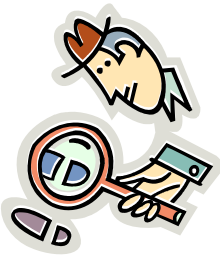
Mitchell M. Holland, Ph.D.
Professor, Biochem & MolBio
Former Director, Forensic Science Program
Eberly College of Science
Penn State University, University Park, PA



Assessing DNA Damage in mitoMPS Data from Low Template Samples

https://sites.psu.edu/hollandresearch/

A Massively Parallel Sequencing (MPS) Approach to Mitochondrial (mt or mito) DNA Analysis

A recent search of the literature identified …

915 publications on “MPS mtDNA”
128 publications on “forensic MPS mtDNA”

Forensic Science International: Genetics 44 (2020) 102151

Contents lists available at ScienceDirect

Forensic Science International: Genetics

journal homepage: www.elsevier.com/locate/fsigen

Validation of NGS for mitochondrial DNA casework at the FBI Laboratory

Michael D. Brandhagen*, Rebecca S. Just, Jodi A. Irwin

FBI Laboratory, 2501 Investigation Parkway, Quantico, VA 22135, USA

September 23rd	**September 24th**	September 25th	September 26th	September 27th

8:30 am - 5:00 pm

The Future is Now for MPS mtDNA Analysis

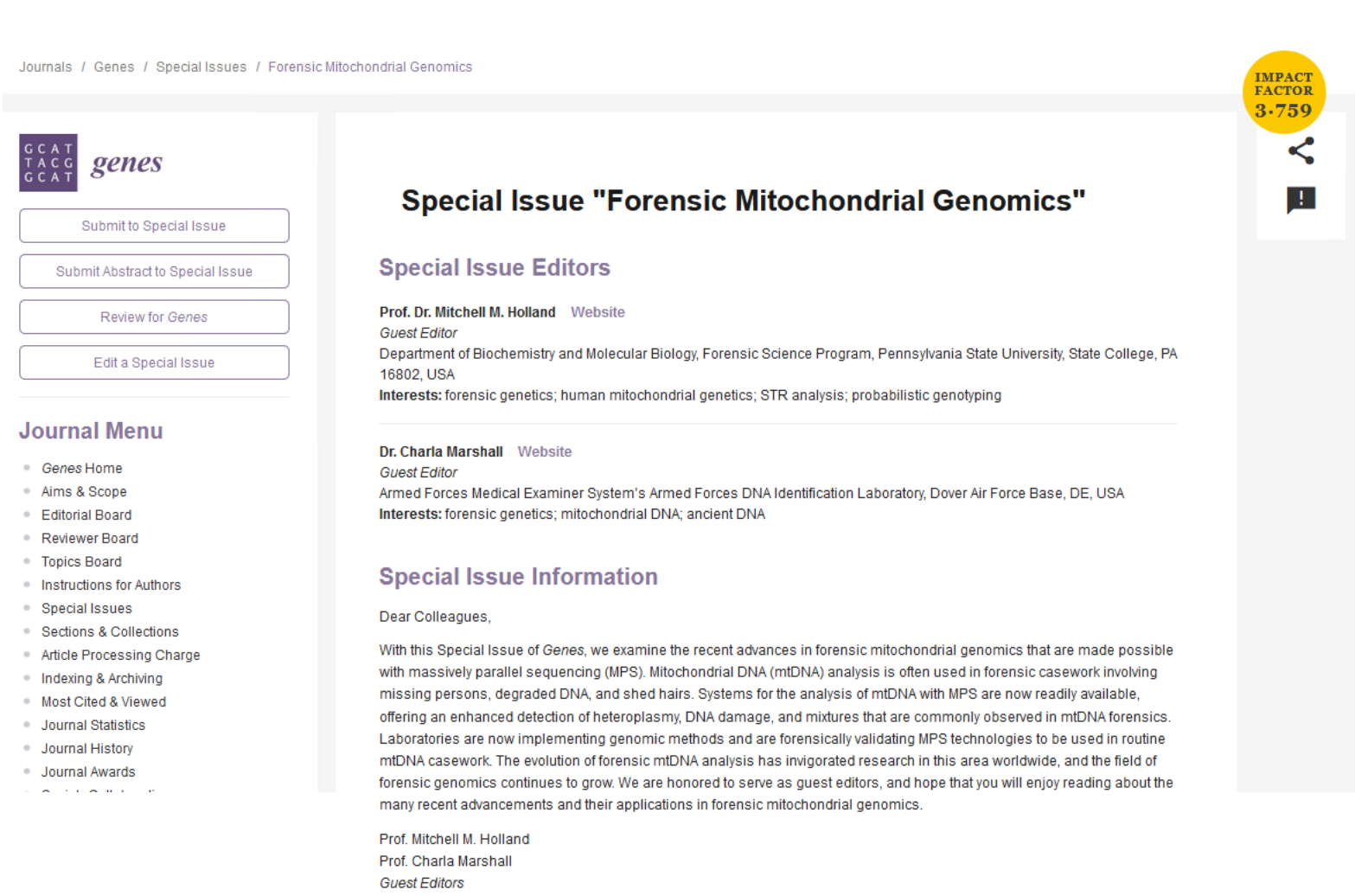
Location TBA

Michael Brandhagen *Co-Chair*
Forensic DNA Scientist, FBI Laboratory

Mitch Holland *Co-Chair*
Associate Professor, Biochemistry and Molecular Biology, Eberly College of Science, Pennsylvania State University

The purpose of this workshop is to educate the community on the availability of complete systems for MPS analysis of mtDNA; including enrichment approaches, library preparation methods, instrument choices, and analysis software solutions.

The Time is Now for mitoMPS Analysis

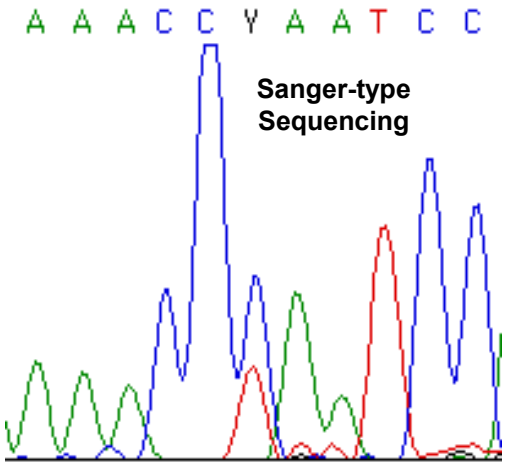


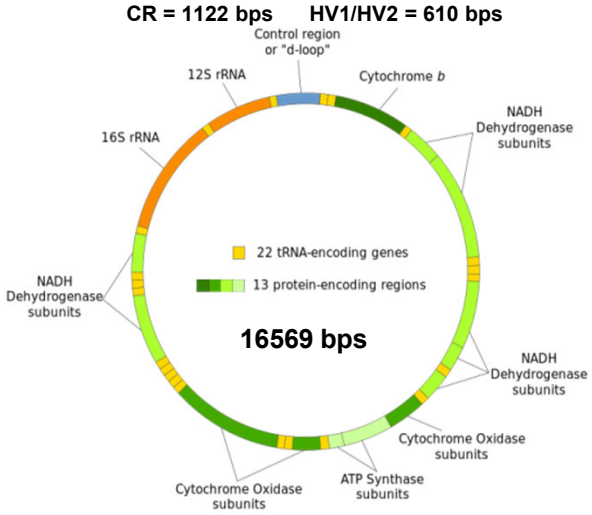
Deadline for manuscript submission is 10 February 2021

