



TITLE **ARM Assay Report: DNA Sequence of the Entire wtAd5 Reference Material (ARM) Genome**

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KEY WORDS **Adenovirus Reference Material Working Group (ARMWG)
Ad5 Reference Material
Wild-type Ad5
DNA Sequencing**

REFERENCE **Attachments**

SUMMARY DNA was isolated by Canji from a purified ARMWG wtAd5 sample. Some of this material was sent to Seqwright DNA Sequencing (Houston, TX) to determine its sequence. Forty differences were observed between the wtAd5 nucleic acid sequence in GenBank (i.e., NC_001406) and the sequence derived for the ARMWG wtAd5 genome. All of these differences were noted and assessed for their potential impact.

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Restricted Release

DNA Sequencing of the ARMWG wtAd5 Genome

Procedure: Purification of DNA from the ARMWG wtAd5 Sample and Sequencing Its Genome

Analyst: Diane McAllister

Reviewer: Barry Sugarman

Description: The starting material was a 45 mL aliquot of ARMWG final product in the form of “concentrated bulk, predilution, P/N 09-00159, C/N 001471” (i.e., refer to the Introgen product insert authored by Dr. Schrock sent with this material). The concentration of wtAd5 in this preparation—estimated to be 2.5×10^{12} particles per mL—was determined to be 3.5×10^{12} P/mL using the Resource Q HPLC assay (QC0008). DNA was purified using QIAamp Maxi-Kit protocol (QIAGEN). As an identity check, an aliquot of this DNA was digested with ten different restriction enzymes to determine whether or not it was consistent with the fragment array predicted for wtAd5 before it was shipped for sequencing. After the fragment array was observed to be consistent with the predicted array, approximately 100 μ g of DNA was shipped to SeqWright on November 13, 2001. A summary of the results was forwarded to Canji via email on November 30, 2001.

Results/Comments:

The identity of the purified ARMWG wtAd5 DNA was confirmed by restriction enzyme mapping using ten different enzymes that cut throughout the wtAd5 viral genome. Figure 1 depicts the distribution of these restriction enzyme recognition sites.

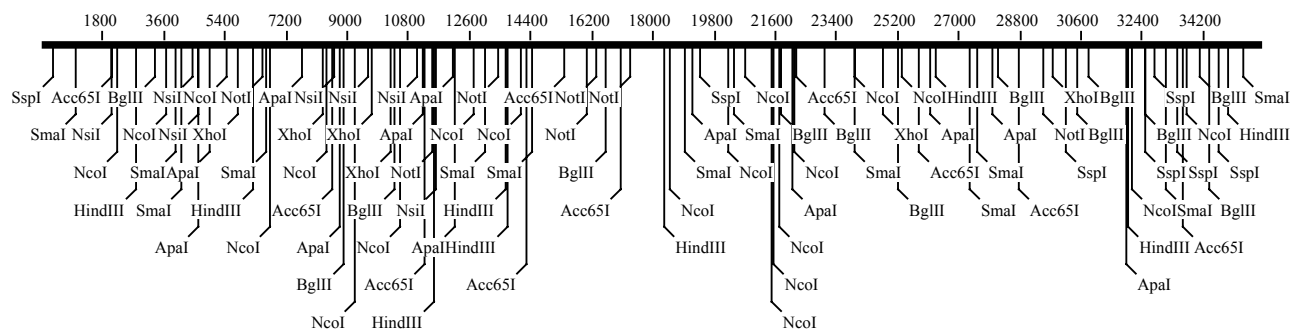


Figure 1. Predicted Locations of Different Restriction Enzyme Recognition Sites within the wild-type Ad5 Genome. The restriction enzyme sites in the above illustration include *Apa* I, *Acc65* I, *Bgl* II, *Hind* III, *Nco* I, *Not* I, *Nsi* I, *Sma* I, *Ssp* I, and *Xho* I. Numbers cite the location within the vector genome.

The restriction enzyme mapping data (Figure 2B) were consistent with the predicted fragment array (Figure 2A) suggesting that the DNA being tested was in fact wtAd5. The only anomaly was that an *Acc65* I (or *Kpn* I) recognition site predicted to reside at base pairs 11282-11287 does not exist; this was confirmed by the DNA sequencing data.

