Nucleotide sequence of conjugative prophage \( \Phi 1207.3 \) (formerly Tn1207.3) carrying the \( \text{mef}(A)/\text{msr}(D) \) genes for efflux resistance to macrolides in \textit{Streptococcus pyogenes}

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\textbf{INTRODUCTION}

In \textit{Streptococcus pyogenes}, the \( \text{mef}(A)/\text{msr}(D) \) pair of genes encoding efflux resistance to 14- and 15-membered macrolides is carried by a mobile genetic element originally described as a conjugal transposon which was called Tn1207.3 (Santagati et al., 2003; Pozzi et al., 2004). This element was found to be 52.5 kb in size, and to contain a complete copy of Tn1207.3, a 7,244-bp defective transposon previously found to carry \( \text{mef}(A)/\text{msr}(D) \) in \textit{S. pneumoniae} (Santagati et al., 2000). Integration of the element into the \textit{S. pyogenes} chromosome occurred at a specific GA dinucleotide target site located into the \textit{comEC} coding sequence, with integration producing a duplication of the GA site. Upon conjugal transfer to \textit{S. pneumoniae}, chromosomal integration occurred in \textit{celB}, the pneumococcal homolog of \textit{comEC}, at the same insertion site of Tn1207.1 (Santagati et al., 2003; Pozzi et al., 2004). A copy of Tn1207.1 was also found integrated in the 58,761-bp genetic element \( \Phi 10394.4 \), described as a prophage integrated at the same GA site within the \textit{comEC} coding sequence of an erythromycin resistant clinical strain of \textit{S. pyogenes} (Bank et al., 2003, 2004).

Here we report the manually annotated DNA sequence of Tn1207.3 which indicates that the element is in fact a prophage, identical to the right end of \( \Phi 10394.4 \). For this reason the element was renamed \( \Phi 1207.3 \).

\textbf{MATERIALS AND METHODS}

\textbf{Streptococcus pyogenes STRAINS AND GROWTH CONDITIONS}

2812A is an erythromycin-resistant italian clinical isolate containing \( \Phi 1207.3 \) (Santagati et al., 2003). Bacteria were routinely grown in tryptic soy broth or tryptic soy agar (Difco) supplemented with 3% horse blood and, where appropriate, in presence of 1 \( \mu \text{g/ml} \) erythromycin.

\textbf{PCR AND SEQUENCING}

Long PCR fragments were obtained with Takara LA Taq (Takara) following essentially the protocol suggested by the manufacturer. Briefly, the 25-\( \mu \text{l} \) reaction mixture was in 1X LA PCR Buffer II Taq buffer and contained: (i) 2.5 mM MgCl\(_2\), (ii) 200 \( \mu \text{M} \) dNTPs, (iii) 10 pmol of each primer, (iv) 0.25 units of Takara LA Taq, (v) 1 \( \mu \text{l} \) of liquid bacterial culture. Thermal cycling profile was as follows: 1 cycle at 92\( ^\circ \text{C} \) for 2 min, then 30 cycles at 50\( ^\circ \text{C} \) for 10 s, 68\( ^\circ \text{C} \) for 15 min, 92\( ^\circ \text{C} \) for 10 s, and 1 cycle at 50\( ^\circ \text{C} \) for 1 min and 68\( ^\circ \text{C} \) for 20 min. A primer walking approach (Santoro et al., 2010) was used to sequence the PCR products. The Expand High Fidelity
The complete nucleotide sequence of \( \Phi 1207.3 \) was obtained by primer walking on four long PCR fragments spanning the whole element. Inverse PCR on genomic DNA of \( S. pyogenes \) strain 2812A was carried out with divergent primers matching the already known \( 7,244 \)-bp sequence of \( \Phi 1207.3 \) and its chromosomal junction sequences. Amplicons obtained were identified searching the protein family database Pfam available at the Wellcome Trust Sanger Institute. The nucleotide sequence of \( \Phi 1207.3 \) is assigned GenBank accession no. AY657002.

RESULTS

\( \Phi 1207.3 \) NUCLEOTIDE SEQUENCE

The complete nucleotide sequence of \( \Phi 1207.3 \) was produced PCR fragments of about 1,000 bp in size which were used as sequencing starting template to confirm sequence on the other strand. Four primer pairs were used to amplify the four fragments, ranging from 10,358 to 16,223 bp in size, containing \( \Phi 1207.3 \) and its chromosomal junction fragments.

