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# The Variation of DLL3 and LFNG in Class III skeletal malocclusion with mandible prognathia

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## Abstract

**Introduction** Malocclusion is defined as a dentition disorder or an improper relationship between the maxillary and mandibular arches, and is one of the most common craniofacial developmental anomalies experienced by humans of various races and ethnicities. The prevalence of malocclusion in Indonesia reaches more than 80% with class III malocclusion reaching 15% in the Asian population.

**Aim** To define the genetic pathway and the role of DLL3 and LFNG in skeletal class III malocclusion with mandibular prognathism.

**Material and Method** A quantitative observational study was conducted with a total of 64 samples, divided into a control group, namely class I malocclusion and class III malocclusion group. Through strict inclusion and exclusion criteria, one sample was selected from each group for further analysis using the whole genome sequencing method to obtain SNPs in the DLL3 and LFNG genes.

**Results** There were 4 DLL3 mutations (rs8107127, rs8106337, rs1110627, and rs2304214) and 2 LFNG mutations (rs61564232 and rs34637446). DLL3 mutations are exonic synonymous and exonic missence. LFNG mutations are frameshift deletion and frameshift insertion.

**Conclusions** The presence of DLL3 and LFNG mutations may play an important role in the process of mandibular bone formation through inhibition of NOTCH signaling and through interference with cyclical effects.

**Keywords:** Class III skeletal malocclusion; NOTCH signalling; Cyclical effect; Endochondral ossification

## 1. Introduction

Malocclusion is one of the developmental anomalies of the craniofacial structure that is most commonly experienced by humans of various races and ethnicities. Diagnosis and etiology of malocclusion are two important components in determining the appropriate and correct orthodontic treatment plan for the patient. (Mtaya *et al.*, 2009; Karaiskos *et al.*, 2005). The etiology of malocclusion in general is multifactorial, genetic and environmental factors. Skeletal malocclusion is a form of abnormality or distortion in the development of the maxilla and/or mandible which will have a major impact on the patient's general health. Skeletal malocclusion with a normal maxilla and long mandible (mandibular prognathia) is an example of a malocclusion with a strong association with genetic factors. (Josi, Hamdan, & Fakhouri, 2014; Mageet, 2016; Singh, 2007).

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The mandibular ossification process is an important process in the formation of the mandible with the condylar cartilage as the center of growth. (Long & Ornitzz, 2013; Mizoguchi *et al.*, 2013). Previous research has revealed that there are genetic variations that influence hard and soft tissue, (Ardani *et al*., 2020) and the current research aims to examine other genetic variations (*DLL3* and *LFNG*) that may influence the developmental of class III skeletal malocclusion.

## 2. Material and methods

This ethical clearance was approved by number 042/HRECC. FODM/II/2020; all these samples are willing to follow this study with fulfill written inform consent.

The research sample was selected using a random sampling method based on inclusion and exclusion criteria.

The inclusion criteria were individuals whose in the permanent dentition phase and all teeth have erupted completely, has a concave profile, has class III molar relations, and cephalometric parameters indicate a skeletal class III conclusion.

Meanwhile, patients who do not have permanent teeth, patients with impacted teeth, patients with dental anomalies, and congenital syndromes are excluded in this study.

The cephalometric parameter used in this study were saddle angle, articular angle, facial axis, SNA, SNB, ANB, facial angle, Y-axis, FMA, upper and lower gonial angle, occlusal angle, maxilla-mandible proportion and posterior cranial base: mandibular height ratio.

A total of 64 samples of class I (32 samples) and class III (32 samples) skeletal malocclusions met the inclusion and exclusion criteria. The samples then were analyzed using the SPSS test to prove statistical differences in indicators between groups. One sample from each group was taken and blood was taken for whole genome sequencing testing. Whole genome sequencing results must go through the stages of quality control, sequence depth, and sequence error rate until they are declared valid for bioinformatics testing. After fulfilling the requirements, analysis was carried out to read the genetic variations contained in *DLL3* and *LFNG*.

