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Instigator of Type 1 Diabetes Mellitus (T1D): Connecting Human Leukocyte Antigen (HLA) with Infant Gut Microbiome

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Abstract: Type 1 Diabetes Mellitus (T1D) is driven by the interplay between genetics and other factors, though the exact relationship between gut microbiome and T1D onset remains unclear. This study aims to investigate the connections between Human Leukocyte Antigen (HLA) genetics, gut microbiome, and their relationships to T1D seroconversion. Data from the Diabimmune website provided stool samples (n=1443) from children aged 16 to 36 months from Finland, Russia, and Estonia, categorized by HLA risk factors and seroconversion status. Statistical analyses using the Wilcoxon rank-sum test measure were conducted. High-risk HLA individuals generally had a lower relative abundance of beneficial bacteria such as *Lachnospira*. Predicted metabolic pathways PWY.5676 and PWY.7220/7222 had an increased abundance in low-risk HLA infants in multiple age groups. *Prevotella* was more abundant in seroconverted samples, while *Ruminococcus*, *Hungatella*, and *Sutterella* were more abundant in non-seroconverted samples. Shared pathways between different age groups such as GLYOXYLATE.BYPASS showed higher abundance in non-seroconverted samples, each with similar median abundance across different age groups. The findings suggest that gut microbiome dysbiosis, characterized by a lower abundance of beneficial SCFA-producing bacteria and the prevalence of pathways supporting bacterial persistence and immune stimulation, contributes to T1D onset. Future research should focus on advanced genomic and metabolomic analyses, functional assays, co-culture experiments, and developing predictive models using machine learning to assess autoimmune disease risk based on bacterial strains and HLA haplotypes.

Keywords: Type 1 Diabetes (T1D), HLA, Infant Gut.

1. Introduction

1.1. Type 1 Diabetes

Type 1 Diabetes Mellitus (T1D) is one of the most prevalent autoimmune diseases in childhood, affecting more than one million children and adolescents under the age of 19 globally. T1D is driven by the interplay between genetics and other factors, though the mechanism for seroconversion

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remains unclear. Despite this, it's predicted that global incidence of T1D is increasing at an annual rate of 3% (1, 2) and is projected to increase between 13.5 and 17.4 million by 2040 (3, 4, 5).

1.2. HLA and T1D

T1D is strongly associated with genetic predisposition (6, 7). Approximately 50% of the genetic risk for T1D is attributed to Major Histocompatibility Complex (MHC) class II alleles, also known as the Human Leukocyte Antigen (HLA) alleles (8). HLA alleles, including HLA-DR3, DR4, and DR9, are correlated with increased susceptibility to T1D (8, 9). Even populations with lower-risk genotypes are experiencing an increase in T1D incidence, which suggests other contributing factors (9, 10).

1.3. Inflammation and T1D

Dysbiosis in T1D has been hypothesized to have close ties with inflammation. Inflammation results in higher than normal exposure of HLA proteins to bacterial antigens, leading to increased expression of HLA class II in the intestinal epithelium (8). The upregulation enhances the presentation of bacterial antigens to CD4+ T cells, which results in a heightened immune activation and modulation, altering the balance of the gut microbiota by targeting and eliminating bacteria (6, 9, 11) (Fig. 1). Gradually, beneficial bacteria are reduced, and potentially harmful ones may overgrow, exacerbating dysbiosis. The altered gut environment perpetuates ongoing inflammation and immune activation, maintaining a disturbed microbiome composition.