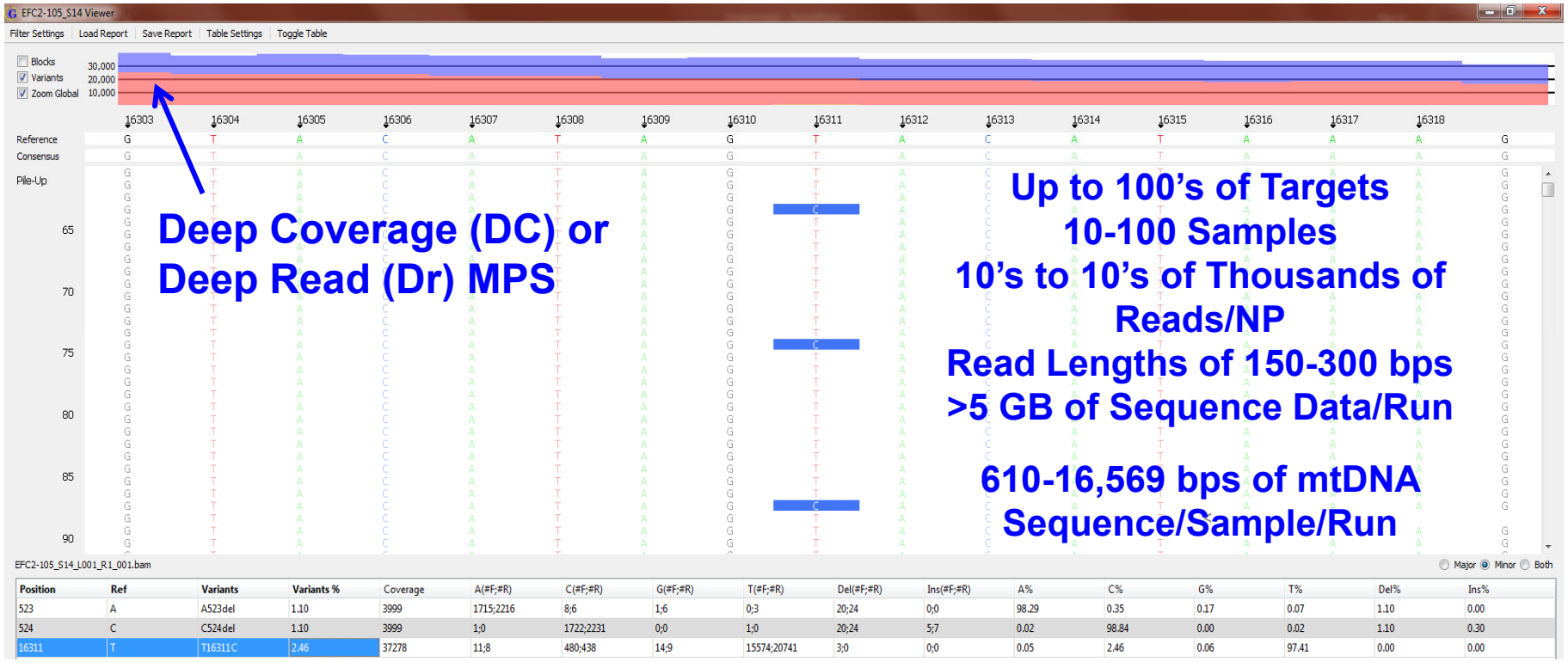
https://www.mdpi.com/journal/genes/special_issues/forensic_mitochondrial_genomics

