Title : Comparison of oral microbial diversity and metabolic pathways between patients with Inborn Errors of Immunity (IEI) and healthy controls: A pilot study in a Thai population.

Author(s) :

1. Natthasukon Jongmanatsak **Student ID :** 650510577
2. **Student ID :**
3. **Student ID :**

Major : Statistics

Advisor(s) :

1. Dr. Suttipong Kawilapat
2. Associate Professor Dr. Patrinee Traisathit
3.

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ABSTRACT

Inborn Errors of Immunity (IEI), a heterogeneous group of genetically determined immune disorders, are increasingly associated with disruptions in host–microbiome homeostasis, particularly within the oral cavity; however, the specific microbial signatures and their functional metabolic consequences remain insufficiently characterized. This study aimed to comprehensively characterize and compare the taxonomic diversity and functional potential of the oral microbiome in patients with IEI and healthy controls. Thirty-three oral biofilm samples from fifteen Thai patients with IEI and eighteen age- and sex-matched healthy controls were analyzed using 16S rRNA gene amplicon sequencing. Alpha-diversity (Chao1, Shannon, Simpson and Evenness indices) were compared using the Wilcoxon rank-sum test, while Beta-diversity was assessed using Bray–Curtis distance, visualized by Principal Coordinates Analysis, and validated with Permutational Multivariate Analysis of Variance. Functional profiling was conducted using linear discriminant analysis effect size (LEfSe; score > 2.0) to identify significantly enriched metabolic pathways, and all statistical analyses were performed in RStudio. Taxonomic profiling of oral biofilms from patients with IEI and healthy controls identified a total of six phyla and 372 species. Although Alpha-diversity analysis did not demonstrate a statistically significant difference between the groups, Beta-diversity analysis (p=0.0120) demonstrated distinct microbial community structures between patients with IEI

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and healthy controls. LEfSe analysis identified key discriminatory taxa: twenty-seven health-associated species (including *Actinobaculum sp*. oral taxon 183, GGB10025 SGB15902, *Actinomyces gerencseriae*, *Actinomyces massiliensis*, etc.) were enriched in controls, whereas *Streptococcus gordonii*, an opportunistic pathogen particularly prevalent in immunocompromised individuals, was enriched in the IEI group. Functionally, Seven metabolic pathways (including Inosine 5'-monophosphate (IMP) degradation, Fatty acid biosynthesis initiation (mitochondria), Queuosine biosynthesis I (de novo), Heme b biosynthesis II (oxygen dependent) etc.) were significantly elevated in IEI. These alterations may support the survival and persistence of *Streptococcus gordonii* in the IEI group. In conclusion, IEI was associated with a significant shift in the oral biofilm microbiota, characterized by enrichment of *Streptococcus gordonii* and an increased risk of opportunistic infections, particularly in immunocompromised hosts. The upregulation of metabolic pathways that support *S. gordonii* survival provides mechanistic insights into its potential role as a candidate biomarker, warranting further investigation.

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