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Intestinal microflora dysbiosis and resistome in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

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ABSTRACT

The aim of the present study is to explore the bacterial diversity within the gut microbiome of chronic inflammatory demyelinating polyneuropathy patient. A stool sample was collected and analyzed to study the gut microbiota through bacterial 16S rRNA gene sequencing. The gut microbiota of chronic inflammatory demyelinating polyneuropathy patient exhibited a dominance of *Firmicutes* and *Bacteroides phyla,* with 58.19% and 33.31%, respectively. The data showed a notable abundance of *Lachnospiraceae bacterium* and *Bacteroides sp* species, 17.79% and 16.56%, respectively within the gut microbiota chronic inflammatory demyelinating polyneuropathy patient. *Lachnospiraceae*, a member of the *Firmicutes phylum*, plays a pivotal role in the production of short-chain fatty acids. At high concentration, short-chain fatty acids can trigger autoimmune leading to the chronic inflammatory demyelinating polyneuropathy. These findings strengthen the possible involvement of short-chain fatty acids in the chronic inflammatory demyelinating polyneuropathy pathogenesis process and could pave new paths in its diagnosis and therapies based on regulation of microbiota dysbiosis.

Keywords: autoimmune, gut microbiota, dysbiosis, *Firmicutes, Lachnospiraceae*

Abbreviations (in alphabetical order):

CIDP – Chronic inflammatory demyelinating polyradiculoneuropathy

INTRODUCTION

The human gut microbiota can be described as the collection of microorganisms residing in the human digestive system, which produce a myriad of different metabolites [1]. Moreover, the gut microbiome serves as a significant reservoir for antibiotic resistance genes (ARGs) [2]. Comprising at least several thousand-different species, the microbiome and ARGs have evolved into an important and intricate subject of study, with a particular focus on the

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gut microbiome, which is linked to over hundred diseases and conditions including: obesity, inflammatory bowel disease (IBD) and autoimmune disorder [3]. Recent investigations revealed that gut microbiota and ARGs involve in development of inflammatory bowel disease (IBD) and autoimmune disorder. Patients diagnosed by this disease showing an imbalance in the microbial community, called dysbiosis [3,4]. This imbalance is marked by a decrease in the variety of microorganisms, a change in the prevalence of *Firmicutes phylum* bacteria in favor of Proteobacteria, and disturbances in the levels of various metabolites, such as acyl carnitines, bile acids, and short-chain fatty acids (SCFAs). Furthermore, the dysbiosis support colonization resistance imbalance leading to a shift toward predominance of resistant pathogens [5].

Chronic inflammatory demyelinating polyneuropathy (CIDP) is one of a rare acquired immune-mediated neuropathy [6]. Initially reported in the mid-1900s, CIDP is characterized by significant muscle weakness and a reduction of motor functions. Subsequently, it was recognized as an autoimmune disorder that impacts the peripheral nerves [7]. Population-based studies on CIDP prevalence, report an incidence rate of 0.4 to 1.6 per 100,000 peoples [6]. The apparent wide range in this distribution could stem from various factors, including genetic and environmental influences, as well as the criteria used for diagnosis [8]. Typically, there is a higher incidence in men compared to women at a ratio of 2 to 1, with an average age of onset of around 40 to 50 years old [9]. The exact causes of CIDP remain unknown. Scientists have suggested that its development is attributed to inflammatory infiltrates occurring in specific nerve perivascular regions [7]. According to other studies the involvement of humoral immune elements is likely because most patients respond to treatments such as corticosteroids, intravenous immunoglobulins (IVIg), or plasma exchange [10]. Moreover, the gut microbiome can be involved in the evolution of CIDP disease; it has an important role in the establishment and preservation of immune tolerance [11]. Structural alterations have been observed in autoimmune diseases such as rheumatoid arthritis and multiple sclerosis (MS) [12].

Numerous investigations carried out on CIDP patient, have shown that gut microbiota, particularly commensal microorganisms can impact inflammation in the central nervous system inflammation in both beneficial and detrimental ways. For instance, when fecal material from CIDP patients was transferred to germ-free mice, it resulted in heightened neuroinflammation in these experimental models. Moreover, studies suggest that bacterial metabolites have the ability to suppress inflammatory responses [11,13–16]. To date, there has been no experimental case study on CIDP conducted in Algeria. Here fore we sought to motivate us to explore the gut microbiota diversity in this rare clinical case of CIDP. In this ongoing study, we used whole-genome sequencing of the 16S RNA to identify specific bacterial species signatures in a CIDP diagnosed woman from North African country (Algeria).

