Propionibacterium acnes is a universal inhabitant of human skin and is found at high population densities on the fat-rich areas of the face, scalp, and upper trunk (16, 23). P. acnes has been implicated in the pathogenesis of inflammatory acne, as treatments that reduce the numbers of P. acnes cells on the skin are therapeutic and the failure of such therapies has been associated with the emergence of resistance in P. acnes (7, 9, 30). Acne vulgaris is the most common disease of skin in adolescents and affects approximately 80% of individuals at some stage in their lives (5). This disease can be extremely painful and can lead to numerous psychological problems. Inflammatory lesions give rise to significant scar formation in 30% of patients (6). In addition to its association with inflammatory acne, P. acnes is an increasingly common opportunistic pathogen, causing a wide range of infections in immunocompromised patients (2, 8, 31, 34).

Bacteriophages that infect P. acnes can be readily isolated from human skin. The study of these bacteriophages has until now been limited to the development of phage typing systems to distinguish the different serotypes of P. acnes (19, 33). Bacteriophages are the most abundant organisms on Earth, and they play an important role in bacterial diversity and pathogenesis. Greater study of P. acnes bacteriophages should make a significant contribution to the study of propionibacterial genetics and to the wider field of phage biology and evolution.

Genome Sequence and Analysis of a Propionibacterium acnes Bacteriophage

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Cutaneous propionibacteria are important commensals of human skin and are implicated in a wide range of opportunistic infections. Propionibacterium acnes is also associated with inflammatory acne vulgaris. Bacteriophage PA6 is the first phage of P. acnes to be sequenced and demonstrates a high degree of similarity to many mycobacteriophages both morphologically and genetically. PA6 possesses an icosahedral head and long noncontractile tail characteristic of the Siphoviridae. The overall genome organization of PA6 resembled that of the temperate mycobacteriophages, although the genome was much smaller, 29,739 bp (48 predicted genes), compared to, for example, 50,550 bp (86 predicted genes) for the Bxb1 genome. PA6 infected only P. acnes and produced clear plaques with turbid centers, but it lacked any obvious genes for lysogeny. The host range of PA6 was restricted to P. acnes, but the phage was able to infect and lyse all P. acnes isolates tested. Sequencing of the PA6 genome makes an important contribution to the study of phage evolution and propionibacterial genetics.

With the sequencing of bacteriophages comes the potential to genetically manipulate the host bacterium. Although the physiology of P. acnes has been well studied in vitro (4, 13, 14), genetic studies have been limited by the lack of genetic transfer systems. The inability to manipulate P. acnes genetically has severely hindered progress toward understanding the role of this organism in acne and other diseases. Similar problems existed several years ago with the study of pathogenic mycobacteria, which are closely related to propionibacteria taxonomically. The development of transformation systems and plasmid vectors for mycobacteria has allowed greater study of the genetics of these organisms (18, 27). In addition, several mycobacteriophages have been characterized in detail, and the genomes of several such phages have been sequenced and analyzed (10, 11, 15, 24, 25). These phages have been proposed to be useful tools for the genetic manipulation of mycobacteria and for understanding mycobacterial gene expression. Studies of them have also made a significant contribution to the study of phage evolution and have demonstrated that there is a high degree of mosaicism among the mycobacteriophages.

Further studies of P. acnes bacteriophages may also lead to the development of phage therapy for acne. Such therapy may overcome the current problems surrounding long-term use of antibiotics and the emergence of resistance in P. acnes and other skin commensals. We present here the first genome sequence of a P. acnes bacteriophage along with an extensive sequence analysis and characterization of the phage morphology and host range.

MATERIALS AND METHODS

Strains of bacteria and phage PA6. P. acnes bacteriophage PA6 was isolated from a skin scrub wash sample taken from a patient attending the Department of Dermatology at Leeds General Infirmary. A plaque was observed among heavy bacterial growth following plating of this sample on media selective for propi-
FIG. 1. Transmission electron micrograph of negatively stained PA6 particles. Bar = 100 nm.

RESULTS

Morphology of PA6 particles. The morphology of PA6 particles was assessed by transmission electron microscopy (Fig. 1). PA6 possessed an icosahedral head with a diameter of approximately 50 nm and a flexible tail that was 165 nm long. PA6 resembles phages of the Siphoviridae family that possess icosahedral heads and long, noncontractile tails (10, 15, 24).