DNA SEQUENCE ANALYSIS

DNA sequence analysis was performed with the software Artemis version 11. Manual gene annotation was carried out conducting BLAST homology searches of the databases available at the National Center for Biotechnology Information. Protein domains were identified searching the protein family database Pfam available at the Wellcome Trust Sanger Institute. The nucleotide sequence of \( \Phi 1207.3 \) is assigned GenBank accession no. AY657002.

ORFs OF \( \Phi 1207.3 \)

For 34 out of 58 ORFs it was possible a manual homology-based annotation with functional prediction of the hypothetical gene product (Table 1). Public protein databases and the Pfam protein family database were used for Blast searches of predicted gene products, taking into account significant homologies with functionally characterized proteins or good matches with Pfam domains. A putative ribosome binding sequence preceded all ORFs except \( \text{orf}36 \) and \( \text{orf}37 \). The alternative start codon TTG was present in \( \text{orf}34, \text{orf}36, \text{orf}43, \) and \( \text{orf}56 \), whereas \( \text{orf}37, \text{orf}38, \) and \( \text{orf}51 \) started with GTG. In the left arm of the element, the gene product of \( \text{orf}2 \) was predicted to be a site-specific resolvase of the serine recombinase family, \( \text{mef}(A) \) (\( \text{orf}4 \)) and \( \text{msr}(D) \) (\( \text{orf}5 \)) encoded respectively the transmembrane domains and the ATP-binding domains of the ABC transporter responsible for the \( \text{M} \)-type resistance to macrolides (Iannelli et al., 2014, Abstract C1-1188, 44th Interscience Conference Antimicrobial Agents Chemistry, 2004), \( \text{orf}8 \) and \( \text{orf}11 \) were homologous to the Tn5253 \( \text{umu}C/\text{umu}D \) operon conferring UV resistance by activation of the SOS repair system (Munoz-Najar and Vijayakumar, 1999). SpyLM, encoded by \( \text{orf}12 \), is a C-5 cytosine-specific DNA methylase belonging to the SpyI type II restriction-modification system (Iannelli et al., 2014).

FIGURE 1 | Schematic diagram of \( S. pyogenes \) \( \Phi 1207.3 \). The element is 52,491 bp in size and contains 58 open reading frames (ORFs). ORFs and their direction of transcription are represented by arrows and the annotated ORFs are indicated only by their numbers. Macrolide resistance genes and resolvase genes are reported as red and yellow arrows respectively. The region homologous to Tn1207.1 is indicated by a solid bar. The different GC content of the various regions are indicated with dotted bars. Scale is in kilobases.
### Table 1 | Annotated open reading frames (ORFs) of ϕ12073.

| ORF (aa) | Annotation and comments (reference) | Pfam domains[^b] | Homologous protein ID/origin | Amino acid identity-similarity | E value[^c] |
|----------|--------------------------------------|------------------|------------------------------|-------------------------------|-------------|
| orf1 (218) | CpXC protein, contains four conserved cysteines forming two CpXC motifs | CpXC (15–138) [1.3e-31] | EU351020 orf70/Tn5253 | 344/471 (73%) – 398/471 (85%) | 0.0 |
| orf2 (370) | Resolvase (Yang and Steitz, 1995) Resolvase, N terminal domain (44–193) [5.4e-25] Recombinase (217–325) [2.9e-20] | | | |
| mefA/orf4 (405) | Macrolide ABC transporter, transmembrane domain | Transmembrane secretion effector (7–404) [1.7e-24] | | |
| msr(D)/orf5 (487) | Macrolide ABC transporter, ATP-binding domain | ABC transporter, ATP-binding domain (20–86; 167–284; 312–437) | | |
| orf7 (122) | YolD-like protein, functionally equivalent to UmuD | YolD-like protein (28–111) [3.2e-12] | | |
| umuC/orf8 (471) | SOS response UmuC protein (Munoz-Najar and Vijayakumar, 1999; Iannelli et al., 2014) | | | |
| umuD/orf11 (229) | UmuD MucA homolog (Munoz-Najar and Vijayakumar, 1999; Iannelli et al., 2014) | | | |
| spyIM/orf12 (408) | C-5 cytosine-specific DNA methylase (Euler et al., 2007) | | | |
| orf13 (555) | Restriction endonuclease subunit | AAA domain (dynein-related subfamily) (227–387) [9.1e-9] | | |
| orf14 (415) | Restriction endonuclease subunit | Llaj restriction endonuclease (13–383) [5.7e-120] | AAS99180/pNP40 | 157/406 (38%) – 251/406 (61%) | 5e-81 |
| orf15 (384) | DNA binding, zinc finger domain protein | CGNR zinc finger (338–380) [4.2e-5] | | |
| orf17 (651) | DNA polymerase | DNA polymerase family A (247–520) [3.7e-14] | | |
| orf19 (190) | Conserved phage-associated protein | DUF2815 (11–188) [9.7e-65] | | |