MATERIALS AND METHODS

Case presentation

The patient was a 68-year-old woman from Algeria and mother of three, had no smoking history or known allergies. Her vital signs were within the normal range, with an average blood pressure was 140/85, her weight 66 kg and she was 168 cm tall. Her clinical history included a recent hysterectomy and travel between France and Algeria.

In 2017, she consulted doctors for neurological disorders with lower limb paresthesia. After an electromyogram and magnetic resonance imaging (MRI) diagnosis, chronic inflammatory demyelinating polyneuropathy was confirmed. She was initially treated at the university-affiliated Hospital in Algiers with corticosteroid boluses and Imuran, which the patient did not tolerate. Currently, her treatment has been changed with an immunostimulant: Rituximab injection. Since her diagnosis with the immunosuppressive effects of the initial medications, her immunity has weakened and become very vulnerable. In fact, she has been diagnosed with recurrent cystitis. In fact, she is receiving antibiotic treatment consisting mainly of third generation cephalosporin including: ciprofloxacin, cefuroxim, cefalexin, cefixim, sulfamethoxazole and trimethoprim. It is important to highlight that before being diagnosed and starting her initial medication of corticosteroids (boluses and Imuran - to treat CIDP), our patient had initiated antibiotic treatment due to a cystitis diagnosis.

Stool sampling and whole genome sequencing (WGS)

Out of any antibiotic therapeutic prescription, we collected stool samples from patient according to standard methods. The samples were then stored in a DNA Shield solution (Zymo Research, USA) at room temperature before undergoing metagenomic analysis.

The sample was sent to CosmosID company (Rockville, MD, USA) for DNA extraction and WGS sequencing. The DNA was extracted from the sample using QIAGEN DNeasy Power Soil Pro Kit, following the manufacturer's protocol, and quantified using Qubit 4 fluorometer and QubitTM dsDNA HS Assay Kit (Thermofisher Scientific). DNA libraries were prepared using the Nextera XT DNA Library Prepa-

ration Kit (Illumina) and IDT Unique Dual Indexes with a total DNA input of 1ng. Genomic DNA was fragmented using a proportional amount of Illumina Nextera XT fragmentation enzyme. Unique dual indexes were added to each sample followed by 12 cycles of PCR to construct libraries. DNA libraries were purified using AMpure magnetic beads (Beckman Coulter) and eluted in QIAGEN EB buffer. DNA libraries were quantified using a Qubit 4 fluorimeter and a QubitTM dsDNA HS Assay Kit. The libraries were then sequenced on an Illumina NovaSeq 6000 platform at 2 × 150bp. CosmosID also performed bioinformatic 16S analysis using a high-performance data-mining k-mer algorithm.

RESULTS

Bacterial diversity and its relation to CIDP disease

A total of 1.987M reads were generated post initial quality filtering. At the *phylum* level, *Firmicutes* was the most abundant, representing 58.91% to the gut microbiota in the CIDP patient, followed by *Bacteroides* with 33.31% relative abundance, then followed by *Actinobacteria* (7.19%) and *Proteobacteria* (0.58%). The least abundant bacteria were recorded by *Verrucomicrobia* (0.02%) and *Fusobacteria* (>0.01%) (Figure 1. a).

At the class level, *Clostridia* was significantly abundant (48%), followed by *Bacteroidia* (33.31%) and *Negativicutes* and *Actinomycetia* (9.23 and 7.2% respectively). Lower abundance was recorded for *Bacilli* (1.41%), *Gammaproteobacteria* (0.3%), *Deltaproteobacteria* and *Erysipelotrichia* with 0.28% abundance.

At the family level, sixteen families were identified. Six of them were represented with significant abundance including *Lachnospiraceae* (34.38%), *Bacteroidaceae* (23.17), *Veillonellaceae* (9.23%), *Clostridiales* (9.14%), *Bifidobacteriaceae* (7.2%) and *Enterococcaceae* (1.23%). Whereas, *Enterobacteriaceae*, *Lactobacillaceae* and *Streptococcaceae* are at low proportions 0.3, 0.13 and 0.03%, respectively (Figure 1. b).