One Amplicon Target & Sample with One Read/NP

100-450 bps of mtDNA Sequence/Sample



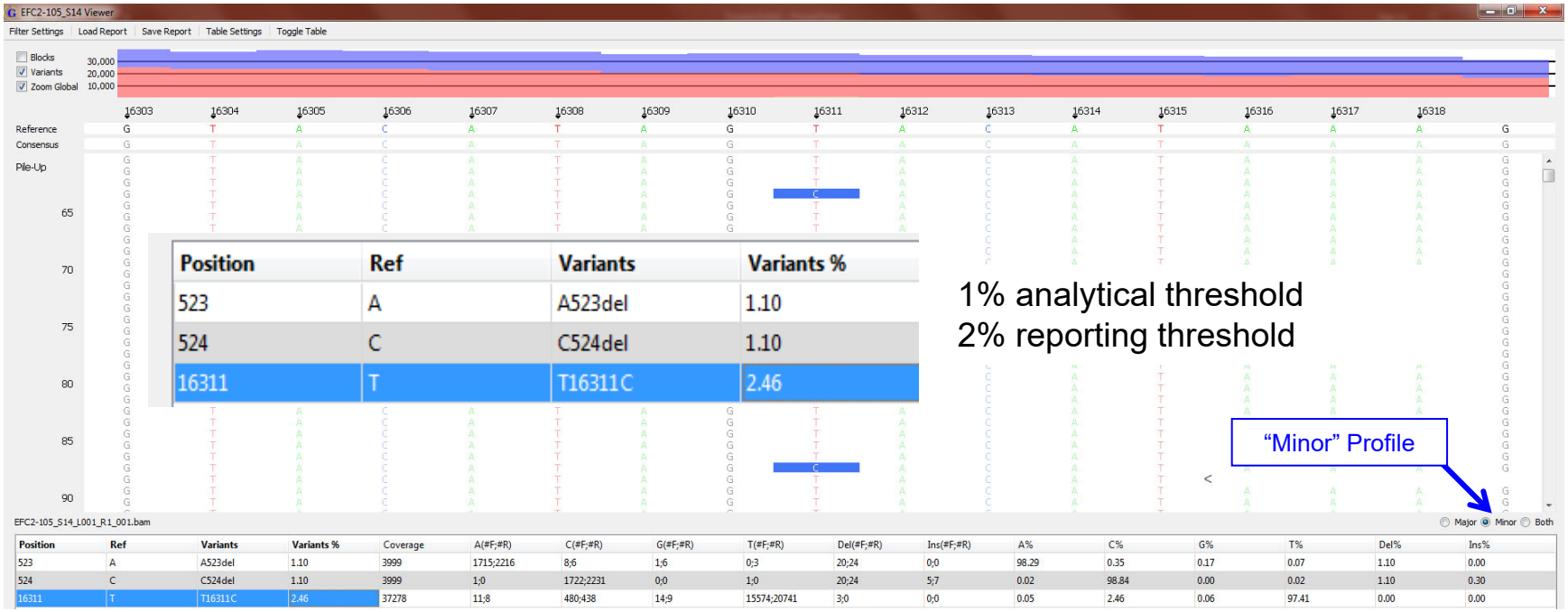




Position	Ref	Variants	Variants %	Coverage	A(#F;#R)	C(#F;#R)	G(#F;#R)	T(#F;#R)	Del(#F;#R)	Ins(#F;#R)	A%	C%	G%	T%	Del%	Ins%
523	A	A523del	1.10	3999	1715;2216	8;6	1;6	0;3	20;24	0;0	98.29	0.35	0.17	0.07	1.10	0.00
524	C	C524del	1.10	3999	1;0	1722;2231	0;0	1;0	20;24	5;7	0.02	98.84	0.00	0.02	1.10	0.30
16311	T	T16311C	2.46	37278	11;8	480;438	14;9	15574;20741	3;0	0;0	0.05	2.46	0.06	97.41	0.00	0.00

MPS can resolve heteroplasmy

Threshold of 2%



Position	Ref	Variants	Variants %	Coverage	A(#F;#R)	C(#F;#R)	G(#F;#R)	T(#F;#R)	Del(#F;#R)	Ins(#F;#R)	A%	C%	G%	T%	Del%	Ins%
523	A	A523del	1.10	3999	1715;2216	8;6	1;6	0;3	20;24	0;0	98.29	0.35	0.17	0.07	1.10	0.00
524	C	C524del	1.10	3999	1;0	1722;2231	0;0	1;0	20;24	5;7	0.02	98.84	0.00	0.02	1.10	0.30
16311	T	T16311C	2.46	37278	11;8	480;438	14;9	15574;20741	3;0	0;0	0.05	2.46	0.06	97.41	0.00	0.00

3/30 C variants = 10% Minor Variant Frequency (MVF)