Host range of PA6. In order to determine the host range of PA6, plaque assays were carried out with 32 different isolates of P. acnes (type I and II), other species of cutaneous propionibacteria, and members of other genera commonly found on human skin. PA6 was able to infect and lyse all 32 isolates of P. acnes. The majority of these isolates were clinical isolates from acne patients and included strains that were either sensitive or resistant to erythromycin/clindamycin. Also included were a laboratory strain (P37), the type strain (NCTC737), and the recently sequenced strain KPA171202 (3). PA6 was not able to infect isolates of Propionibacterium granulosum, Propionibacterium avidum, Staphylococcus epidermidis, or Corynebacterium bovis that are also members of the human skin microflora.

DNA sequence and organization of the PA6 genome. The linear, double-stranded DNA genome of phage PA6 was sequenced using a shotgun strategy. A single contig consisting of 29,739 bp was assembled from 681 sequences and was identified as the full-length phage genome, and >9-fold coverage was achieved. An additional 13-base single-stranded extension (CTCTCGTACGGCCTT) was identified at each end of the PA6 genome. The overall G+C content of the PA6 genome was 54.0%, which is slightly lower than the G+C content determined for the genome of P. acnes (60%) (3). A total of 48 ORFs were identified in the genome of PA6. Seventeen ORFs possessed potential AUG initiation codons, and the remaining ORFs had AUG initiation codons. All three of the standard termination codons were used, and 29 ORFs had a UGA termination codon. No tRNA genes were found in the genome. The coordinates of the protein-encoding genes identified are shown in Table 1, and a diagram of the PA6 genome is presented in Fig. 2.

The PA6 genome has an organization similar to that of other Siphoviridae with a left arm containing rightward-transcribed genes (genes 1 to 23) and a right arm containing leftward-transcribed genes (genes 45 to 24). There is little noncoding DNA between these genes, suggesting that there is a single transcript for each set of genes. The final three genes (genes 46 to 48) at the extreme right end of the genome are transcribed rightward and are separated from the other left arm genes by a 1,447-bp segment of noncoding DNA (bases 27431 to 28877). The most notable feature of this region is its much lower G+C content compared to that of the rest of the genome (45%). This right arm gene organization closely resembles that of mycobacteriophage Bxb1, although the noncoding region between the leftward-transcribed genes and three rightward-transcribed genes at the far right of the Bxb1 genome is much smaller, 213 bp. The codon usage of PA6 is somewhat different from that of P. acnes KPA171202 (see the supplemental material), suggesting that in evolutionary terms, PA6 may have only recently become a phage of P. acnes.

Genes encoding structural and assembly proteins. The left arm of the PA6 genome contains genes encoding proteins of the viral particle. The organization of these genes is similar to that of many of the mycobacteriophages, and as expected, the morphology of the PA6 virion is similar to that observed for these phages (25). Many of the predicted gene products are related to those of mycobacteriophages. Predicted functions have been assigned based on homology to other phage proteins having known or predicted functions and on matches to the COG (http://www.ncbi.nlm.nih.gov/COG/) and Pfam (http://www.sanger.ac.uk/Software/Pfam/) databases.

PA6 gp2 is a putative terminase large subunit and shows a high degree of homology to other members of this protein family (43% similarity to TM4 gp4 and 47% similarity to the
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lactococcal phage r1t). The smaller gp1 protein shows weak homology to gp32 of phage VWB that is predicted to be the terminase small subunit (32). This homology, along with the size and position of gene 1, makes the gp1 protein the likely terminase small subunit of PA6. This family of proteins is involved in the packaging of phage DNA into the head of the virus particle (12). This process also involves the portal protein (gp3 of PA6) that lies at the head-tail interface and enables passage of genomic DNA into phage heads during packaging and ejection during infection. The gp5 and gp6 proteins are most likely components of the phage head. gp5 is likely to be the scaffold protein that directs assembly of the head proteins, and gp6 is likely to be the major head protein that shows homology to the gp7 head protein of mycobacteriophage Che9d (55% similarity over 312 residues). Three proteins were identified that are proposed components of the phage tail. gp11 exhibits homology with the major tail protein of lactococcal phage δLC3. gp14 is a putative tape measure protein that in bacteriophage δH9278 LC3. gp114 exhibits homology with the major tail protein of lactococcal phage δLC3. gp14 is a putative tape measure protein that in bacteriophage δH9278 LC3. gp114 exhibits homology with the major tail protein of lactococcal phage δLC3. gp14 is a putative tape measure protein that in bacteriophage δH9278 LC3. gp114 exhibits homology with the major tail protein of lactococcal phage δLC3. gp14 is a putative tape measure protein that in bacteriophage δH9278 LC3. gp114 exhibits homology with the major tail protein of lactococcal phage δLC3. gp14 is a putative tape measure protein that in bacteriophage δH9278 LC3. gp114 exhibits homology with the major tail protein of lactococcal phage δLC3.