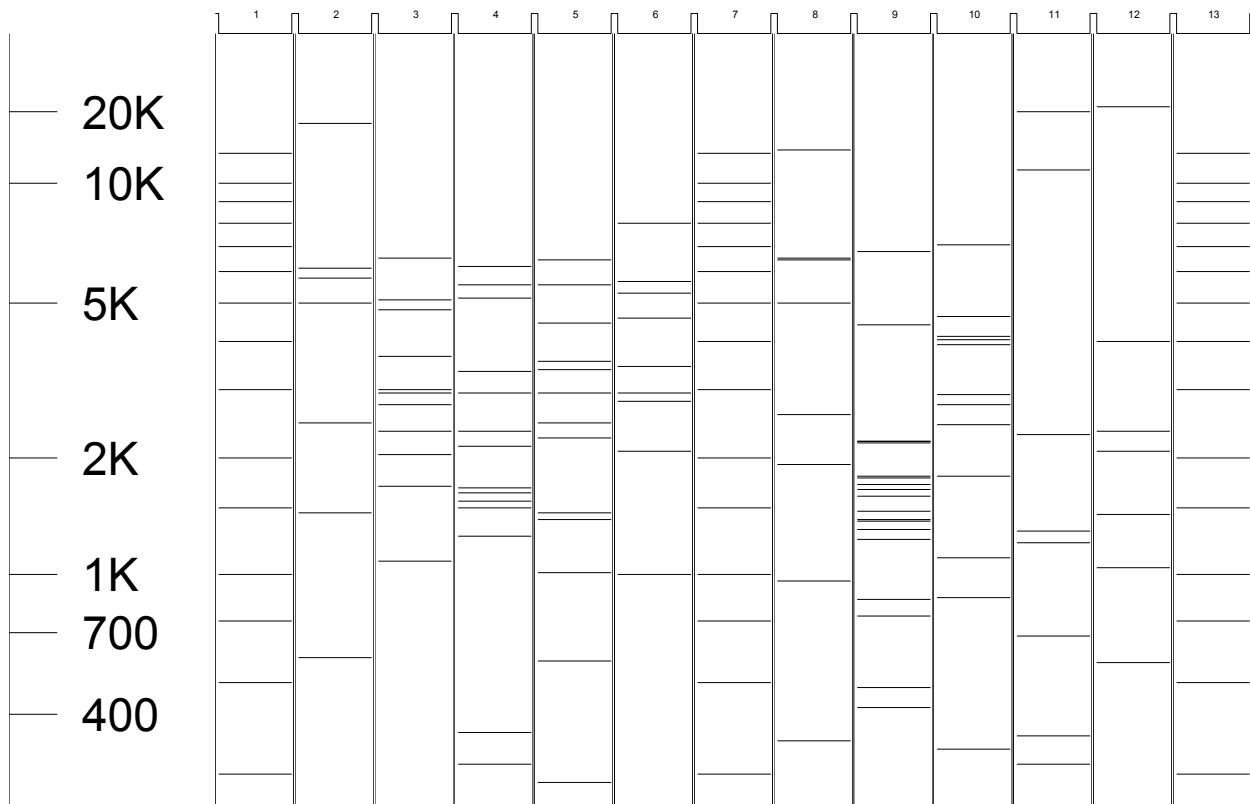


Figure 2A. Hypothetical Restriction Fragment Array Predicted for wtAd5. The hypothetical array of restriction fragments was produced using Vector NTI v6. The lanes correspond to those described in Figure 2B.