2000 total read minimum/np
40 read minimum for minor variants
2% reporting threshold
(1% analytical threshold)
Balance ratio filters

Holland et al., FSIG 2017
GeneMarker™ HTS

CASE REPORT

Mitochondrial DNA:
State of Tennessee v. Paul Ware

By C. Leland Davis, ADA
District Attorney's Office, Chattanooga, TN

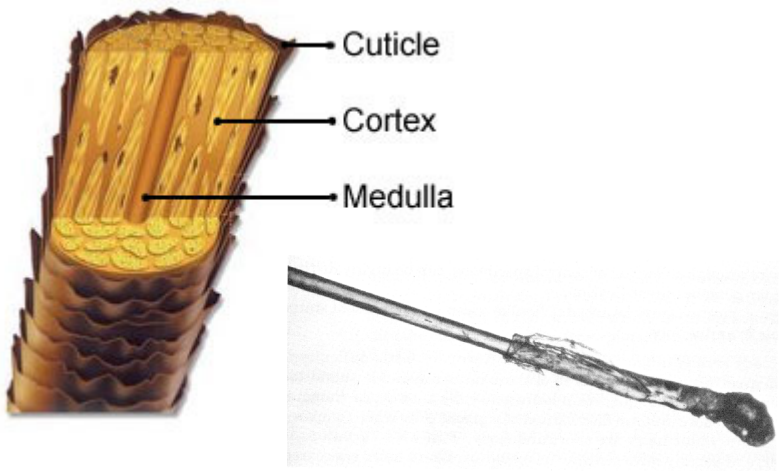
FBI 1996

Mitochondrial DNA sequence heteroplasmy in the Grand Duke of Russia Georgij Romanov establishes the authenticity of the remains of Tsar Nicholas II

Pavel L. Ivanov[1], Mark J. Wadhams[2], Rhonda K. Roby[2], Mitchell M. Holland[2], Victor W. Weedn[2] & Thomas I. Parsons[2]

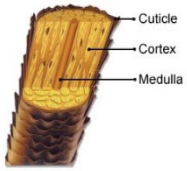
nature genetics volume 12 april 1996

mtDNA analysis is a useful tool for testing of **hair shafts** and **skeletal remains** associated with criminal and identification cases

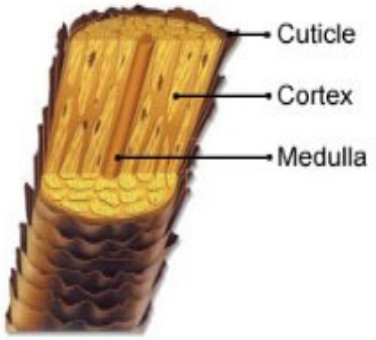


mtDNA Workflow

DNA Extraction



DNA extraction is the same, but with MPS the amount of information gained from the extract is significantly increased



Routinely obtain CR sequence from hair shafts

With recent advancements to a hair extraction protocol published in 2018, routine mtgenome sequence from as little as 1 mm of shaft material (unpublished findings)

Forensic Science International: Genetics 32 (2018) 7–17

Contents lists available at ScienceDirect

Forensic Science International: Genetics

journal homepage: www.elsevier.com/locate/fsigen

Research Paper

Assessing heteroplasmic variant drift in the mtDNA control region of human hairs using an MPS approach

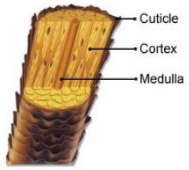
Jamie M. Gallimore, Jennifer A. McElhoe, Mitchell M. Holland*

