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Rapid repeat infection of SARS-CoV-2 by two highly distinct delta-lineage viruses

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ABSTRACT

An instance of sequential infection of an individual with, firstly, the Delta variant and secondly a Delta-sub-lineage has been identified. The individual was found positive for the AY.26 lineage 22 days after being found positive for the Delta [B.1.617.2] variant. The viruses associated with the cases showed dramatic genomic difference, including 31 changes that resulted in deletions or amino acid substitutions. Seven of these differences were observed in the Spike protein. The patient in question was between 30 and 35 years old and had no underlying health conditions. Though singular, this case illustrates the possibility that infection with the Delta variant may not itself be fully protective against a population of SARS-CoV-2 variants that are becoming increasingly diverse.

1. Introduction

Cases of reinfection with SARS-CoV-2 are well-documented [1–3]. Efforts to determine the frequency of the phenomenon have been made and have shown that the occurrence may be rare to date [4,5]. The true incidence of reinfection is difficult to determine due to the possibility that secondary infections are harder to detect due to decreased or absent symptoms or less testing. The frequency of reinfection cases will increase over time, as more cases in the human population denotes more opportunities for the phenomenon, but also because genomic variation in the virus over the course of pandemic time can lead to variants that can evade immunities [6–9]. Variants occurring later in a pandemic's course would not be expected to be recognized with the same acuity by an immune system that has been stimulated [vaccinated] by an earlier version of a virus. The immune response to SARS-CoV-2 appears similar to that of other respiratory viruses. Within 1 to 3 weeks, antibodies including IgM, IgG and IgA class appear with specificity against spike protein, with one report showing 100% of patients seroconverting with IgG reactivity by day 15 [10,11]. Neutralizing antibodies are thought to persist but a clear decay rate of their functional titer is currently unknown and is likely to vary considerably between individuals [12–15]. Certain studies have shown that rare individuals do not develop IgG after infection [16,17].

Cases of immune evasion / vaccine breakthrough have been investigated for the "Delta" variant of SARS-CoV-2 [8,18,19]. The variant appears to possess lower sensitivity to antibody neutralization and higher transmissibility [8,18–22]. To date, the variant is highly successful and has generated multiple sub-lineages. Herein, we describe a case of infection with the Delta variant, that was followed up 22 days later by a subsequent case of infection with a sub-lineage of the Delta variant. Sequence analysis of both cases reveals substantial genetic difference between the associated viruses. Epidemiologic investigation of each case revealed contacts who were positive for SARS-CoV-2 and whose specimens were also genomically analyzed by the Nevada State Public Health Laboratory.

2. Materials and methods

The Nevada State Public Health Laboratory [NSPHL] performed sequencing and subsequent analysis of positive SARS-CoV-2 specimens. In each case, nasal specimens collected in viral transport medium were transported to the public health laboratory and were evaluated by real-time polymerase chain reaction [RT-PCR] to confirm reactivity and to determine cycle threshold (Ct) value. RT-PCR

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was performed using the CDC Influenza SARS-CoV-2 Multiplex Assay. Nucleic acid extractions were performed by Apostle MagTouch Nucleic Acid Extraction Automation Systems [Apostle Inc, San Jose, CA]. Amplification and detection were performed using an ABI Quant Studio 7 [Thermo Fisher Scientific, Waltham, MA]

Extracted nucleic acid was subject to SARS-CoV-2 genomic sequencing on the Clear Labs DX platform [Clear Labs Inc, San Carlos, CA] which utilized Oxford Nanopore Technology [ONT].

The workflow begins with a cDNA synthesis step [reverse transcription] followed by a target capture PCR to amplify specific regions of the SARS-CoV-2 cDNA. A modified version of the ARTIC v3 primer panel [98 tiled primers in 2 pools] is used to capture target regions of roughly 400bp in length through 2 separate PCR reactions for each sample. Following PCR, the resulting amplicons from the independent PCR reactions are pooled together and are subject to a SPRI bead cleanup, filtering out the PCR products below the expected amplicon size range and other unused PCR components. The purified amplicons of each sample are then barcoded and pooled together for library preparation. During library preparation, ONT-specific adapters are attached to each of the barcodes. An additional SPRI clean-up is performed to remove any unattached adapters from the sequencing library. The library is then mixed with other sequencing reagents, loaded onto the Flow Cell and sequenced for 8 hours. Read base calling is processed live on the GridION instrument [long-read sequencing technology]. Data is uploaded to the Clear Labs Server for bioinformatics analysis including read quality/length filtering, and consensus-based assembly. The resulting FASTQ and FASTA files are provided via the Clear Labs WGS Web App for download.