Genus-level analysis was more informative (Figure 1. c). The data showed that the genus *Bacteroides* (29.13%) was significantly overrepresented in CIDP stool samples. This was followed by *Lachnospiraceae* (17.49%), *Veillonella* (9.23%) and *Clostridiales* (9.14%).

At the species level the abundances are quite similar to the genus abundances. *Lachnospiraceae* and

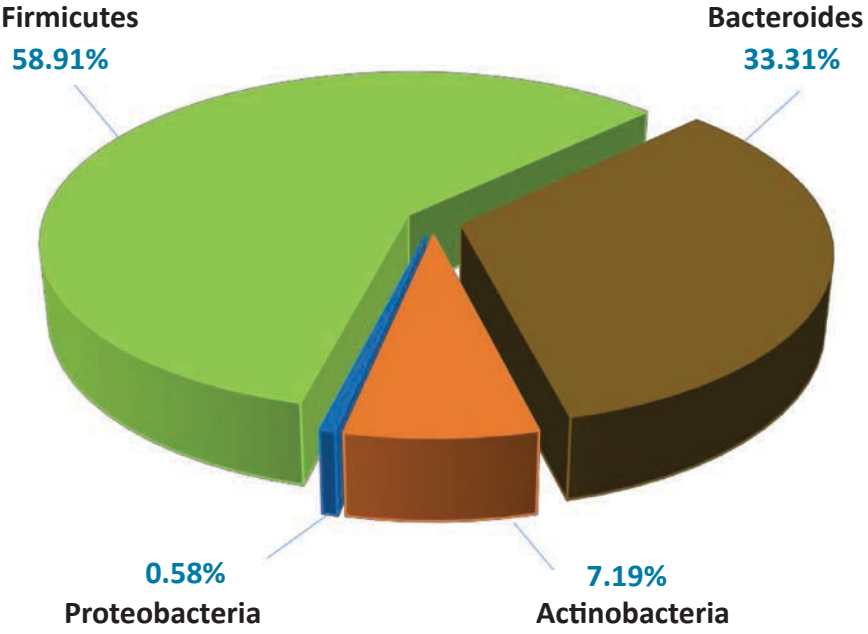

FIGURE 1. a. *Bacterial phylum* relative abundance within CIPD patient sample

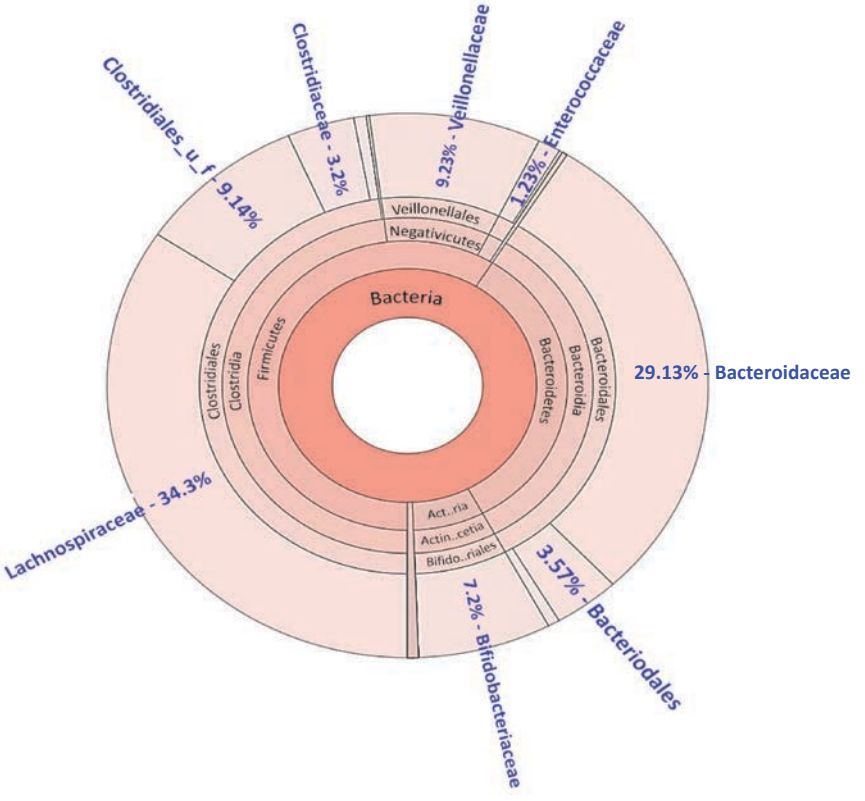

FIGURE 1. b. Bacterial family level relative abundance within CIPD patient sample