Forensic Science Program, Department of Biochemistry and Molecular Biology, The Pennsylvania State University, 014 Thomas Building, University Park, PA 16802, United States

mtDNA Workflow

MPS

DNA Extraction

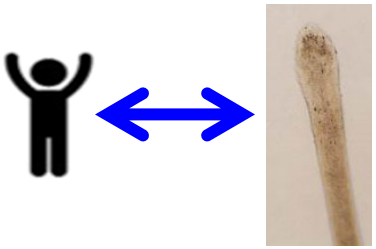
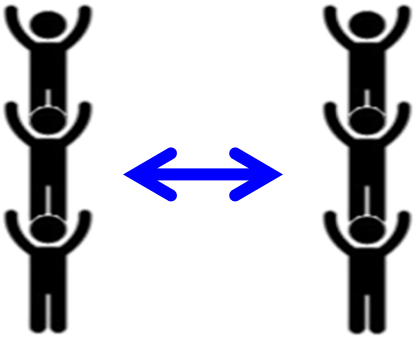
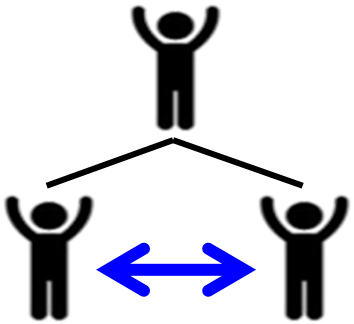


DNA extraction is the same, but with MPS the amount of information gained from the extract is significantly increased

- **Amplification of mtDNA**
- **Library Preparation**
- **Sequencing**
- **Data Analysis**

Amplification Approaches & Kits Available

- Promega
  - PowerSeq CRM (control region, 1 multiplex, 144-237 bps)
  - PowerSeq WGM (mtgenome, 1 multiplex of 161 amplicons averaging 167 bps, research product)
- Verogen
  - ForenSeq mtDNA Control Region (2 multiplexes, 18 amplicons averaging 118 bps)
  - ForenSeq mtDNA Whole Genome (2 multiplexes, 245 amplicons averaging 131 bps)
- ThermoFisher
  - Precision ID mtDNA Control Region Panel (2 multiplexes)
  - Precision ID mtDNA Whole Genome Panel (2 multiplexes of 81 amplicons averaging 161 bps)

Better Discrimination Potential	Differentiate BETWEEN Maternal Lineages	Differentiate WITHIN Maternal Lineages
		

DCMPS of mtDNA heteroplasmy allows us to accomplish these goals

44% of Mother-Child Pairs were Differentiated

genes

MDPI

Article

Deep-Coverage MPS Analysis of Heteroplasmic Variants within the mtGenome Allows for Frequent Differentiation of Maternal Relatives

Mitchell M. Holland [1,*], Kateryna D. Makova [2] and Jennifer A. McElhoe [1]

[1] Department of Biochemistry & Molecular Biology, Forensic Science Program, Eberly College of Science, Pennsylvania State University, University Park, PA 16802, USA; jam760@psu.edu
[2] Department of Biology, Eberly College of Science, Pennsylvania State University, University Park, PA 16802, USA; kmakova@bx.psu.edu
* Correspondence: mmh20@psu.edu

Received: 1 January 2018; Accepted: 20 February 2018; Published: 26 February 2018

Table 2. Differentiating heteroplasmy for 17 of the 39 mother-child pairs; buccal cell (Bu) and blood (Bl) samples. Frequency of heteroplasmy at each np in percentage (%), with the minor variant annotated as the letter after the np; i.e., T2746C is heteroplasmy at np 2746, with 20.11% of the C variant. Coverage and read distribution (forward reads, #For, compared to reverse reads, #Rev) are provided for each np of differentiating heteroplasmy, along with the gene annotation and whether sites in protein coding genes result in a synonymous change (Y) or not (N). The gene annotations include: CR = control region, 12S & 16S = 12S & 16S rRNAs, ATP6 = ATP synthase 6, ND = NADH dehydrogenase, $tRNA^{thr}$ = tRNA for threonine, and CO = cytochrome oxidase. Metadata for samples without the heteroplasmy are provided to illustrate that read percentages are clearly below reporting threshold and that coverage was adequate for this assessment.