Analysis of SARS-CoV-2 genomic data was performed using *Titan ClearLabs* and *Titan_Augur_Run*, 2 workflow description language [WDL] workflows within the Theiagen Public Health Viral Genomics [PHVG] DockStore collection [https://dockstore.org/organizations/Theiagen/collections/PublicHealthViralGenomics]. PHVG WDL workflows consist of freely-available containerized bioinformatics algorithms, such as those hosted on the StaPH-B DockerHub repository [https://hub.docker.com/u/staphb], and were designed to run on general-purpose containerized workflow execution infrastructures including light-weight compute resources running miniwdl [https://github.com/chanzuckerberg/miniwdl], local- or cloud-based high-performance compute [HPC] systems with access to the Cromwell engine [https://cromwell.readthedocs.io/en/stable/], or various web applications that provide a graphical user interface to non-technical users, such as DNANexus or Terra. For this study, *Titan_ClearLabs* and *Titan_Augur_Run* were accessed and run using the Terra platform [app.terra.bio].

Source code for the PHVG WDL workflows has been made publicly available with the AGPL-3.0 License on GitHub [https://github.com/theiagen/public_health_viral_genomics].

The *Titan_ClearLabs* workflow was utilized to generate consensus assemblies from raw Clear Labs read data and to perform SARS-CoV-2 lineage and clade designations for each sample. Briefly, human reads were removed from Clear Labs read data using the NCBI SRA-Human-Scrubber [https://github.com/ncbi/sra-human-scrubber]. De-hosted reads were then assembled as per the Artic nCoV-2019 novel coronavirus bioinformatics protocol [https://artic.network/ncov-2019/ncov2019-bioinformatics-sop.html] with a modification whereby the artic minion normalize flag

Table 1
Case data describing symptoms of illness, patient information, and quality indications of sequence data obtained in each case

	Case A 8/16/2021	Case B 9/7/2021
Cycle Threshold [Ct]	25.42	24.87
Percent reference coverage	92.09%	97.32%
Mean coverage depth	286X	857X
Pangolin lineage	B.1.617.2	AY.26
Symptom onset	8/12/2021	9/2/2021
Symptoms	Cough	Cough
	Shortness of breath	Shortness of breath
	Muscle aches	Muscle aches
	Fever [>100.4F]	Fever [>100.4F]
	Chills	Chills
	Headache	Headache
	Loss of Taste and Smell	Loss of Taste and Smell
	Sore throat	Fatigue
	Runny nose	Dizziness
	Pre-existing conditions, ruled out:	
	Chronic Lung Diseases [any]	
	Diabetes Mellitus	
	Cardiovascular Disease	
	Chronic Renal Disease	
	Immunocompromised Condition	
	Neurologic/intellectual disability	
	Other Chronic Diseases	
	Current or Former Smoker	

Table 2
Mutations associated with virus in each case. Mutations are described relative to reference strain sequence MN908947.3 derived from isolate USA-WA1/2020

	Case A: 8/16/2021	Case B: 9/7/2021
Pango lineage:	B.1.617.2	AY.26
Membrane	I82T	I82T
Nucleocapsid	D63G	D63G
		A134V
	R203M	R203M
	G215C	
	D377Y	D377Y
NS-3	S26L	S26L
	G100C	
		N257del
		P258del
		V259del
		M260del
NS-7a	V82A	V82A
	T120I	T120I
NS-7b	T40I	
NS-8		D119N
NSP-1		S17del
		L18M
NSP-2	A411V	
NSP-3	A488S	
		P822L
	P1228L	
	A1736V	
NSP-4	V167L	
		A446V
	T492I	
NSP-6	T77A	
		V149A
		T181I
NSP-12	F192V	
	P323L	P323L
	G671S	G671S
NSP-13	P77L	P77L
NSP-14	A394V	
Spike	T19R	T19R
		E156G
		F157del
		R158del
		A222V
		L452R
		T478K
	D614G	D614G
	P681R	P681R
	D950N	D950N
		V1264L

was adjusted to 20000 to account for Clear Labs sequencing depths. The resulting consensus assemblies were then analyzed with Pangolin [https://github.com/cov-lineages/pangolin] and NextClade [https://github.com/nextstrain/nextclade] to perform lineage and clade designations, respectively. NCBI'S VADR tool [https://github.com/ncbi/vadr] was also employed to screen for potentially errant features [e.g., erroneous frame-shift mutations] in the consensus assembly.