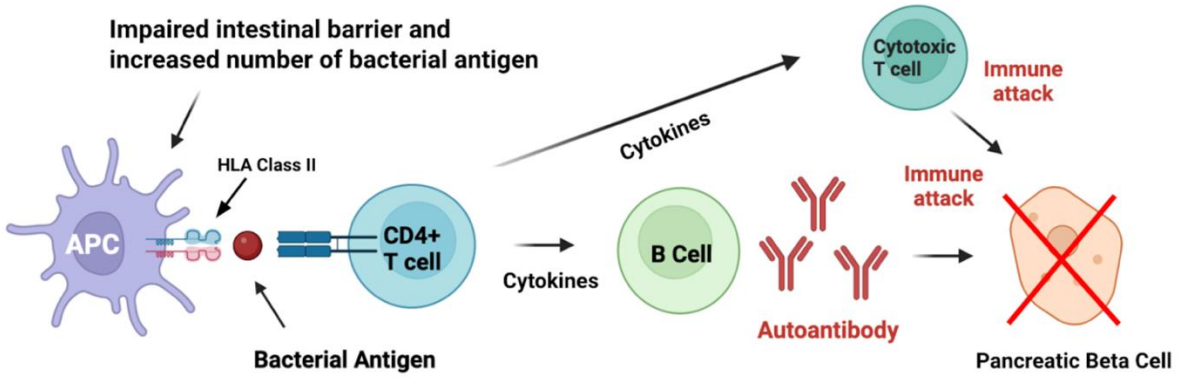

Figure 1: Pathway from antigen presenting cell (APC) to the destruction of pancreatic beta cell that leads to T1D onset. APC with HLA class II protein present on the surface captures bacterial antigen, and the antigen is recognized by CD4+ T cells. CD4+ T cells release cytokines, which attract immune cells like B cells and cytotoxic T cells. B cells mistakenly produce autoantibodies. Autoantibodies and cytotoxic CD8+ T cells target and destroy pancreatic beta cells, leading to a decrease in insulin production.

1.4. Infant Gut Microbiome

In infants, gut bacterial composition significantly impacts immune development and evolves rapidly through three phases: developmental (3-14 months), transitional (15-30 months), and stable (31-46 months) (12, 13). During the first three years, the microbiota becomes more adult-like, dominated by Firmicutes and Bacteroidetes (14). From 16 to 20 months, children in urban China show a dominance of Bacteroidetes, Firmicutes, and Proteobacteria, with rising Bacteroidaceae and Prevotellaceae, and decreasing Enterobacteriaceae. These trends continue between 21 and 25 months, with further increases in Ruminococcaceae (15). By 31 to 36 months, microbial diversity stabilizes, reflecting established dietary habits (16).

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1.5. Lack of Connection between HLA, Gut Microbiome, and T1D

The definitive relationship between HLA alleles, the gut microbiome, and T1D, especially in infants and young children, remains poorly understood. The rapid changes in gut microbiota composition during early childhood and the potential implications for T1D pathogenesis make understanding this relationship crucial. Addressing the knowledge gap could provide critical insights into the early mechanisms of T1D development and pave the way for novel preventive and therapeutic strategies.

1.6. Objective

To explore the intricate connections between HLA alleles, gut microbiome diversity, and the risk of T1D in infants and young children, the study aims to explore and compare the bacterial strains influenced by low-risk and high-risk HLA genes across different age groups, assess the microbiota's spread and composition in these HLA groups, determine the key functional pathways of the bacterial strains, seek correlations between the identified strains and seroconversion, analyze the functional pathways of the identified strains.

2. Methodology

2.1. Statistical Analysis

Statistical analysis was conducted using R version 4.4.1 and the phyloseq package.

2.2. Data Source and Phyloseq Generation

16S rRNA sequencing data from the Diabimmune website (https://diabimmune.broadinstitute.org/) included ~8,000 fastq files, which were merged using PEAR and processed through DADA2 with filtering parameters: maxN=0, maxEE=0.5, truncQ=5, rm.phix=TRUE, truncLen=0. Taxonomic classification was assigned using the Ribosomal Database Project (RDP). Low abundant sequences (fewer than five reads in ≤5 stool samples) were filtered, reducing the total from 73,852 sequences to 2,610. Stool samples with fewer than 1,000 total reads were also removed, leaving 3,196 samples. Metadata from the Diabimmune Excel file, covering children aged 16-36 months from Finland, Russia, and Estonia, was integrated.

A phyloseq object was created, converting raw counts to relative abundance for bacterial genera (n=253). An OTU/ASV table with sample counts and a phylogenetic tree of representative sequences were also generated for comprehensive analysis.

2.3. Categorizing and Grouping the Samples

The Sample Metadata spreadsheet was divided into four age groups (16-20, 21-25, 26-30, and 31-36 months) to compare HLA risk factors, focusing on class 2 (Low Risk HLA) and class 4 (High Risk HLA); total sample (n=744). To compare seroconversion status, the same age groups were used, analyzing bacterial genus abundance and seroconversion data from the phyloseq object. The total sample (n=1443) included 57 seroconverted and 1341 non-seroconverted individuals.

2.4. Bacterial Composition Analysis

For each age group, the Wilcoxon rank-sum test was used to compare the bacterial compositions at the genus level between populations with high and low risk HLA genes. Significant genera ($p<0.05$) were identified, eliminating those with a median of both high and low risk being 0 and only having

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outliers. P-values were adjusted using the Benjamini-Hochberg method, but unadjusted p-values were used eventually.