Mother-Child Pair	Nucleotide Position	Sample Number	Major Allele	Coverage (≠For:≠Rev Reads)	Major Frequency (%)	Minor Allele	Coverage (≠For:≠Rev Reads)	Minor Frequency (%)	Gene Annotation	Synonymous (Y or N)	
T2746C		Mother - Bu (693)	T	2920:6014	79.67	C	655:1600	20.11	16S		
		Child - Bu (677)	T	4838:14038	99.64	C	1:9	0.053			
		Mother - Bl (M207)	T	14187:14328	80.3	C	3440:3528	19.62	16S		
		Child - Bl (M207-C)	T	24044:24176	99.88	C	6:12	0.037			
3	T9179C	Mother - Bu (1134)	T	3063:5076	85.02	C	538:892	14.93	ATP6	N (Val to Ala)	
		Child - Bu (1099)	T	6651:8730	99.82	C	8:7	0.097			
		Mother - Bl (M502G)	T	16583:20269	87.14	C	2468:2934	12.77	ATP6	N (Val to Ala)	
		Child - Bl (M501)	T	38769:44060	99.81	C	32:24	0.067			
4	G14040A	Mother - Bu (659)	G	5770:4227	92.01	A	474:381	7.86	ND5	Y (Gln)	
		Child - Bu (722)	G	20789:16141	99.86	A	8:12	0.054			
		Mother - Bl (M242)	G	13200:12992	94.07	A	831:811	5.89	ND5	Y (Gln)	
		Child - Bl (M242-C)	G	10355:10087	99.88	A	5:5	0.049			

… heteroplasmy must be observed in both tissues of one relative but not the other

genes

MDPI

Article

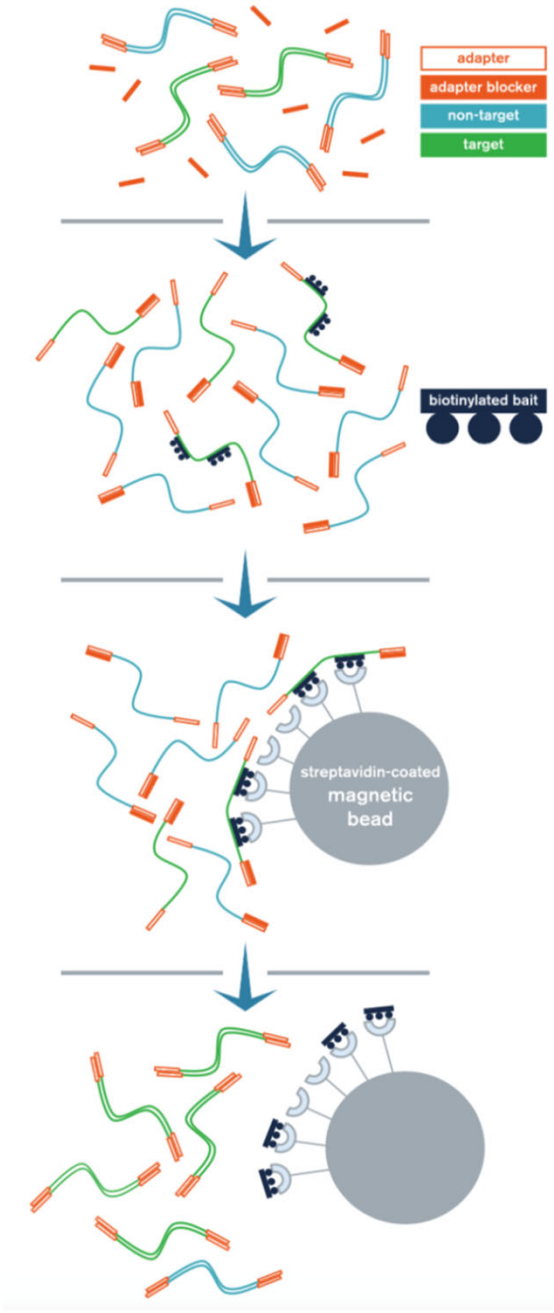
A Forensic Genomics Approach for the Identification of Sister Marija Crucifiksa Kozulić