## 3. Results

### 3.1. SNP Found

**Table 1** Cephalometric calculation results of selected samples

| Indicator | Normal range | Class III Means | Class I Means |
|---|---|---|---|
| Saddle angle | 125.90 ± 4.40 | 116.65 ± 3.22 | 125.60 ± 1.61 |
| Articular angle | 148.7 ± 5.70 | 147.43 ± 4.05 | 129.31 ± 3.96 |
| Facial Axis | -3.65 ± 3.58 | 15.75 ± 5.70 | -0.01 ± 1.69 |
| SNA | 79.2 – 85.6 | 82.58 ± 1.61 | 82.03 ± 1.08 |
| SNB | 77.3 – 83.5 | 90.13 ± 2.02 | 80.06 ± 2.15 |
| ANB | 2.40 ± 1.80 | -7.62 ± 0.63 | 2.03 ± 0.22 |
| Facial angle | 89.00 ± 2.60 | 96.28 ± 1.62 | 85.35 ± 1.62 |
| Y Axis | 61.00 ± 2.80 | 54.71 ± 1.79 | 63.82 ± 1.88 |
| FMA | 16 – 35 | 25.24 ± 3.02 | 30.11 ± 2.10 |
| Upper gonial angle | 53.50 ± 1.50 | 50.61 ± 1.77 | 53.58 ± 2.24 |
| Lower gonial angle | 72.50 ± 2.50 | 77.32 ± 3.20 | 75.34 ± 2.11 |
| Maxillary - mandibular length difference | 88.6 – 95.8 | 48.46 ± 2.15 | 43.89 ± 1.62 |
| Posterior cranial base and mandibular height ratio | | 0.60 ± 0.07 | 0.57 ± 0.09 |

Table 1 showed that several cephalometric indicators measurement results were outside the normal range, and in general the interpretation of these measurement results is that class III samples have long mandibles with normal maxilla.

After carrying out several tests on related samples, it was found that there were 3,803,971 SNPs in class I malocclusions and 3,809,476 in class III skeletal malocclusions. Previous studies found several genes associated with class III malocclusion, and this study focused on finding SNPs in DLL3 and LFNG in skeletal class I and class III malocclusions. Table 5.3 showed the summary of the findings of SNPs in DLL3 and LFNG.

**Table 2** SNPs DLL3 and LFNG in the research sample

| Gene | SNPs | Gene References | Alteration | Function | Position | Regio | Character |
|---|---|---|---|---|---|---|---|
| DLL3 | rs8107127 | T | G | Exonic-missense SNV | 39502920 | 19q13.2 | Benign |
| | rs8106337 | C | G | Exonic- synonymous SNV | 39502951 | 19q13.2 | Benign |
| | rs1110627 | T | C | Exonic-missense SNV | 39504071 | 19q13.2 | Benign |
| | rs2304214 | C | T | Exonic - synonymous SNV | 39505387 | 19q13.2 | Benign |
| LFNG | rs61564232 | AGATG | A | Exonic - frameshift deletion | 2513247 | 7p22.3 | Benign |
| | rs34637446 | A | AGATG | Exonic - frameshift insertion | 2513247 | 7p22.3 | Benign |

Table 2 showed the results of SNPs findings from DLL3 and LFNG in the sample. From the WGS results, DLL3 in class III malocclusion in the research sample had 4 SNPs, and one of the SNPs (rs1110627) was also found in the control group, namely class I malocclusion. There are two functions of these SNPs, namely exonic_missense SNV and exonic_synonymous SNV. This means that in the control group samples (class I) there was only one missence mutation in SNPs DLL3, whereas in the selected group samples (class III) there were two missence mutations and one synonymous mutation from SNPs DLL3.

In LFNG there are 2 SNPs with one of the SNPs (rs61564232) also found in the control group. WGS results show that the function of this gene is frameshift deletion and frameshift insertion. This shows that in the control group samples (class I) there were only deletions in the LFNG SNP, whereas in the selected group samples (class III) there were deletions and insertions in the LFNG.