2.5. Functional Pathways Analysis using PICRUSt2

The PICRUSt2 software was installed, and the pipeline was executed using prepared input files to predict gene family abundances from 16S rRNA sequences, enzyme commission (EC) numbers, and metabolic pathways. Data was categorized by HLA risk (high and low) and age groups, and mean abundance for each pathway in every group was calculated. Log fold changes were determined, and t-tests (p=0.05) were performed to compare pathway abundances between high and low HLA risk groups across different age groups. P-values were adjusted using the Benjamini-Hochberg method, but unadjusted p-values were used eventually since none were significant.

2.6. Seroconversion Analysis

Data was transformed into a long format with bacterial genera as variables and their respective abundances as values, converted into numeric format, and non-numeric rows and columns were removed. The Wilcoxon rank-sum test was performed for each bacterial genus to compare abundances between seroconverted and non-seroconverted populations. P-values were adjusted using the Benjamini-Hochberg method, but unadjusted p-values were used eventually (p=0.05).

3. Results

3.1. HLA and Bacterial Composition Analysis

Significantly differentially abundant genera were observed between high and low risk infants, and generally had a lower relative abundance in high-risk infants across all age groups (Fig. 2).

Faecalibacterium, higher in low-risk infants, and *Lachnospira*, lower in low-risk infants, were found in both Groups 2 and 4 (Fig. 2B, 2D). In Age Group 1 (Fig. 2A), *Intestinimonas* showed the most significant difference between high-risk and low-risk HLA (p=0.014). In Age Group 2 (Fig. 2B), *Sutterella* showed the most significant difference (p=0.0057), with *Faecalibacterium* having a higher median in low-risk infants (0.09 vs. 0.06). In Age Group 3 (Fig. 2C), *Intestinibacter* showed the most significant difference (p=0.036), with higher relative abundance in high-risk infants. Alternatively, *Dialister* had the highest median in low-risk infants. In Age Group 4 (Fig. 2D), *Lachnospira* showed the most significant difference (p=0.0057), with higher abundance in low-risk infants, while *Bacteroides* had a higher abundance in low-risk infants (Median=0.13 vs 0.08).

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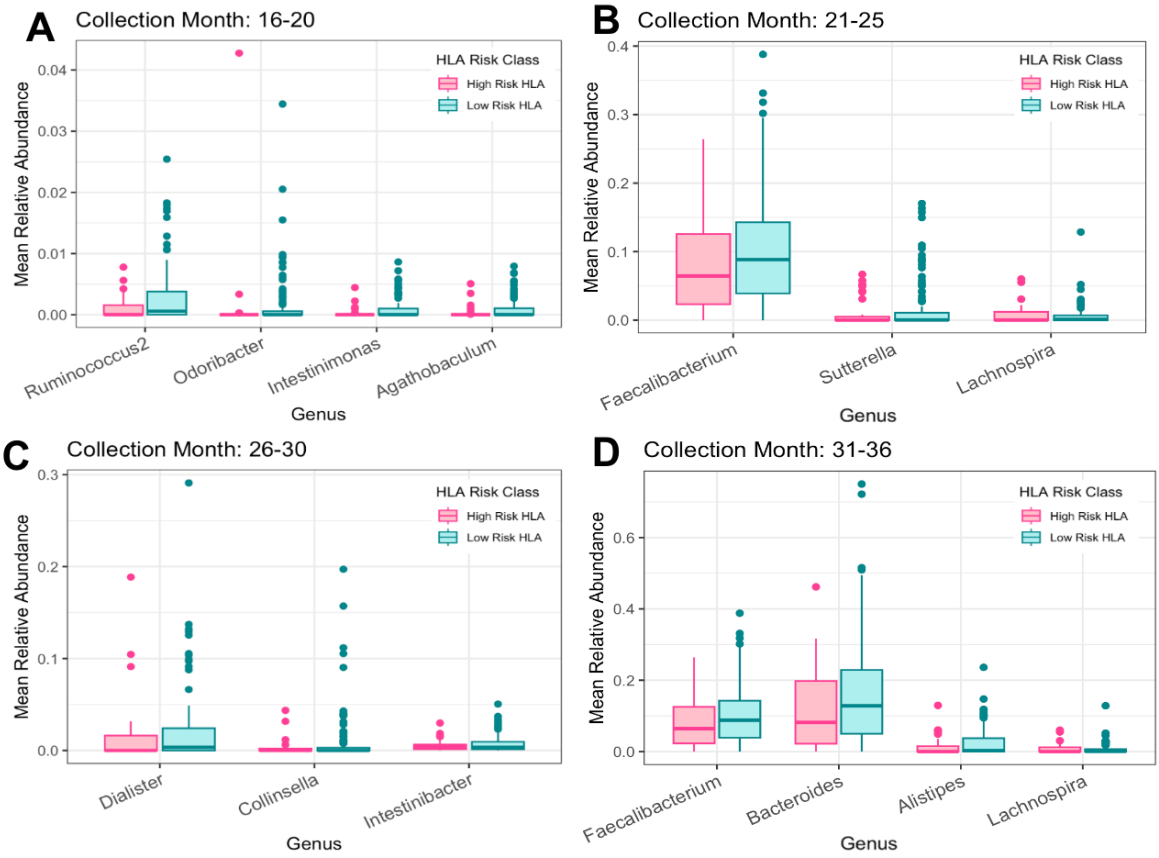