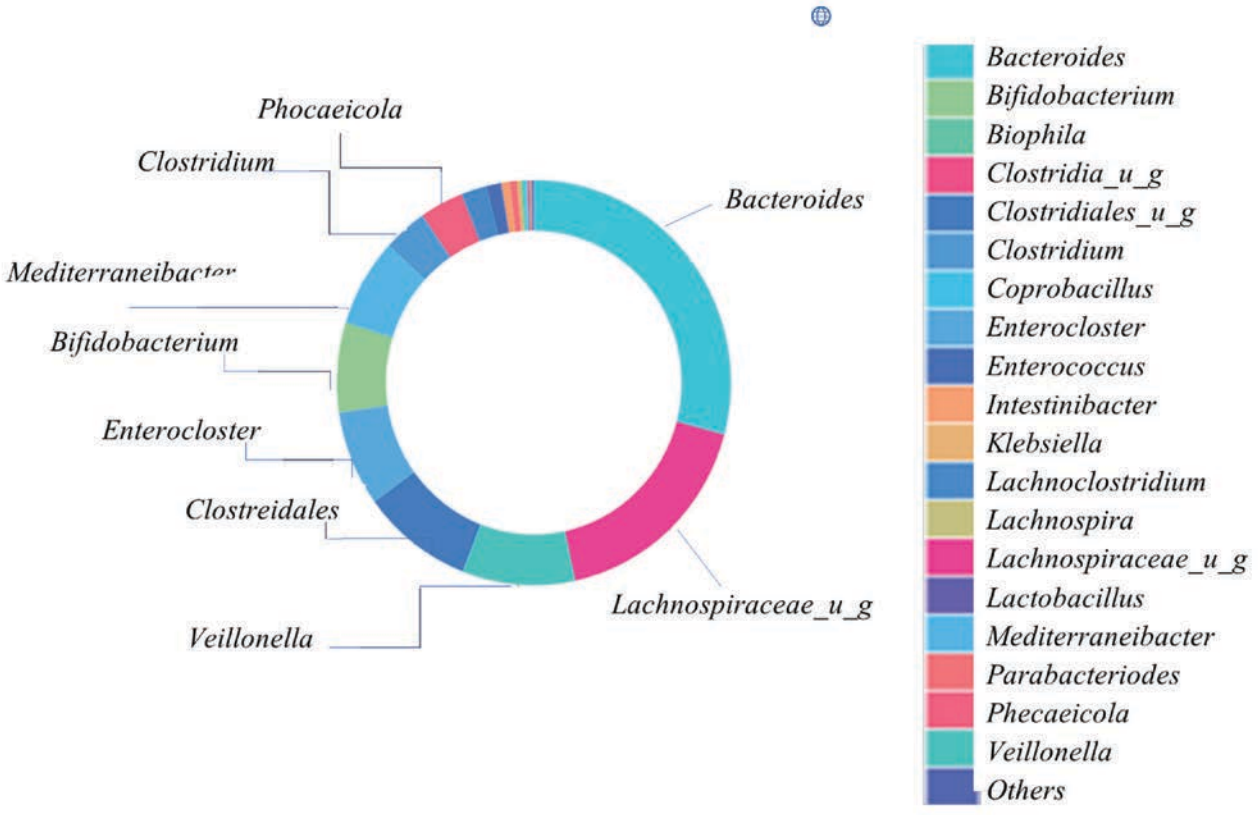

FIGURE 1. c. Genus level relative abundance within CIPD patient sample

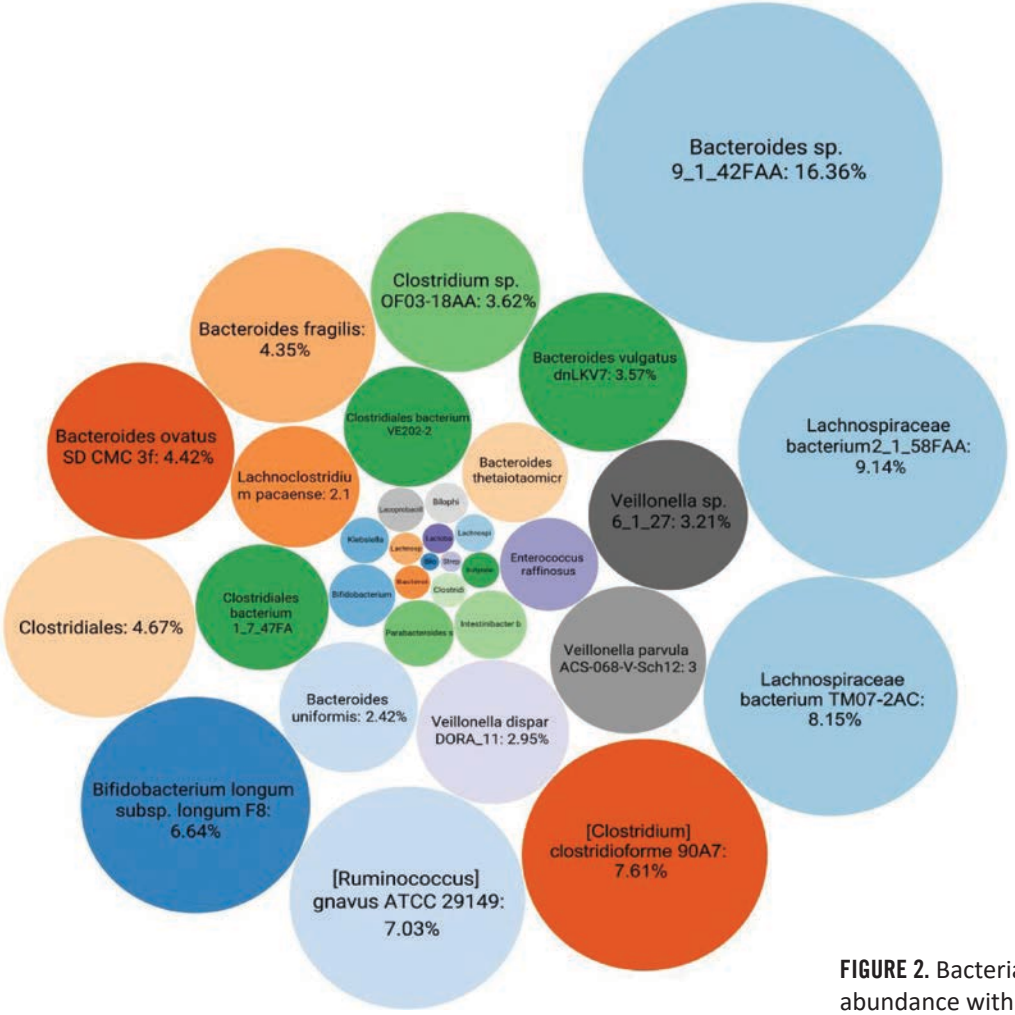

FIGURE 2. Bacterial species level relative abundance within CIPD patient sample