The sequence alignment file [BAM] generated by the Titan_ClearLabs workflow was visualized and manually assessed using the CLC Genomic Workbench software.

The *Titan_Augur_Run* workflow was utilized to perform phylogenetic and cluster analysis of the SARS-CoV-2 datasets. *Titan_Augur_Run* executes subcommands from the NextStrain Augur Toolkit [github.com/nextstrain/ncov] through the use of a modified version of The Broad Institute's sarscov2_nextstrain WDL workflow [https://github.com/broadinstitute/viral-pipelines/blob/master/pipes/WDL/workflows/sarscov2_nextstrain.wdl] to construct SARS-CoV-2 maximum likelihood [ML] and time trees as well as an Auspice-compatible JSON file for interactive visualization.

Phylogenetic tree visualizations were constructed by uploading the Auspice-compatible JSON files generated by *Titan_Augur_Run* to the Auspice web application [ausice.us].

Ambiguity of the case's age is provided for deidentification purposes due to the small size of the county in which the individual resides. The patient provided consent, in writing, for the facts of this case to be published.

Identity testing was performed as previously described in Tillett et al. 2020 [23].

3. Results

An unvaccinated 30 to 35-year old male, resident of a rural county in Nevada, was symptomatic for COVID-19 and was tested by nasal swab on August 16, 2021, whereupon he was found reactive for SARS-CoV-2 RNA ["Case A"]. During Case A, the patient reported mild symptoms (described in Table 1) that resolved in less than a week. Three weeks later, the patient reported being exposed to additional COVID-19 cases and became symptomatic. The patient was tested again for the presence of SARS-CoV-2 by nasal swab on September 7, 2021 and was found to be reactive for SARS-CoV-2 RNA ["Case B"] [See Table 1]. The patient reported that the symptoms (Table 1) were more significant during Case B, in comparison to Case A (personal communication) No additional testing was performed on the patient between Case A and Case B.

As part of a comprehensive SARS-CoV-2 genomic surveillance program at the Nevada State Public Health Laboratory [NSPHL], samples from both instances were subjected to genomic sequencing. Successful sequencing and subsequent lineage analysis of assembled genomes revealed that the first instance of infection detected on 8/16