![FIG. 2. Genome organization of PA6. The 29,739-bp genome is represented by a horizontal bar with 1-kb intervals marked. Putative ORFs are indicated by boxes at three different heights representing the three frames on each strand. Rightward-transcribed genes are above the genome, and leftward-transcribed genes are below the genome. Predicted functions and homologues are indicated. ORFs with phage and nonphage homologues are indicated by gray and black boxes, respectively. ORFs unique to PA6 are indicated by white boxes.](http://jb.asm.org/)
with nonpolar C termini. It is possible that this protein is involved in some proteolytic process during phage assembly. Alternatively, this protein may be involved in entry of the phage into the host cell through degradation of peptide linkages in the cell wall to allow injection of viral DNA. The location of the gene encoding gp16 suggests that it may be a component of the PA6 tail, making this function not unlikely.

**Lysis functions.** ORF20, located near the end of the section of rightward-transcribed genes, encodes a putative N-acetylmuramoyl-L-alanine amidase. This enzyme is most likely involved in cell lysis following phage assembly rather than in phage entry as the gene immediately downstream of ORF20 (ORF21) encodes a putative holin. Following phage assembly, holin proteins assemble to form pores in the cellular membrane, allowing the amidase enzyme access to the surrounding peptidoglycan (35). PA6 gp21 appears to belong to the class II group of holins. Members of this group are usually 65 to 95 residues long and possess two transmembrane domains. Although gp21 is larger (113 residues), it is predicted to contain two transmembrane domains instead of the three transmembrane domains of the class I holins. The PA6 amidase exhibits homology with amidases from the PG1 and Che8 mycobacteriophages. However, the highest degrees of similarity are with amidases from the PG1 and Che8 mycobacteriophages. Members of this group of holins. The PA6 amidase exhibits homology with amidases from the PG1 and Che8 mycobacteriophages. Members of this group are usually 65 to 95 residues long and possess two transmembrane domains. Although gp21 is larger (113 residues), it is predicted to contain two transmembrane domains instead of the three transmembrane domains of the class I holins. The PA6 amidase exhibits homology with amidases from the PG1 and Che8 mycobacteriophages. However, the highest degrees of similarity are with amidases from the PG1 and Che8 mycobacteriophages. Members of this group of holins.

**DNA replication functions.** The leftward-transcribed section of the genome contains genes predicted to encode proteins involved in phage DNA replication. PA6 gp31 and gp32 are both putative DNA primases. PA6 gp31 exhibits homology with one of the DNA primases of Bxb1, gp50 (35% identity over 154 residues). The organization of these genes is similar to that of the DNA primase-encoding genes of mycobacteriophages Bxb1, L5, and D29, with an extensive overlap of genes 31 and 32. It has been suggested that in these mycobacteriophages, the primase proteins are produced through a programmed translational frameshift resulting in a single functional protein (24). PA6 gp34 is proposed to be a DNA helicase based on its match to the COG DNA helicase group. This protein contains an ATP-binding domain and exhibits homology to Bxb1 gp57 and L5 gp65, which are also predicted DNA helicases. The functions of other genes in this region encode proteins with no predicted functions but with homology to proteins of other phages (Table 1).

One significant aspect of the PA6 genome is the absence of any gene encoding an obvious integrase-type enzyme. Plaques of PA6 on lawns of *P. acnes* are clear with hazy centers and not turbid, as is characteristic of truly lysogenic phages. This plaque morphology has been observed for TM4, which is not temperate but may be capable of forming pseudolysogens in some strains of mycobacteria (11). Also absent from the PA6 genome is any gene encoding a repressor-like protein that would indicate a lysogenic function. Although the presence of such a protein cannot be completely ruled out, the lack of these two lysogeny-related proteins strongly suggests that PA6 is a lytic phage and does not integrate into the host genome. Other PA6 proteins possibly involved in DNA regulation/replication include gp37 and gp48. These proteins are predicted to be an exonuclease and an endonuclease, respectively, due to matches to the COG RecB exonuclease group and Pfam HNH endonuclease family, respectively.