Figure 2: Mean relative abundance of bacterial genera that significantly differ ($p<0.05$) between high risk and low risk HLA groups. Relative abundance is analyzed separately for four age groups based on collection months. (A) Collection months 16-20; (B) Collection months 21-25; (C) Collection months 26-30; (D) Collection months 31-36.

3.2. Functional Pathways for Bacteria Genera

Age Groups 1 (Fig. 3A) and 2 (Fig. 3B) share the pathway acetyl-CoA fermentation to butanoate (PWY.5676), which is more abundant in low-risk infants across all groups. Age Groups 3 (Fig. 3C) and 4 (Fig. 3D) share pathways guanosine deoxyribonucleotides de novo biosynthesis II (PWY.7222) and adenosine deoxyribonucleotides de novo biosynthesis II (PWY.7220), both more abundant in low-risk infants, with identical median levels in high and low-risk HLA.

In Age Group 1, reductive TCA cycle I (P23.PWY) is the most abundant in high-risk HLA, and PWY.5676 is most abundant in low-risk HLA. Interestingly, P23.PWY is the only pathway with a higher abundance in high-risk HLA (Median = 0.0018 vs 0.0012) .

In Age Group 2, glycolysis I is the most abundant in both high and low-risk HLA. Multiple pathways, like GDP-mannose biosynthesis (PWY.5659), show higher abundance in high-risk HLA .

In Age Group 3, PWY.7222 and PWY.7220 share the same abundance for both HLA types. Notably, L-tyrosine and L-phenylalanine biosynthesis pathways mirror one another in both high and low-risk infants. Only two pathways, Inosine-5'-phosphate biosynthesis III and UDP-glucose-derived O-antigen building blocks biosynthesis, show higher abundance in high-risk HLA .

In Age Group 4, PWY.7222 and PWY.7220 again have the same abundance, with eight pathways showing greater abundance in high-risk HLA .