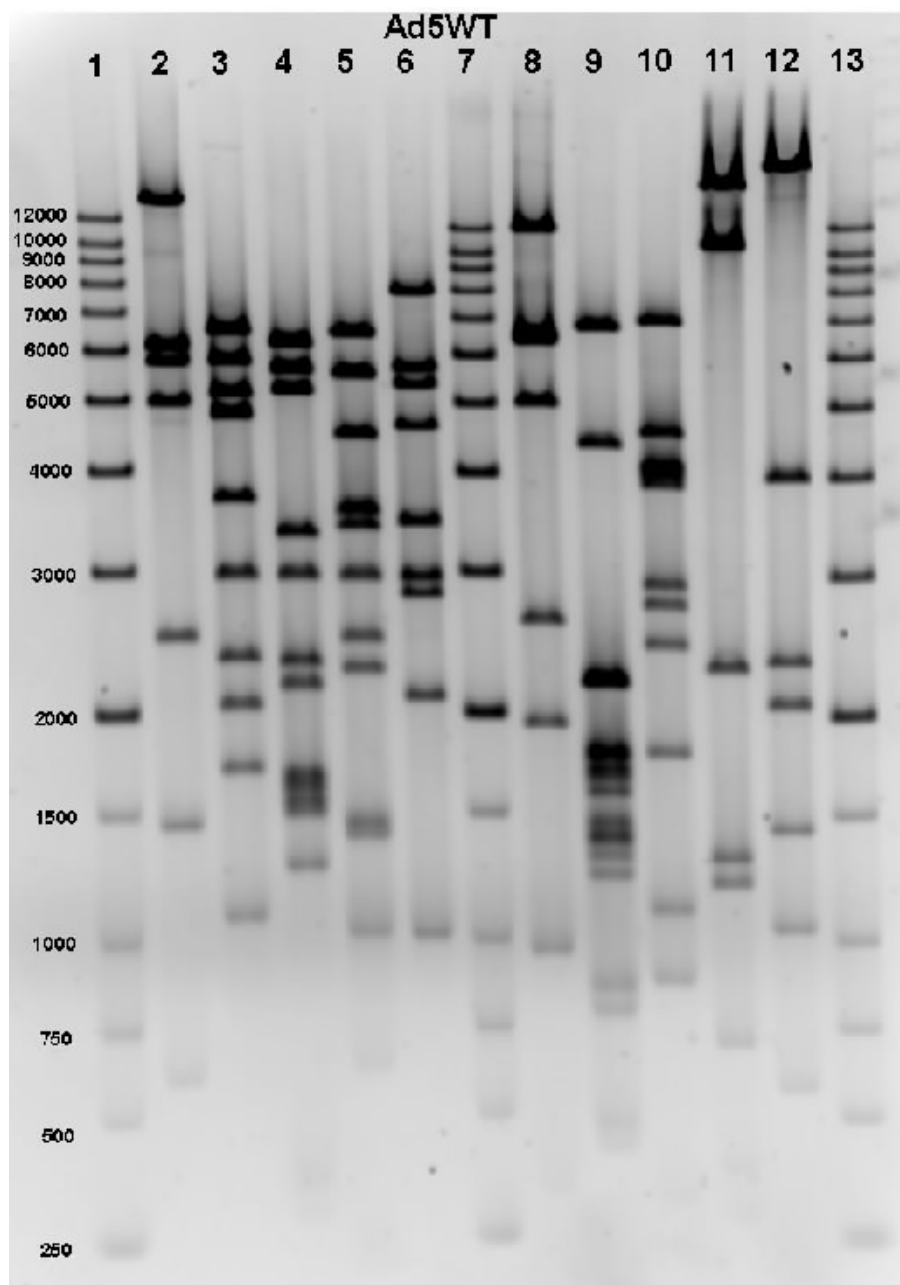


Figure 2B. Electrophoretic profile of DNA fragments from ARMWG Ad5WT viral reference material digested with various restriction enzymes. The resulting fragments were resolved on a 1% (w/v) agarose gel and visualized using SYBR Green I. The contents of each lane are as follows: Lanes 1, 7 and 13, DNA molecular weight standards (Kb ladder, Stratagene); lane 2, Ad5WT (*Xho* I); lane 3, Ad5WT (*Acc65* I); lane 4, Ad5WT (*Bgl* II); lane 5, Ad5WT (*Sma* I); lane 6, Ad5WT (*Hind* III); lane 8, Ad5WT (*Not* I); lane 9, Ad5WT (*Nco* I); lane 10, Ad5WT (*Apa* I); lane 11, Ad5WT (*Ssp* I); lane 12, Ad5WT (*Nsi* I). The size of each band in the molecular weight standard is depicted in base pairs.

The consensus ARMWG Ad5 DNA sequence reported by SeqWright is 35934 base pairs in length (Figure 3, pages 6 through 15). A detailed base-by-base analysis showed that the

sequence of the ARMWG Ad5 material was similar but not identical to the Ad5 sequence in GenBank (i.e., accession number NC_001406). These differences are depicted in the attachment entitled “Sequence Alignment between GenBank NC_001406 and S16549 CNJ_1_CON Reverse (the consensus sequence for the ARMWG wtAd5).” A total of forty differences—including substitutions, deletions, and insertions—were observed in the alignment. These changes were confirmed using multiple sequence overlaps. All of these discrepancies are summarized in the attachment entitled “Summary of the Differences Between GenBank NC_001406 and the consensus DNA Sequence for the ARMWG wtAd5 Sample.” Of these, only nine were not observed in sequences for other vectors developed at Canji (e.g., known as ACN53, IACB, and TOCB). Within this group, only one results in significant change, i.e. a pre-mature termination of the E3 10.4K (RID α) protein. A detailed review of the individual electropherograms within this domain does confirm this *de facto* change in the sequence.

Since the GenBank DNA sequence (NC_001406) was a composite of disparate sequence data published years ago (*Virology* 186: 280-285 (1992)) being “spliced” together. It is therefore plausible that many of the minor differences that were observed between the ARMWG Ad5 sequence and GenBank NC_001406 are in fact real because the original data deposited in GenBank were generated using multiple variants of Ad5.

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Figure 3. Complete DNA Sequence of the ARM Ad5 Reference Material. ARMWG Ad5 DNA was subcloned into an M13 sequencing vector using a shot-gun cloning approach by SeqWright DNA Sequencing. The consensus DNA sequence was generated from greater than 200 overlapping sequence fragments of these M13 clones using Genecodes Sequencer.

Appendices

- Introgen Product Insert
- Canji Resource Q HPLC Assay Results for the “ARM final product in the form of “concentrated bulk, predilution, P/N 09-00159, C/N 001471”
- Photocopy of the Laboratory Notebook references (Canji 2001-532) for the Purification of DNA from the “ARM final product in the form of “concentrated bulk, predilution, P/N 09-00159, C/N 001471”
- Restriction Enzyme Analysis of the DNA Purified From the “ARM final product in the form of “concentrated bulk, predilution, P/N 09-00159, C/N 001471”
- Insert for material shipped to SeqWright
- GenBank NC_001406
- Sequence Alignment between GenBank NC_001406 and S16549 CNJ_1_CON Reverse (the consensus sequence for the ARMWG wtAd5)
- Summary of the Differences Between GenBank NC_001406 and the Consensus DNA Sequence for the ARMWG wtAd5 Sample