**Other genes and features of interest.** Two other predicted ORFs of PA6 are worthy of mention. ORF19 encodes a protein with considerable homology to the human collagen α1(III) chain precursor. In particular, gp19 contains many G-X-Y repeats that are characteristic of many collagens (Fig. 3). The function of such proteins is unknown, but it has been suggested that they stabilize the tail structure. It is tempting to speculate that in PA6 this protein may have evolved a second function, binding to the host cell and, more specifically, to potential collagen-binding surface proteins of *P. acnes*. The *P. acnes* genome contains several genes encoding putative surface adhesins that are likely to be important for the colonization of human skin, one or more of which may bind collagen.

A second gene of interest is ORF24. A BLAST search of the gene product revealed that this protein has a conserved sigma factor domain. The gene encoding this protein is transcibed in the same direction as the genes encoding proteins predicted to be involved in DNA replication. This protein may therefore be a phage-specific sigma factor that directs the host RNA polymerase to transcribe from phage-specific promoters.

Within the 1.4-kb noncoding region of the PA6 genome there is an approximately 500-bp section that contains numerous direct, inverted, and symmetric repeats (Fig. 4). This 500-bp section has a particularly low G+C content (35%).

![Comparison of PA6 gp19 with the human collagen α1(III) chain. Protein sequences are aligned, and identical amino acid residues are marked with asterisks. The glycine residues of the repetitive G-X-Y motifs are in bold type. The numbers indicate the positions of the amino acid sequences in the proteins.](http://jb.asm.org/)

**FIG. 3.** Comparison of PA6 gp19 with the human collagen α1(III) chain. Protein sequences are aligned, and identical amino acid residues are marked with asterisks. The glycine residues of the repetitive G-X-Y motifs are in bold type. The numbers indicate the positions of the amino acid sequences in the proteins.
Such repeat sequences may be binding sites for transcription factors and/or may form secondary structures important for the regulation of gene transcription and DNA replication. The gene organization and direction of transcription indicate that this region is likely to contain promoters for phage gene transcription. The presence of a cryptic prophage (3). Genome analysis of other Propionibacterium species, including those for lysogeny, reveals the presence of a cryptic prophage in the KPA171202 genome (3).

**DISCUSSION**

Bacteriophages of *P. acnes* have been isolated previously, but this is the first report of the genomic sequence of a *P. acnes* phage. The organization of the PA6 genome and the similarity of predicted proteins to the proteins of other phages, especially the mycobacteriophages, provide interesting insights into the phylogenetic relationships of these phages and further highlight the mosaic nature of the phage genomes. Obvious differences between these phages include the apparent lack of genes involved in lysogeny within the PA6 genome. The hazy appearance of these phages includes those for lysogeny. The presence of a cryptic prophage within the *P. acnes* KPA171202 genome indicates that *P. acnes* phages capable of integration may exist. Genome analysis of other *P. acnes* bacteriophages could establish phylogenetic relationships and show whether phage PA6 is a derivative of a much larger temperate phage. The host range of PA6 is restricted to *P. acnes*. Although it infects and lyses all strains of *P. acnes* tested to date, PA6 cannot infect other members of the genus *Propionibacterium*. This restricted range is likely to be dictated by the phage receptor and/or other components of the phage tail involved in entry of the phage into the cell. The PA6 minor tail subunit gp15 may be involved in host specificity. This protein has homology to D29 gp27, L5 gp27, and Bxb1 gp23, which have been proposed to be host specificity determinants (24). Isolation of phages capable of lysing the closely related cutaneous propionibacteria *P. granulosum* and *P. avidum* would allow comparisons of these genes to be made. However, phages with the ability to infect these species have not been isolated to date. The sequencing of PA6 makes a valuable contribution to the study of bacteriophage evolution. The close relationship between mycobacteria and propionibacteria is reflected in the relationships between their respective phages, and PA6 is more closely related to mycobacteriophages than to phages of any other bacterial group. More significantly, PA6 should contribute to the study of propionibacterial genetics. Finally, the sequencing of PA6 should greatly enhance the development of a potential bacteriophage therapy to treat acne and therefore overcome the significant problems associated with long-term antibiotic therapy and bacterial resistance.

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**REFERENCES**