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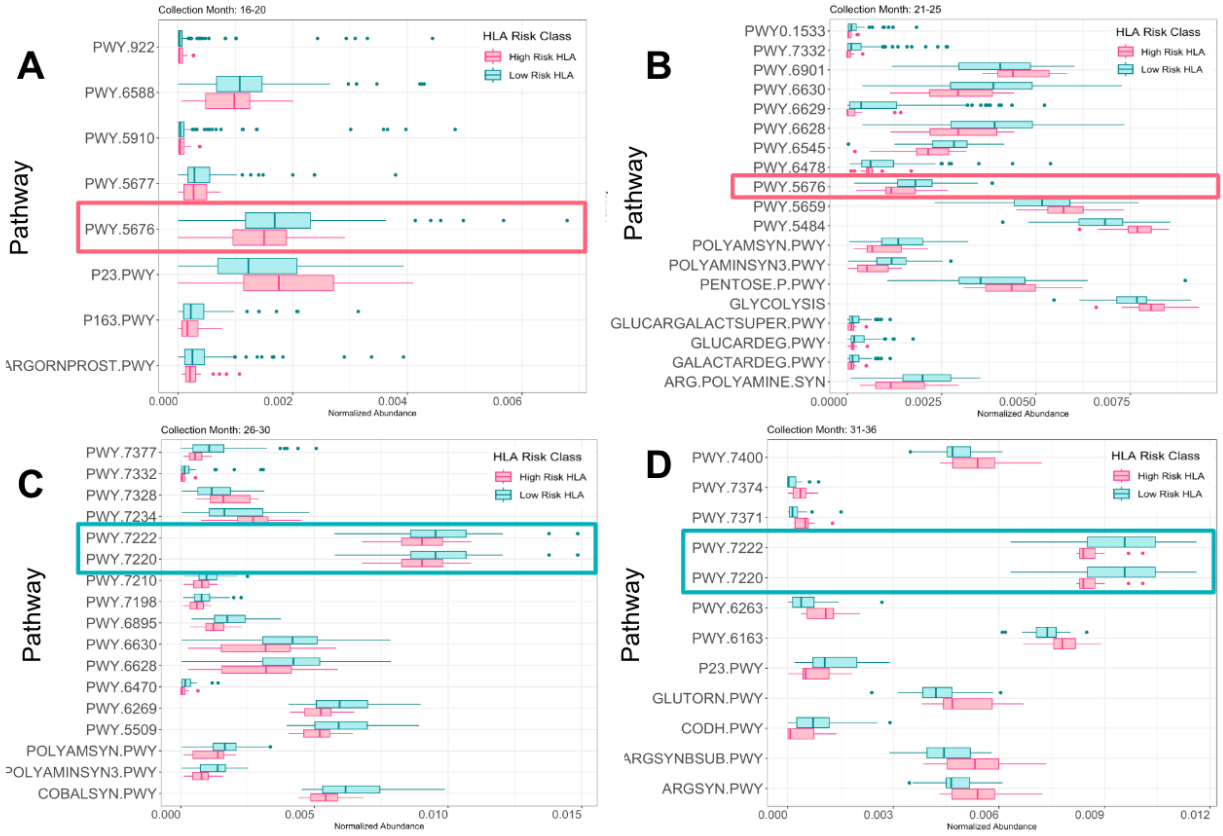

Figure 3: Significant functional pathway differences ($p<0.05$) between high-risk HLA and low-risk HLA in different age groups. (A) Collection months 16-20; (B) Collection months 21-25; (C) Collection months 26-30; (D) Collection months 31-36. The red box indicates the shared pathway between Age Groups 1 (Fig. 4A) and 2 (Fig. 4B), the blue box for groups 3 and 4.

3.3. Seroconversion and Bacteria Composition Analysis

Bilophila occurs in groups 1 (Fig. 4A), 2 (Fig. 4B), and 3 (Fig. 4C). In Age Group 1 (Fig. 4A), *Romboutsia* shows the greatest abundance in seroconverted infants (Median = 0.0018), and *Romunicoccus* shows the greatest abundance in non-seroconverted infants (Median = 0.0096). In Age Group 2 (Fig. 4B), *Prevotella* shows the greatest abundance in seroconverted infants (Median = 0.14), and the abundances for non-seroconverted are 0 for all bacteria genera listed. In Age Group 3 (Fig. 4C), *Faecalibacillus* shows the greatest abundance for seroconverted (Median = 0.011), and *Hungatella* for non-seroconverted (Median=0.0046). In Age Group 4 (Fig. 4D), abundances for seroconverted are 0 for all the genera listed, and *Sutterella* shows the greatest abundance for non-seroconverted (Median = 0.0045).

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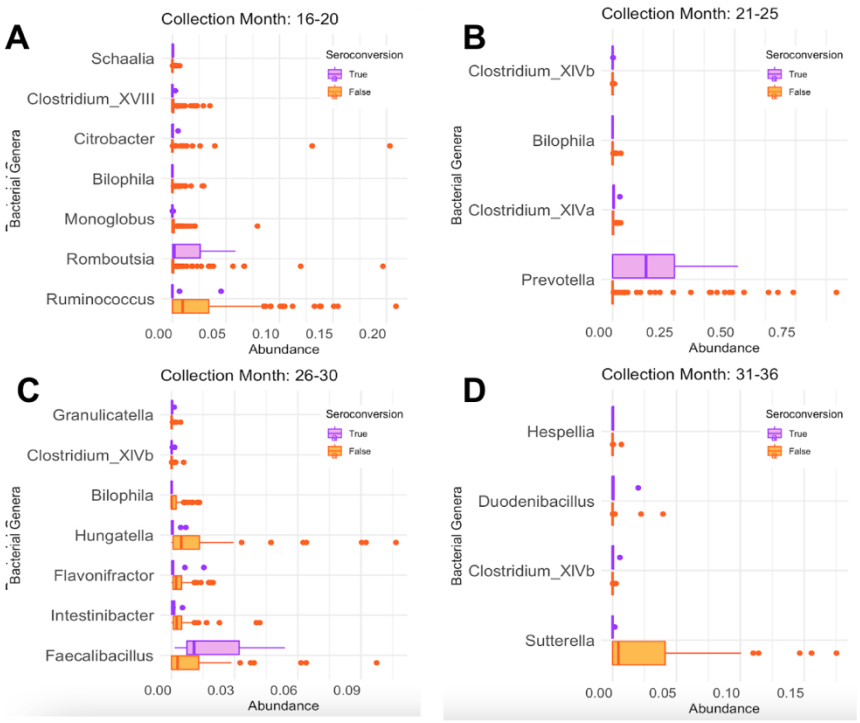