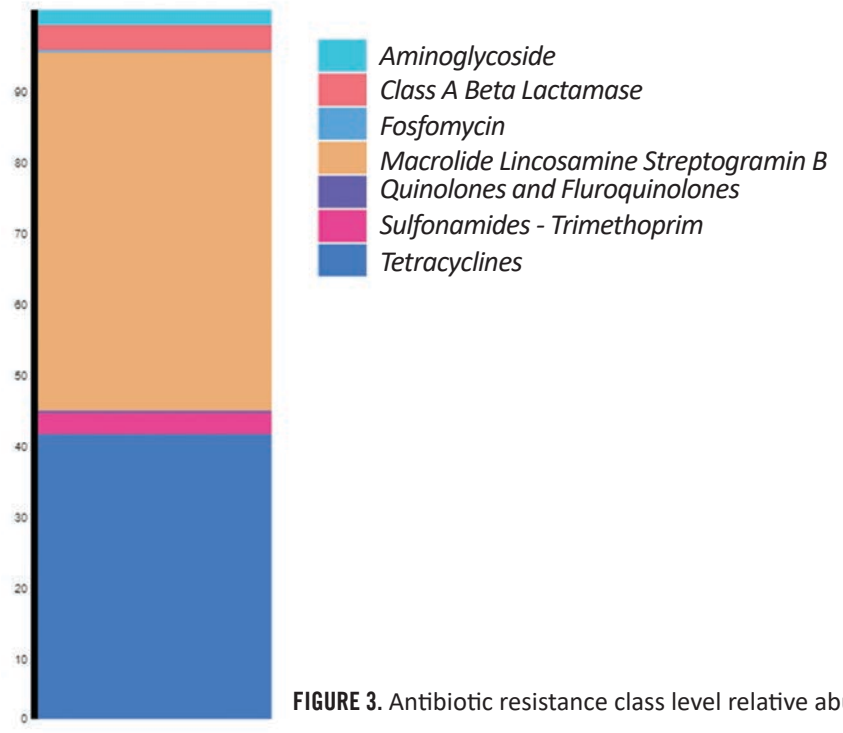

FIGURE 3. Antibiotic resistance class level relative abundance within CIPD patient sample

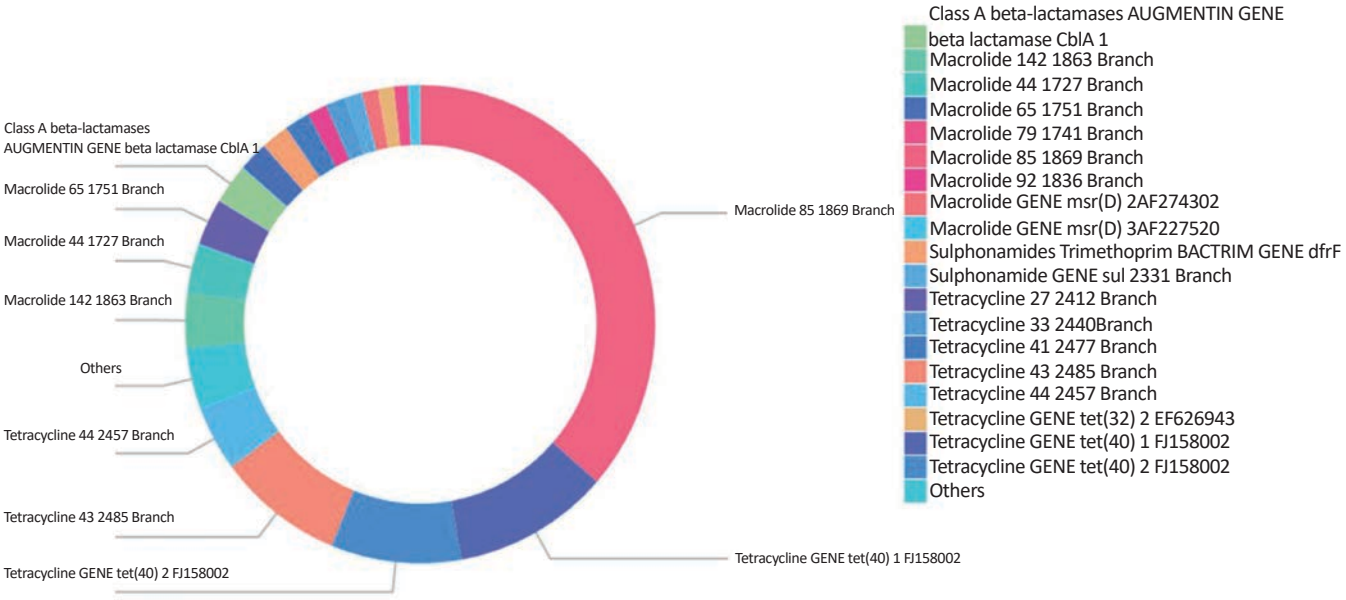

FIGURE 4. Antibiotic resistance genes level relative abundance within CIPD patient sample

Bacteroides (17.79 and 16.56%, respectively) are more abundant. While *Bifidobacterium longum* subsp. Longum (6.64%) and *Bifidobacterium breve* (0.56%) have low abundances (Figure 2).