### 3.2. Three Dimensional Visualization of the Related Genes

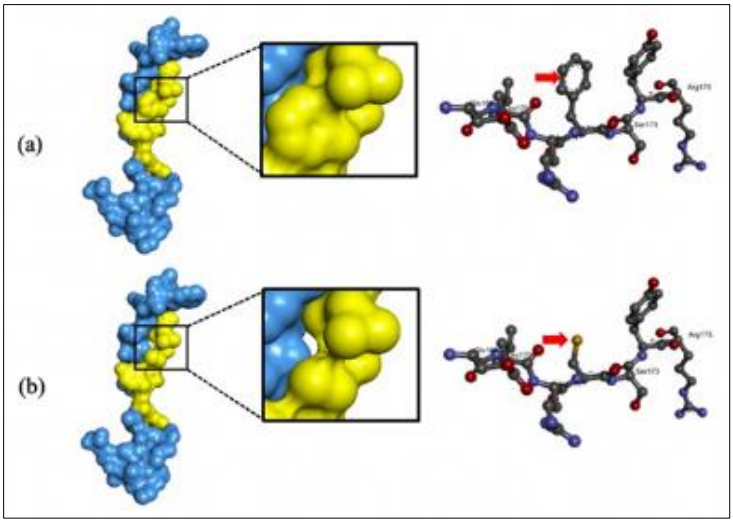


**Figure 1** showed the 3D protein visualization image of DLL3. Normal DLL3 protein structure (a) and mutated DLL3 protein structure (b). The red arrow in image (a) shows the protein structure of phenylalanine and the red arrow in image (b) shows the change in protein structure to cysteine

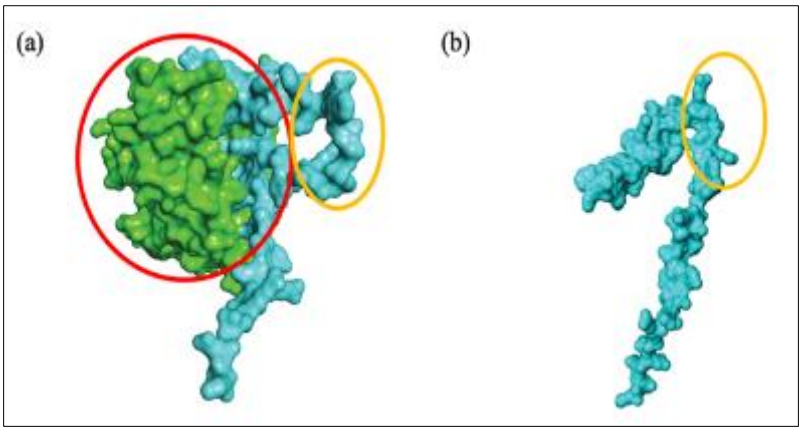


**Figure 2** showed the 3D visualization image of proteins from LFNG. Normal LFNG protein structure (a) and mutated LFNG protein structure (b). The red circle in image (a) in normal LFNG is not found in structures experiencing variations. The yellow circles in images (a) and (b) indicate changes. This difference causes the amino acid glutamine (a) to change to glycine terminate (b) due to the presence of a primary stop codon

## 4. Discussion

Diagnosis of malocclusion is important in the field of orthodontics. Until now, the classification of malocclusion that is often used is the Angle classification which uses the position of the molar teeth as a reference. However, in reality, the molar teeth are not always in the correct position, so they can provide a distraction in the diagnosis and treatment plan that will be taken. So in 1960, Salzmann used skeletal bone as a reference for diagnosing malocclusion.

In the field of orthodontics, one of the most challenging aspects of treating patients is predicting the patient's craniofacial growth pattern. In this case, it is important to understand how genetic factors and their interactions with environmental factors influence facial growth in certain individuals (Mokhtar, Bakar, & Hanani, 2020).

Genetic factors are considered important in diagnosing a disorder, because all mechanisms that occur in the body are regulated by the smallest unit in the cell nucleus. The human body is formed by organ systems, organ systems are formed by organs, organs are formed by tissues and tissues are formed by cells. (Atteeri et al., 2021). Further studies on genetics have been developed in recent years to find out the causes of several diseases down to the smallest level in the body. Genetic variations are also found in diseases caused by genetic disorders.

The data obtained from the whole genome sequencing process is a very long series. Previous research (Ardani *et al.*, 2020) has discussed several genes that may play a role in the formation of the class III skeletal malocclusion phenotype. These genes are ACTN3, COL11A1, MYO1H, MSX1, and EPB41 in hard tissue. Meanwhile, MYO1H, ACTN3, and ACTN2 are thought to have an effect on the soft tissue of patients with class III skeletal malocclusion. Other research that has been conducted also states that the DUSP6 gene is also associated with the incidence of class III skeletal malocclusion (Nikopensius et al., 2013). The current research is a development of previous research by selecting other genes and estimating their possible role in forming the class III skeletal malocclusion phenotype. The genes of choice are DLL3 and LFNG.