Figure 4: Significant bacterial general abundance differences ($p<0.05$) between samples with islet autoantibody seroconversion (True) and without seroconversion (False) in four age groups. (A) Collection months 16-20; (B) Collection months 21-25; (C) Collection months 26-30; (D) Collection months 31-36.

3.4. Functional Pathways for Seroconversion

Interestingly, Age Group 1 (Fig. 5A) and Age Group 3 (Fig. 5C) share three pathways: glyoxylate cycle (GLYOXYLATE.BYPASS), superpathway of glyoxylate bypass and TCA (GLYCOLYSIS.TCA.GLYOX.BYPASS), and enterobactin biosynthesis (ENTBACSYN.PWY). While GLYOXYLATE.BYPASS shows greater abundance in seroconverted infants than in non-seroconverted ones, both GLYCOLYSIS.TCA.GLYOX.BYPASS and ENTBACSYN.PWY show greater abundance in non-seroconverted infants rather than in seroconverted ones.

Age Group 3 (Fig. 5C) and Age Group 4 (Fig. 5D) share five common pathways: superpathway of Clostridium acetobutylicum acidogenic fermentation (PWY.6590), glutaryl-CoA degradation (PWY.5177), reductive acetyl coenzyme A pathway I (homoacetogenic bacteria) (CODH.PWY), pyruvate fermentation to butanoate (CENTFERM.PWY), superpathway of L-aspartate and L-asparagine biosynthesis (ASPASN.PWY). All pathways show greater abundance in non-seroconverted infants than in seroconverted infants.

In Age Group 1 (Fig. 5A), sucrose degradation III (sucrose invertase) (PWY.621) has the greatest abundance for both seroconverted true (Median = 0.0082, 0.0071, true vs false). PWY.621 and GLYOXYLATE.BYPASS are the two pathways where the abundance for seroconverted true is greater than that for seroconverted false (2 out of 17).

In Age Group 2 (Fig. 5B), L-tryptophan biosynthesis (TRPSYN.PWY) has the greatest abundance for both seroconverted and non-seroconverted (Median = 0.0051, 0.0054, true vs false). L-ornithine biosynthesis I (GLUTORN.PWY) has the second greatest abundance for both seroconverted true (Median=0.0040, 0.0044, true vs false). None of the pathways have greater abundance for seroconverted than non-seroconverted (0 out of 5). Age Group 2 is the only group that does not have any shared significant pathways with other groups.