(Continued)
Table 1 | Continued

| ORF (aa) | Annotation and comments (reference) | Pfam domains (E value) | Homologous protein | Amino acid identity-similarity | E value |
|---------|-------------------------------------|-----------------------|--------------------|-------------------------------|---------|
| orf23 (761) | DNA primase (Ye et al., 2002) | D5 N terminal like [285–472] [2.4e-29] | | | |
| orf24 (100) | Restriction-modification enzyme, putative (Kinch et al., 2009) | VRR-NUC domain [8–88] [3.3e-16] | | | |
| orf25 (458) | Helicase, putative | SNF2 family N-terminal domain [5–293] [8.9e-19] | | | |
| orf29 (353) | S-adenosylmethionine synthetase (Tagusagawa et al., 1996) | S-adenosylmethionine synthetase: N-terminal domain [9–85] [6.9e-28] | Central domain (105–214) [75e-30] C-terminal domain Domain (216–353) [1.2e-57] | | |
| orf30 (121) | HNH endonuclease, putative | HNH endonuclease [62–110] [1.6e-11] | | | |
| orf32 (410) | DNA methylase | ParB-like nuclease domain [5–93] [1e-10] | DNA methylase [189–381] [5.2e-29] | | |
| orf33 (888) | C-5 cytosine-specific DNA methylase | C-5 cytosine-specific DNA methylase [4–382] [1.5e-59] | | | |
| orf38 (158) | Phage terminase, small subunit, putative | Phage terminase, small subunit [50–150] [8.2e-31] | | | |
| orf39 (530) | Phage terminase, large subunit, putative (Schouler et al., 1994) | Phage Terminase [48–515] [1.1e-103] | | | |
| orf40 (413) | Phage portal protein, putative (Moore and Prevelige, 2002) | Phage portal protein [30–381] [4.8e-121] | | | |
| orf41 (228) | Clp protease, putative (Wang et al., 1997) | Clp protease [8–179] [4.5e-40] | | | |
| orf42 (399) | Phage capsid protein, putative | Phage capsid family [124–393] [6.4e-78] | | | |
| orf44 (109) | Phage head-tail adaptor, putative | Phage head-tail joining protein [7–105] [9.8e-15] | | | |
| orf45 (126) | Tail component protein, putative | Bacteriophage HK97-gp10, putative tail-component [11–92] [1.2e-6] | | | |
| orf50 (1039) | Tail tape measure protein, putative (Pedersen et al., 2000) | Phage-related minor tail protein [311–554] [2.7e-14] | AAG32164.1/Lactococcus phage TP901-1 | 152,693 (22%) – 280,693 (40%) | 1e-22 |
| orf52 (967) | Host specificity protein (Duplessis and Moineau, 2001) | | AAK83249/S. thermophilus phage DT1.2 | 113,418 (27%) – 186,418 (44%) | 5e-40 |