The antibiotic resistance genes within the CIDP patient

A total of 4.4889M reads were generated post initial quality filtering. At the class level, macrolide Lincosamine Streptogramin B was the most abundant, representing 50.47% to the gut microbiota in the CIDP, followed by Tetracyclines with 40.14% relative abundance, then followed by Class A Beta lactamases (3.48%) followed by Sulfonamides-trimethoprim (3.11%) and Aminoglycoside (2.1%). The least abundant antibiotic resistance genes were affiliated to Sulfa drugs (0.65%), Fosfomycin (0.36%), quinolones fluoroquinolones (0.33%) and phenicol (0.12) (Figure 3).

At the genes level, we notified a dominance of macrolide genes with an abundance over than 40%, followed by tetracycline genes (over than 30%). Lower abundance was recorded for Class A beta-lactamases genes with 10% abundance; followed by Sulfa Drugs Sulfonamides Trimethoprim genes (dfrF and sul); quinolone (qnr B) and phenicol with less than 5% of dominance (Figure 4).

DISCUSSION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune neuropathy disease, mediated by both humoral and cellular immunity against self-antigens present in the peripheral nerves [17,18]. Nowadays investigations revealed that microbiome dysbiosis is involved in the evolution of CIDP.

In the current clinical case study, the whole genome sequencing (WGS) of CIDP stool sample highlighted the abundance of the *Firmicute phylum* at 58.19% followed by the *Bacteroides* (33.31%). Our research findings reveal that the gut microbiome CIDP patient aligns with the typical composition observed in Western European countries characterized by a high prevalence of the *Firmicute* and *Bacteroides phyla* [08]. The results obtained are consistent with those reported by Svačina and collaborators [11].

At the species level in this CIDP patient, *Lachnospiraceae* and *Bacteroides* were the predominant gut microbiota, representing 17.79% and 16.56%, respectively. Contrasting these findings, Fu and co-workers identified lower levels of *Bacteroides* in CIDP patients compared to non-CIDP [19]. In contrast, studies by Svačina et al. [11] and Hiippala et al. [20] observed an elevated presence of *Firmicutes*, including *Lachnospiraceae* in CIDP patients. *Lachnospiraceae*, integral to the gut microbiota from birth, are crucial in producing short-chain fatty acids (SCFAs), key regulators of inflammasome activation [21].

Recently, the gut microbiome and his metabolites has been implicated in contributing to autoimmune disorders via the pro-inflammatory and immune deregulatory effects that imbalance (dysbiosis) of the microbiome can induce [22]. Thus, any imbalance of immune homeostasis induces a predominance of effector Th1, Th17 lymphocytes and plasma cells is important requirement for the development of autoimmune disease states [23,24]. Indeed, the initial study of Svačina et al. of evaluating gut microbiome changes in CIDP demonstrated an increase in microbial diversity and an abundance of SCFA-producing *Firmicutes*, which may generally promote autoimmunity in CIDP through a Th17 pathway [11].

As we highlighted previously, the gut microbiome harbor commensals, symbionts and pathogens germs within human gut. Moreover, resistome or antibiotic resistance genes are contained within the gut microbiome [2].

Over time, the emergence of antibiotic resistance has been acknowledged as a substantial threat to the overall health of the global population. These situations have grown in light with the discovery and rapid spread of antibiotic resistance genes. Furthermore, antibiotic resistance genes (ARGs) have been identified in natural ecosystems outside of clinical environment, including water, soil [25], vegetables [26], pets [27], and even in wildlife [28]. In fact, antibiotic resistance genes (ARGs) could potentially enter the human digestive system through the consumption of water and food or contact with pets, subsequently interacting with the gut microbiota. Numerous investigations have demonstrated the transfer of antibiotic resistance genes (ARGs) into the microbiota of the intestines [29].

In our investigations, macrolide Lincosamine Streptogramin B was the most abundant, representing 50.47% to the gut microbiota in the CIDP, followed by Tetracyclines with 40.14% relative abundance, then followed by Class A Beta lactamases (3.48%) followed by Sulfonamides-trimethoprim (3.11%) and Aminoglycoside (2.1%).