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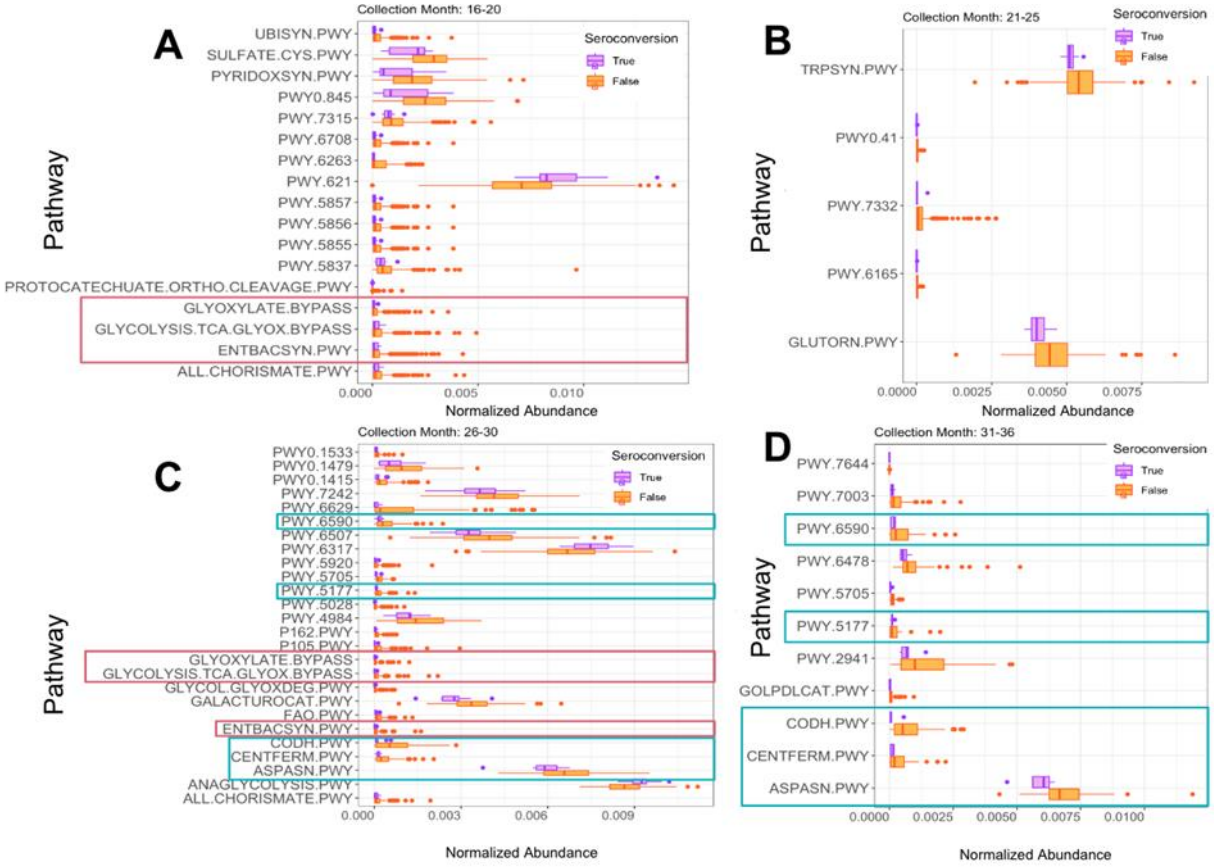

Figure 5: Significant functional pathway differences ($p<0.05$) between seroconverted (true) and non-seroconverted (false) in different age groups. The purple box represents seroconverted, and the orange box represents non-seroconverted. (A) Collection months 16-20; (B) Collection months 21-25; (C) Collection months 26-30; (D) Collection months 31-36. The red box indicates the shared pathway between age groups 1 (Fig. 5A) and 3 (Fig. 5C), the blue box for age groups 3 (Fig. 5C) and 4 (Fig. 5D).

In Age Group 3 (Fig. 5C), glycolysis III (from glucose) (ANAGLYCOLYSIS.PWY) has the greatest abundance for both seroconverted and non-seroconverted (Median=0.0093, 0.0086, true vs false). D-galactose degradation I (Leloir pathway) (PWY.6317) has the second greatest abundance for both seroconverted and non-seroconverted (Median = 0.0075, 0.00667, true vs false). Pathways ANAGLYCOLYSIS.PWY, PWY.6317, and GLYOXYLATE.BYPASS have higher abundance for seroconverted than for non-seroconverted (3 out of 26).

In Age Group 4 (Fig. 5D), superpathway of L-aspartate and L-asparagine biosynthesis (ASPASN.PWY) has the greatest abundance for both seroconverted and non-seroconverted (Median = 0.0060, 0.0067, true vs false). L-lysine biosynthesis II (PWY.2941) has the second greatest abundance for both seroconverted and non-seroconverted (Median = 0.00067, 0.00099, true vs false). No pathway in this group shows greater abundance for seroconverted true than for seroconverted false (0 out of 11).

4. Discussions

The differences in bacterial genera between high-risk and low-risk HLA groups (Fig. 2A-D) emphasize the connection between HLA genotypes, the gut microbiome, and inflammation. High-risk HLA individuals generally have lower levels of beneficial bacteria like *Ruminococcus2* and

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Faecalibacterium, which are known for anti-inflammatory effects and maintaining gut integrity, potentially increasing gut permeability and promoting T1D (17, 18). *Faecalibacterium*, a butyrate producer, showed higher abundance in low-risk HLA, indicating its protective role against gut inflammation and T1D (17). In contrast, *Intestinibacter* (Fig. 2C) was more abundant in high-risk HLA, suggesting a microbiome shift favoring inflammation and autoimmunity (19). As children age, microbial stabilization occurs, with *Bacteroides* showing higher abundance in low-risk HLA (Fig. 2D), further supporting the link between SCFA production, gut health, and reduced T1D risk (17, 20).