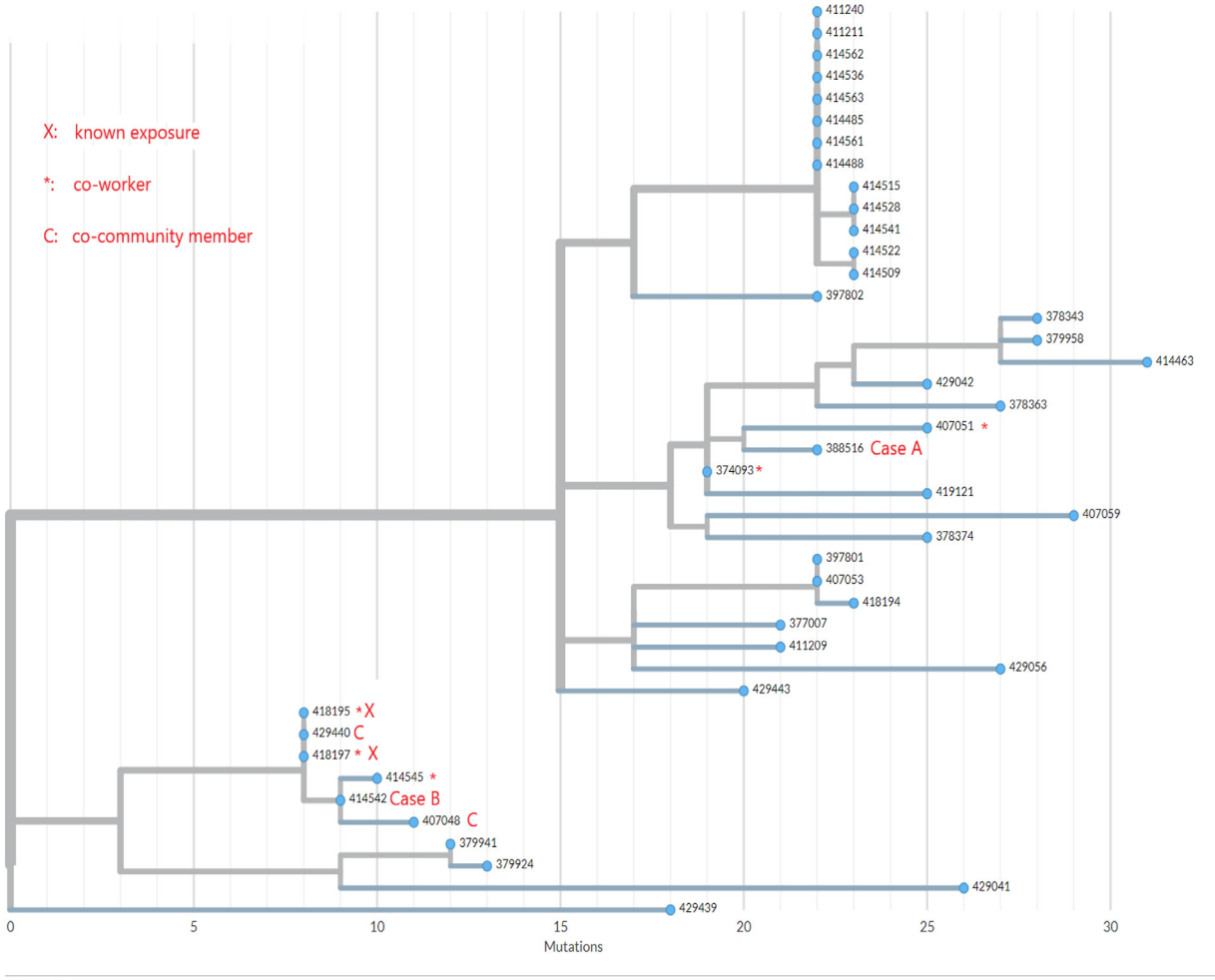

Fig. 1. A phylogenetic tree describing the genomic relationships of Case A and Case B relative to other cases, either from the same County as the patient, or elicited from contact tracing and investigation. C = co-community member; * = co-worker; X = direct contact to patient.

was of the B.1.617.2 lineage. Sequence analysis of the specimen from the second symptomatic episode revealed virus of lineage AY.26. Both lineages were known to be circulating locally at the times of infection. As shown in Table 2 and Fig. 2A and B, the 2 genomes differed at multiple locations, resulting in 31 amino acid coding changes, including 7 in the spike protein. The genome associated with the first infection showed 4 mutations in the Spike protein relative to the reference strain (Wuhan-Hu-1). Human identity testing using short-tandem repeats was performed on both specimens and confirmed that the specimens were collected from the same individual (frequency of match: 1 in 31.62 octillion individuals); additional sequence analysis of all other reactive cases on the same plate and in the same extraction and amplification batches as the second specimen was performed and generated zero genomic matches for AY.26, ruling out contamination with a co-analyzed specimen. The genome associated with the second infection [Case B] showed 11 mutations in the spike protein relative to the reference strain. Phylogenetic analysis of the cases was performed comparing the 2 cases to those detected and sequenced from the patient's home county between July 20, 2021 and September 17, 2021 [Fig. 1]. Interview of the patient was productive and indicated close contact with multiple known COVID-19 cases. The sole direct contact for Case A that was elicited by interview had a positive laboratory test for SARS-CoV-2 but the specimen was unavailable for sequence analysis. Interview regarding Case B elicited contacts that were all positive for SARS-CoV-2 and were assessed by genomic sequencing. Their phylogenetic relationship to the patient's cases is shown in Fig. 1. Also shown in Fig. 1 are the phylogenetic relationships to other SARS-CoV-2 positive