This research focuses on mutations that occur in exons. According to Petrosino (2021), the types of SNPs located in exons are divided according to their nature into two large types, namely synonymous and non-synonymous. Synonymous SNPs cannot change the amino acid sequence, while non-synonymous can change the type of amino acids and protein, so they can also change the function of the protein. Non-synonymous SNPs are classified into two types, namely missense or exonic_missense mutations and nonsense mutations. Missense mutations can result in single amino acid changes, while nonsense mutations can result in shorter proteins or longer proteins.

Based on the results of research on SNPs findings in table 5.2, in DLL3 there were 4 exonic mutations, two of which (rs8106337 and rs2304214) were exonic_synonymous mutations and the other two (rs8107127 and rs1110627) were exonic_missence mutations. One of the SNPs, namely rs1110627, was also found in the control group, namely class I skeletal malocclusion. In LFNG, two SNPs were found to be exonic, namely rs61564232 which was exonic_ frameshift deletion and rs34637446 which was exonic_ frameshift insertion. One of the mutations, namely rs61564232, was also found in the control group.

In general, NOTCH is considered a conserved signaling pathway. NOTCH signaling participates in various biological processes, such as organ formation, tissue function, and tissue repair. The presence of aberrations in NOTCH signaling may lead to pathological consequences (Zhou et al., 2022).

Somitogenesis is a process of somite formation and is crucial in a species and is closely related to oscillatory gene expression regulated by NOTCH, Wnt and FGF signaling. During the process of somitogenesis, the NOTCH signaling pathway triggers excitatory signals that cause the presomitic mesoderm (PSM) to progressively segment into bilaterally symmetric epithelial somites in an anterior to posterior direction. This is a rhythmic process with a frequency that matches the molecular oscillators operating in the PSM cell. This oscillator is believed to function as a segmentation clock that drives the periodic formation of somites. The frequency of formation and final number of somites is very specific depending on the species. Disruption of this process has been reported to lead to the formation of bone and muscle deformities. Four genes namely DLL3, MESP2, HES7, and LFNG were reported to be associated with this segmental defect (Maroto, Bone, & Dale, 2012; Dequeant & Pourquie, 2008; Cooke & Zeeman, 1976).

A study in experimental animals (Bochter et al., 2022) shows that both DLL3 and LFNG play an important role in the somitogenesis process of experimental animals, so that loss of function of one or both genes causes similar skeletal defects. This also shows that these two proteins work together during the process of somitogenesis in experimental animals. The same study demonstrated the importance of protein interactions in the critical timing of somitogenesis supported by the critical function of DLL3. Most studies suggest that DLL3 functions solely through a cis-inhibition process, reducing the level of NOTCH activity when expressed in the same cells as the NOTCH receptor, but unable to activate Notch in trans. Loss of DLL3 segmentation clock function disrupts and causes somite and skeletal phenotypes very similar to those observed after loss of Lfng. This supports the theory that DLL3 modulates Notch signaling in time, and that both glycosylation and cis-inhibition contribute to the integration of Notch pathway activity across processes during somitogenesis (Bochter et al., 2022 ).

As discussed, NOTCH signaling is important at many different points in the development of the skull and facial bones. Adapted from figures in research by Pakvasa et al., (2020), NOTCH signaling is widely expressed in cranial structures, ears and the mandible. As a highly conserved signaling pathway, NOTCH deficiency causes serious embryonic lethality. NOTCH signaling is active in the early stages of embryonic development but is maintained at low levels during the developmental stages of the body. NOTCH also increases rapidly under conditions of injury or stress and is indispensable for injury development and repair (Zhou et al., 2022). NOTCH signaling also functions to suppress chondrogenesis. NOTCH signaling mediates communication between neighboring cells to control cell fate decisions.

LFNG is a glycosyl transferase that functions to inhibit the activation of NOTCH signaling through post-translational modification of the NOTCH extracellular domain and periodically blocks NOTCH receptor cleavage, leading to NICD formation. PSMs are a group of self-oscillating cells, but synchronous oscillations between cells depend on the transmission of NOTCH signaling. A study with experimental animals showed that LFNG is the main coupling factor for synchronous oscillations between cells (Zhou et al., 2022). In this study, it was found that there were indel mutations (insertions and deletions) in LFNG which could convert glutamine into glycine terminate. Changes in proteins in genes can cause changes in the surface of the gene which will disrupt the signaling process that should occur. Changes in the LFNG surface can result in disruption of the inhibition of NOTCH signaling activation so that synchronous oscillations between cells will be disrupted.