For functional pathways, PWY.5676 appears in both age groups 1 (Fig. 3A) and 2 (Fig. 3B) and is more abundant in low-risk HLA, promoting butyrate production and reducing gut permeability and inflammation (18, 20, 22, 23). In age groups 3 (Fig. 3C) and 4 (Fig. 3D), PWY.7220 and PWY.7222 occur with equal abundances in both HLA groups, suggesting a baseline need for nucleotide synthesis essential for cell health and gut resilience (21, 24).

While relationships between bacteria composition and functions and HLA risk classes are highlighted, it remains unclear how these microbial dynamics influence the autoimmune process marked by seroconversion. Therefore, it is necessary to analyze the correlation between bacteria and seroconversion to understand the specific bacterial contributions to immune dysregulation and inflammation in T1D.

The presence of pro-inflammatory bacteria such as *Bilophila* and *Prevotella* (Fig. 4A-C) in seroconverted individuals indicates a shift towards a gut environment that favors immune dysregulation and inflammation (25, 26), with the pro-inflammatory bacteria compromising gut barrier integrity and triggering autoimmune processes. On the other hand, although genera like *Ruminococcus* (Fig. 4A), *Hungatella* (Fig. 4C), and *Sutterella* (Fig. 4D) are more abundant in non-seroconverted individuals, whether or not they are anti-inflammatory bacteria is still being debated (27, 28, 29).

Significant functional pathway differences are observed between seroconverted and non-seroconverted samples (Fig. 5A-D). In age groups 1 (Fig. 5A) and 3 (Fig. 5C), GLYOXYLATE.BYPASS is more abundant in seroconverted infants, while ENTBACSYN.PWY is higher in non-seroconverted. GLYOXYLATE.BYPASS promotes bacterial persistence and immune stimulation, contributing to T1D pathogenesis through chronic inflammation (30). In contrast, ENTBACSYN.PWY, essential for bacterial iron acquisition, helps maintain gut balance in non-seroconverted individuals, reducing immune dysregulation and seroconversion risk (31, 32, 33).

In age groups 3 (Fig. 5C) and 4 (Fig. 5D), pathways like PWY.6590, PWY.5177, and CENTFERM.PWY are more abundant in non-seroconverted infants, supporting SCFA production, metabolite degradation, and microbial homeostasis. This balance promotes immune tolerance, preventing inflammatory responses and lowering the risk of seroconversion and T1D (34).

5. Conclusion

The findings suggest that gut microbiome dysbiosis, characterized by a lower abundance of beneficial SCFA-producing bacteria and the prevalence of pathways supporting bacterial persistence and immune stimulation, contributes to T1D onset.

By advancing the understanding of the interactions between HLA, gut microbiome composition, and T1D pathogenesis, this study points out the link to targeted interventions. By identifying the bacterial genera, such as *Faecalibacterium*, *Intestinibacter* and functional pathways, such as GLYOXYLATE.BYPASS, ENTBACSYN.PWY, associated with T1D onset and seroconversion, this study contributes to creating targeted probiotics and prebiotics. The targeted interventions can restore beneficial bacteria and suppress harmful ones, potentially preventing or delaying the onset of T1D (33). Also, the findings highlight the significance of personalized medicine. Understanding an individual's HLA genotype and gut microbiome profile allows healthcare providers to develop

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customized treatment plans that address specific dysbiotic patterns, thereby improving patient outcomes. Personalized approaches can enhance the effectiveness of interventions and reduce the risk of adverse effects, offering a more tailored and precise method for managing and preventing T1D (34).

Future research should focus on characterizing bacterial strains through whole-genome sequencing and metabolomic profiling, conducting functional analyses, metabolic flux analysis, and co-culture experiments with intestinal epithelial and immune cells to understand their roles in gut barrier function and immune activation. Furthermore, developing predictive models to assess the risk of autoimmune diseases based on bacterial strains and HLA haplotypes can leverage machine learning techniques. Inspired by recent advancements in using machine learning for early detection of systemic autoimmune rheumatic diseases (SARDs) through electronic health records (EHRs), similar methodologies can be adapted to our goal (35). By integrating microbiome and genetic data into machine learning algorithms, we can predict the risk of seroconversion and T1D onset. This approach could facilitate early identification and intervention for at-risk individuals, improving diagnostic accuracy and enabling timely, targeted prevention strategies.

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