These antibiotic resistance genes (ARGs) caused immune dysfunction. After exposer to ARGs from colistin, the levels of inflammatory cytokine including interleukin IL-2, IL-6, tumor necrosis factors-α and interferon γ (INF- γ) were higher increased in the experimental groups particularly in female mice than in the control group. Furthermore, the inflammatory cell aggregation was seen in mucosal layer. In addition, *Bacteroidetes* decreased and *Firmicutes* increased in both female and male adults. The adult female mice had higher level of *Lachnospiraceae* [3].

In CIDP, T cells infiltrate neural connective tissue along with macrophages, releasing cytokines that govern myelin and axonal injury [30]. Th1 cells activate macrophages through the secretion of IFN-γ, and this activation is influenced by IL-12 production by macrophages. Macrophages engulf myelin, function as executors of neural destruction and release proinflammatory cytokines such as TNF and IL-6 [31].

It has been suggested that some microbial antigens have the potential to initiate an autoimmune attack on specific components of peripheral nerves and intestinal tissue due to their molecular similarity [32]. Moreover, an abnormal transformation of metabolites can be observed in CIDP patients due to the imbalanced gut microbiota [19]. This dysfunction can impact the maturation and activity of the immune system. These metabolites include aryl hydrocarbon receptor (AHR) ligands, polyamines, and short-chain fatty acids (SCFAs) derived from undigested complex carbohydrates such as butyrate, acetate, and propionate [33].

The SCFAs are mainly produced by bacterial fermentation of dietary fiber (DF) or glycosylated host proteins such as mucins in the colon [16]. In the synthesis of the three primary SCFAs, acetate can be produced from pyruvate through two distinct pathways. One pathway involves the production of acetyl-CoA by enteric bacteria while the other follows the Wood-Ljungdahl pathway used by acetogens, such as *Blautia hydrogenotrophica.* Butyrate is derived from

acetyl-CoA and is produced by several *Firmicutes*. Propionate is synthesized by two different pathways: the succinate pathway by *Bacteroidetes* and the lactate pathway by *Firmicutes* [34].

The pathways responsible for producing propionate and butyrate appear to be more consistent and tailored to specific substrates, whereas acetate production pathways are distributed across a wide range of bacterial groups. Although present in different phyla, propionate synthesis is primarily regulated by a limited number of bacterial genera [35].

Short chain fatty acids (SCFAs) are compounds that can be either detrimental or beneficial to human health, depending on various factors such as cell type, concentration, duration of exposure, environmental conditions and specific functions [36].

Besides, serving as an energy source for intestinal epithelial cells, it also affects the permeability of tight junctions. Consequently, strengthening the epithelial barrier helps to prevent the entry of harmful substances into the bloodstream [37]. Moreover, SCFAs exert an influence on the host's immune system by promoting anti-inflammatory effects through the stimulation of regulatory T cells (Tregs) [38] or by regulating the immune balance and inducing the generation of Tregs by suppressing histone deacetylases (HDAC) [39]. In addition, SCFAs are often associated with inflammation in the gastrointestinal tract [40 - 42] and can stimulate pro inflammatory T helper 1 (Th1) and T helper 17 (Th17) cells within the gut, and at high levels, they may induce autoimmune responses [16]. Given that abnormal activation of Th17 cells plays a critical role in the development of autoimmunity in CIDP. Indeed, in multiple sclerosis (MS), a decrease in SCFA and the bacteria responsible for their production has been associated with autoimmune inflammation. Substituting with the SCFA propionate has been shown to improve in clinical outcomes [43]. An increased presence of various *Firmicutes* species responsible for SCFA production may promote Th17 activation and contribute to autoimmunity in CIDP [11,44].

CONCLUSION

In conclusion, our study represents the first investigation of gut microbiome changes in CIDP patient from a North African country. These alterations are characterized by an increased microbial diversity and the prevalence of SCFA-producing *Firmicutes*, which could potentially induce autoimmunity in CIDP through the Th17 pathway. These findings should be validated by further studies including treated patients and patients with severe symptoms, to establish connections between changes in the gut microbiome and metabolites, as well as clinical outcomes. Thus, it is important to include the gut microbiome identification within CIDP diagnosis strategy. These findings need validation through larger studies that should include therapy and severely affected patients, in order to examine the relationship between gut microbiome alterations and clinical outcomes.

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The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions:
All authors contributed to the study conception and design.
All authors read and approved the final manuscript.

Data availability:
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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