(Continued)
| ORF (aa)| Annotation and comments (reference) | Pfam domains\(^a\) \([E \text{ value}]\) | Homologous protein ID/origin | Amino acid identity-similarity | \(E\) value\(^c\) |
|--------|-------------------------------------|---------------------------------|-------------------------------|-------------------------------|----------------|
| hol/orf53 (760) | Holin family protein (Lévesque et al., 2005) | Siphovirus protein of unknown function (DUF859) (1-516) \([1.8 \times 10^{-214}]\) Holin family (637-754) \([4 \times 10^{-40}]\) | AAW27943/S. thermophilus phage 2972 | 205/514 (40%) – 279/514 (54%) | \(8 \times 10^{-89}\) |
| skl/orf54 (260) | N-acetyluramoyl-L-alanine amidase (Llull et al., 2006) | CHAP domain (13-142) \([5.6 \times 10^{-10}]\) | CAJ13672/S. mitis phage SK137 | 62/211 (29%) – 96/211 (45%) | \(9 \times 10^{-8}\) |
| orf56 (412) | Resolvase | Resolvase, N terminal domain (20-167) \([3.8 \times 10^{-30}]\) Resolvase (187-291) \([4.2 \times 10^{-21}]\) Recombinase (200-306) \([5.5 \times 10^{-24}]\) Recombinase zinc beta ribbon domain (307-368) \([1.6 \times 10^{-8}]\) | | |
| orf57 (521) | Resolvase | Resolvase, N terminal domain (28-176) \([4.6 \times 10^{-33}]\) Recombinase (200-306) \([5.5 \times 10^{-24}]\) Recombinase zinc beta ribbon domain (316-377) \([2.4 \times 10^{-10}]\) | | |
| orf58 (191) | ADP-ribosyltransferase toxin, putative | ADP-ribosyltransferase exoenzyme (66–181) \([3.7 \times 10^{-17}]\) | | | |

\(^a\)The number of amino acids is shown in parentheses.
\(^b\)The numbers in parentheses represent the part of the protein homologous to the Pfam domain.
\(^c\)Method: compositional matrix adjust.
case, and responsible for inhibition of restriction by SmaI, whereas orf13 and orf14 encoded the two subunits of SpyI restriction endonuclease (Euler et al., 2007). Other genes coding for putative restriction-modification proteins include orf24 (restriction enzyme), orf30 (endonuclease), orf33 (cytosine-specific DNA methylase), while orf29 gene product presented an S-adenosylmethionine synthetase domain which may act as a methyl group donor for Orf33. In the central region, orf17, orf23, and orf25 encoded a DNA polymerase, a DNA primase, and a DNA helicase, possibly involved in phage DNA replication, whereas orf38 and orf39 encoded for the small and large subunit of the phage terminase, which, together with the portal protein encoded by orf40, could be involved in phage DNA packaging. orf42, orf44, orf45, and orf50 code for putative structural phage proteins. A putative lysis cassette, which is typically composed by a holin and an endolysin (Young et al., 2000) was encoded by hol (orf53) and skl (orf54). At the right end of the element, orf56 and orf57 gene products were homologous to resolvases of the serine recombinase family, possibly involved in excision, circularization, and site specific integration of Φ1207.3, whereas orf58 encoded a putative ADP-ribosyltransferase toxin.

**DISCUSSION**

The complete and annotated DNA sequence of the mobile genetic element previously called Tn1207.3 clearly shows that the element is a prophage which we renamed Φ1207.3. At the sequence level, Φ1207.3 (52,491 bp) shows homology to two S. pyogenes prophages: (i) Φ10394.4 (58,761 bp), integrated at the same chromosomal site of Φ1207.3 (Banks et al., 2003; Pozzi et al., 2004); (ii) Φm46.1 (55,172 bp), integrated in the rum gene encoding an RNA uracil methyltransferase (Brenciani et al., 2010). The whole Φ1207.3 is identical to the right end of Φ10394.4, whereas high homology (>70%) to Φm46.1 is limited to 57% of the Φ1207.3 genome. Prophages similar to Φ1207.3 were also described by Giovanetti et al. (2010).

The recombination machinery of Φ1207.3 consists of three resolvases of the serine recombinase family. Serine recombinases are less common than tyrosine recombinases in prophage genomes and are usually present as a single large recombinase gene (Smith and Thorpe, 2002). Most of the S. pyogenes prophages present in sequenced genomes have a tyrosine recombinase (integrase) as the recombination module (Beres and Musser, 2007). The two resolvase genes at the right end of Φ1207.3 encode ADP-ribosyltransferase proteins. A putative lysis cassette, which is typically composed by a holin and an endolysin (Young et al., 2000) was encoded by hol (orf53) and skl (orf54). At the right end of the element, orf56 and orf57 gene products were homologous to resolvases of the serine recombinase family, possibly involved in excision, circularization, and site specific integration of Φ1207.3, whereas orf58 encoded a putative ADP-ribosyltransferase toxin.

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