature review. Narra J 2023;3(2):e237.
19. Simpson C, Schanler RJ LC. Early introduction of oral feeding in preterm infants. Pediatrics 2002;110(3):517-522.
20. Zimmerman E, Maki M, Maron J. Salivary *FOXP2* expression and oral feeding success in premature infants. Mol Case Stud 2016;2(1):a000554.
21. Dzelme K. Critical Review: Is the Neonatal Oral-Motor Assessment Scale, a valid assessment tool to identify and quantify future infant oral-feeding difficulties or oral-motor dysfunction? School of Communication Sciences and Disorders. University of Western Ontario: Canada; 2013.
22. Zarem C, Kidokoro H, Neil J, *et al.* Psychometrics of the neonatal oral motor assessment scale. Dev Med Child Neurol 2013;55(12):1115-1120.
23. Matsuo K, Palmer J. Anatomy and Physiology of Feeding and Swallowing-Normal and Abnormal. Phys Med Rehabil Clin N Am 2008;19(4):691-707.
24. McFarland DH TP. Clinical implications of cross-system interactions. Semin Speech Lang 2006;27(4).
25. den Hoed J, Devaraju K, Fisher SE. Molecular networks of the *FOXP2* transcription factor in the brain. EMBO Rep 2021;22(8):1-15.
26. Watkins KE, Dronkers NF, Vargha-Khadem F. Behavioural analysis of an inherited speech and language disorder: Comparison with acquired aphasia. Brain 2002;125(3):452-464.
27. Enard W. *FOXP2* and the role of cortico-basal ganglia circuits in speech and language evolution. Curr Opin Neurobiol 2011;21(3):415-424.
28. Padovani A, Cosseddu M, Premi E, *et al.* The speech and language *FOXP2* gene modulates the phenotype of frontotemporal lobar degeneration. J Alzheimers Dis 2010;22(3):923-931.
29. Zhou LY. The effects of forkhead box P2 gene on language functional articulation disorder. Am J Biochem Biotechnol 2014;9(4):453-458.
30. Bartolome R, Kaneko-Tarui T, Maron J, *et al.* The utility of speech-language biomarkers to predict oral feeding outcomes in the premature newborn. Am J Speech Lang Pathol 2020;29(2S):1022-1029.