The DLL3 (Chromosome 19) and LFNG (chromosome 7) genes are genes that play a role in the initial growth process. Mutations in these two genes are often found in patients with spondylocostal dysostosis, a growth disorder of hard tissue. Specifically, DLL3 plays a role in the formation of spondylocostal dysostosis (SCDO) type 1 and LFNG plays a role in the formation of spondylocostal dysostosis (SCDO) type 3.

DLL3 variations in patients with SCDO type 1 have been reported reaching 20 variations. One case study (Turnpenny et al., 2003) in a Caucasian patient with SCDO type 1 found 17 other mutations, consisting of a combination of frameshift deletions, splicing deletions, and insertions in DLL3. In this study, the combination of DLL3 variations involved was different from that obtained in case studies with SCDO type 1 patients, so the results of this study are new information for researchers.

To date, 10 types of LFNG variants have been associated with the incidence of SCDO type 3, with 8 of the 10 variants being missence mutations. A recent study of newborn patients with SCDO type 3 found 5 LFNG variants that had never been reported, consisting of 3 missence variants, 1 nonsense variant, and 1 intron variant (Lecca et al., 2023). The results of research carried out by the author show that there are variations in the form of indels (insertions and deletions), and

are different from the results found in patients with SCDO type 3. This strengthens the argument that the variants in malocclusion patients are different from the genetic variants of patients with SCDO type 1 or type 3.

In this study, one of the LNFG (rs61564232) deletion mutations was also present in the controls, and has not been recorded in the NCBI database. This is in accordance with a study of extensive genome data which states that deletions occur more frequently than genome insertions (Fan et al., 2007). This could be a discovery and new information that this mutation (rs61564232) is a mutation that is likely to be present in all Javanese ethnic patients regardless of the type of malocclusion they have.

The results of the SNP search on NCBI for rs34637446 in this study indicate that this SNP is a microsatellite. Microsatellites, also known as simple sequence repeats (SSR) or short tandem repeats (STR), are noncoding repetitive DNA regions consisting of small motifs of 1 to 6 nucleotides repeated in tandem, which are widespread in eukaryotic and prokaryotic genomes. Microsatellites have the special property of experiencing a higher mutation rate than other genomes (Oliviera et al., 2006). Several studies state that mutations that occur in microsatellites will not have an impact on the phenotype of the organism concerned because the mutation rate is mostly located in intron DNA. Microsatellite-related diseases are often reported in patients with mutations in the sex chromosomes. In this study, the SNP results from LFNG stated that there was a mutation with exonic - frameshift insertion properties. This difference in findings could be due to the presence of variants in LFNG. The existence of this finding in SNPs from LFNG is a new finding that must be discussed further with deeper research, and must be studied more deeply which variants have the possibility of influencing mandibular formation. The nature of the mutation is also a concern in this study. All mutations are benign or benign. Recent large-scale DNA sequencing efforts have detected millions of missense variants, where errors in the DNA code change the amino acids (molecular building blocks of proteins) of a protein. Some of these variants are pathogenic, meaning they can change the structure and function of proteins in a way that leads to disease, while others are benign without any serious impact on general health. It is worth studying further whether genetic variations with non-pathological characteristics can cause disease if they are found in a large enough frequency.

Research on the relationship between SNPs and the formation of malocclusion is a phenomenon that needs to be revealed through several series of studies. It should be understood that the mandibular ossification process consists of several signals that run simultaneously with different portions for each stage. The existence of a particular phenotype is the result of a combination of several signaling in the human body. It is important to study the influence of other signaling in the formation of a malocclusion. There is still little research linking the presence of gene SNPs with malocclusion. Further research with a larger sample and other analysis methods is needed to confirm the association between gene SNP findings and the incidence of malocclusion in Indonesia

## 5. Conclusion

Genetic factors play a role in the formation of malocclusion. The combination of genetic variations obtained in patients with class III skeletal malocclusion with mandibular prognathia is different from that obtained in patients with other diseases.

SNPs DLL3 and LFNG might play a role in dentocraniofacial formation through the NOTCH signaling pathway by disrupting the cyclical effect and synchronous oscillations between cells so that they may play a role in the formation of class III skeletal malocclusion.

The LFNG variation (rs61564232) in those with deletions has not been recorded in the NCBI database, and could be new information that this variation may be a genetic marker for malocclusion in Javanese ethnicity because it is found in class I and class III malocclusions.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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