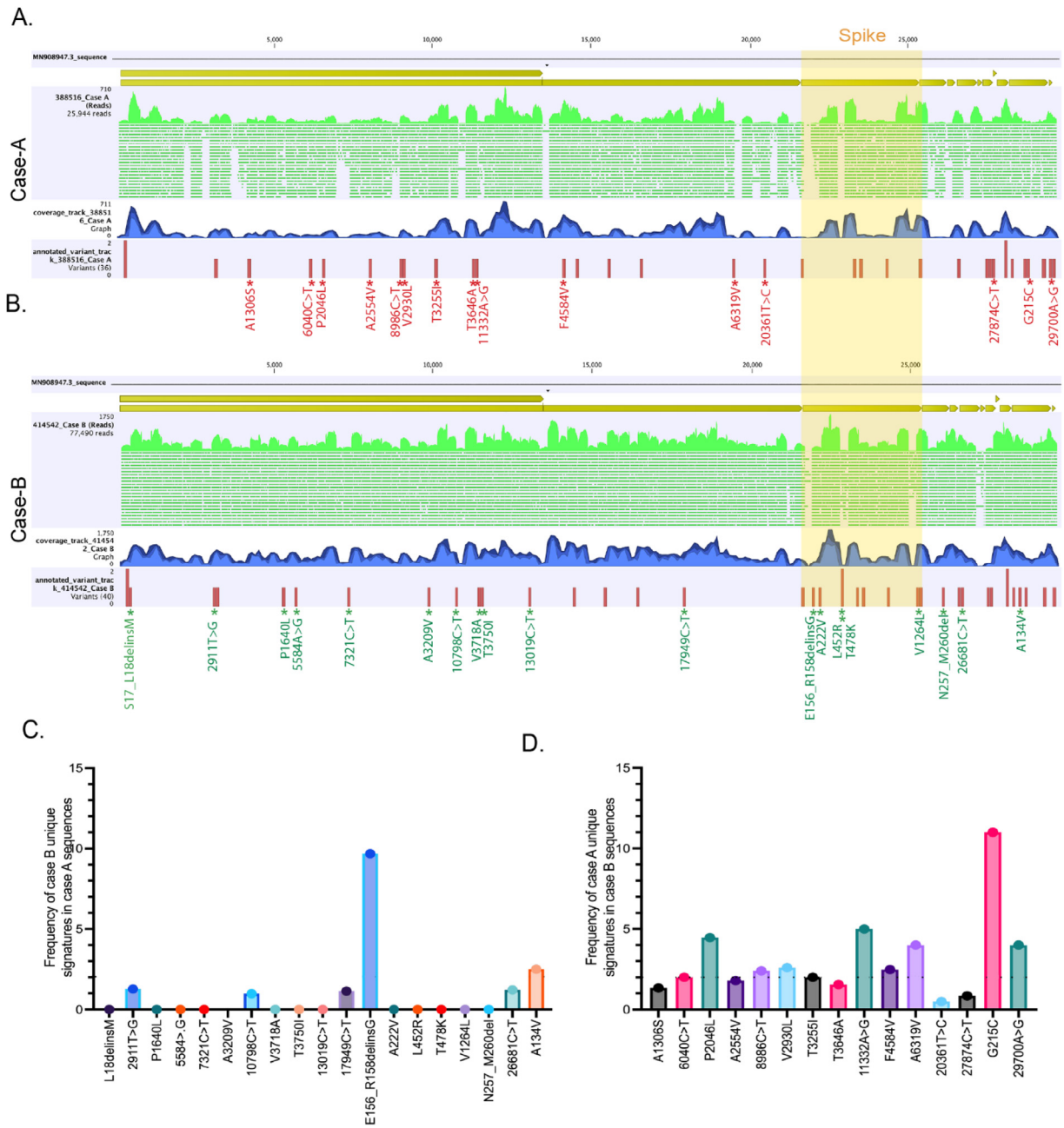

Fig. 2. Alignment generated from the FASTQ files of sequences from Case A and B using CLC Genomic Workbench. Mutations [SNV and MNV] in reference to MN908947.3, are presented by red bars in the associated variant track panels of each specimen. Unique mutations in Case A and B, with respect to each other, are marked with asterisks [Red = Case A specific mutations, Green = Case B specific mutations]. Synonymous mutations and mutations in the non-coding region are highlighted with green shadow. C. Frequency [percent] of Case B specific mutations in the sequences from Case A specimen. D. Frequency [percent] of Case A specific mutations in the sequences from Case B specimen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) MNV = Multi-nucleotide variant; SNV = single nucleotide variant.

co-workers for each case, and for 2 co-community members. These analyses reveal that plausible, genomically related sources of infection for Case A and Case B are identifiable amongst contacts and co-workers of the individual.

In lieu of intervening test results between Case A and Case B, we sought to ascertain whether infection could have been a sequence of events, or a simultaneous infection [e.g., a case of superinfection] with 2 variants. We investigated the sequence alignment file [BAM] generated by the TitanClearLabs workflow from each sequenced specimen from Case A and Case B to determine whether sequence from either case were detectable in the reads of the opposing specimen [Fig. 2A and B]. As shown in Fig. 2C and D, mutations unique to Case A were observable at varying frequency in reads of the raw sequence data for specimen B, while the opposite was very rarely the case. The very low frequency of unique mutation associated with Case B observed in Case A reads [Fig. 2D] is possibly the cause of the poor performance of ONT sequencing in its ability to discern low-frequency variants [24]. The observation that the frequency of Case A-specific mutations detectable in Case B raw reads was much higher than those of the opposite condition is consistent with a sequential infection of A to B.

4. Discussion

Clear evidence is shown herein for an individual to have been infected with 2 distinct sub-lineages of the Delta variant within a 22-day time frame. Cases A and B showed an extrapolated rate of single nucleotide variant and and multi-nucleotide variant accumulation of 501.6 substitutions per year, a rate that greatly exceeds the currently observed rate of 19.9 [25]. Reinfection with SARS-CoV-2 is well-described at this stage of the COVID-19 pandemic. However, the observation of reinfection within such a short timeframe, in a person devoid of known significant underlying conditions, and involving lineages of the Delta variant, is newly described. Such a finding in a relatively young person with no known underlying health conditions may indicate further challenges for controlling the pandemic. As genetic variability in the virus increases and is maintained in the population, infections with one version of the virus may not afford protection against others. It is likely that this scenario is occurring with the arrival of the Omicron variant which exhibits great antigenic (genomic) diversity relative to previous lineages [26]. A novel vaccination strategy, geared toward time-relevant variants and their sub-lineages may become necessary.

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Declaration of competing interest

The authors have no known competing interests/conflicts of interest relevant to the work in this manuscript.

Authors' contributions

Andrew J. Gorzalski performed sequencing and sequence data analysis. Christina Boyles worked to identify the case and gather information by interview; performed disease control investigation. Victoria Sepcic worked to identify the case and gather information by interview; performed disease control investigation. Subhash Verma performed sequence data analysis. Joel Sevinsky aided with bioinformatic analysis and critical review of the manuscript. Kevin Libuit aided with bioinformatic analysis and critical review of the manuscript. Stephanie Van Hooser provided supervision of the laboratory where testing and sequencing took place. Mark W. Pandori authored the manuscript and assembled team to share data.

Notes

Genomes associated with this case were uploaded to Genbank with Accession information as follows:

STUDY: PRJNA657893
- SAMPLE: NV-NSPHL-388516 [SAMN22091718]
  - EXPERIMENT: NV-NSPHL-388516_01 [SRX12504381]
    - RUN: NV-NSPHL-388516_R1.fastq.gz [SRR16222517]
- SAMPLE: NV-NSPHL-407048 [SAMN22091719]
  - EXPERIMENT: NV-NSPHL-407048_01 [SRX12504382]
    - RUN: NV-NSPHL-407048_R1.fastq.gz [SRR16222516]
- SAMPLE: NV-NSPHL-407051 [SAMN22091720]
  - EXPERIMENT: NV-NSPHL-407051_01 [SRX12504383]
    - RUN: NV-NSPHL-407051_R1.fastq.gz [SRR16222515]
- SAMPLE: NV-NSPHL-414542 [SAMN22091721]
  - EXPERIMENT: NV-NSPHL-414542_01 [SRX12504384]
    - RUN: NV-NSPHL-414542_R1.fastq.gz [SRR16222514]
- SAMPLE: NV-NSPHL-414545 [SAMN22091722]
  - EXPERIMENT: NV-NSPHL-414545_01 [SRX12504385]
    - RUN: NV-NSPHL-414545_R1.fastq.gz [SRR16222513]
- SAMPLE: NV-NSPHL-418195 [SAMN22091723]
  - EXPERIMENT: NV-NSPHL-418195_01 [SRX12504386]
    - RUN: NV-NSPHL-418195_R1.fastq.gz [SRR16222512]
- SAMPLE: NV-NSPHL-418197 [SAMN22091724]
  - EXPERIMENT: NV-NSPHL-418197_01 [SRX12504387]
    - RUN: NV-NSPHL-418197_R1.fastq.gz [SRR16222511]
- SAMPLE: NV-NSPHL-419121 [SAMN22091725]
  - EXPERIMENT: NV-NSPHL-419121_01 [SRX12504388]
    - RUN: NV-NSPHL-419121_R1.fastq.gz [SRR16222510]
- SAMPLE: NV-NSPHL-429440 [SAMN22091726]
  - EXPERIMENT: NV-NSPHL-429440_01 [SRX12504389]
    - RUN: NV-NSPHL-429440_R1.fastq.gz [SRR16222509]

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