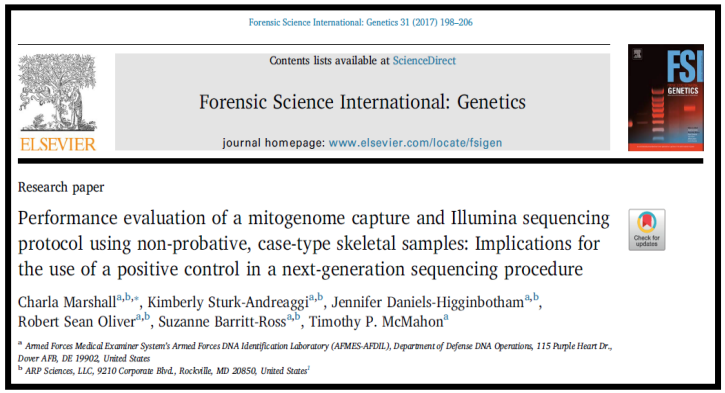
Charla Marshall [1,2,3,*], Kimberly Sturk-Andreaggi [1,2], Erin M. Gorden [1,2], Jennifer Daniels-Higginbotham [1,2], Sidney Gaston Sanchez [1,2], Željana Bašić [4], Ivana Kružić [4], Šimun Anđelinović [5,6], Alan Bosnar [7], Miran Čoklo [8], Anja Petaros [9], Timothy P. McMahon [1], Dragan Primorac [3,5,10,11,12,13,14,15] and Mitchell M. Holland [3,*]

Sister **Marija** was a nun from Rijeka, Croatia who dedicated her life to helping the poor and less fortunate. She is currently under consideration for beatification (Sainthood) by the Vatican, which requires the identification of her remains.

Sister **Marija** died in 1922 and was buried in a tomb along with other nuns belonging to the Society of Sisters of the Sacred Heart of Jesus, including her biological sister, **Tereza Kozulić**.

Capture method using a custom designed bait cocktail developed by AFDIL for the entire mitogenome





Forensic Science International: Genetics 31 (2017) 198–206

Contents lists available at ScienceDirect

Forensic Science International: Genetics

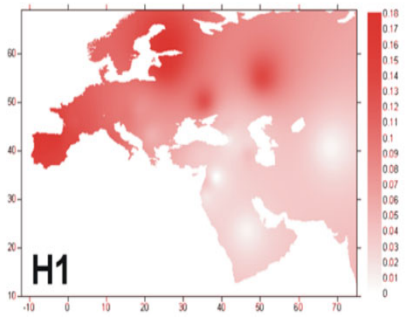
journal homepage: www.elsevier.com/locate/fsigen

Research paper

Performance evaluation of a mitogenome capture and Illumina sequencing protocol using non-probative, case-type skeletal samples: Implications for the use of a positive control in a next-generation sequencing procedure

Charla Marshall[a,b,*], Kimberly Sturk-Andreaggi[a,b], Jennifer Daniels-Higginbotham[a,b], Robert Sean Oliver[a,b], Suzanne Barritt-Ross[a,b], Timothy P. McMahon[a]

[a] Armed Forces Medical Examiner System's Armed Forces DNA Identification Laboratory (AFMES-AFDIL), Department of Defense DNA Operations, 115 Purple Heart Dr., Dover AFB, DE 19902, United States
[b] ARP Sciences, LLC, 9210 Corporate Blvd., Rockville, MD 20850, United States



b subclade is common in Eastern Europe

Stat = no observations in 4289 worldwide samples or 726 European samples = 1 in 197 to 1163

Differentiating Heteroplasmy

Haplotype 1
Haplogroup H1bu

Control Region
Coding Region

A263G
C309insC
C315insC
A750G
A1438G
G3010A
A4769G
A5558G
A8860G
A13327G
A15326G
T16519C

Heteroplasmy

A12337insC (32-34%)
A13327A (28-29%)

R: 39
L: 38

Sister 1

A263G
C309insC
C315insC
A750G
A1438G
G3010A
A4769G
A5558G
A8860G
A13327G
A15326G
T16519C

Heteroplasmy

A13327A (12-13%)

R: 42
L: 43

Sister 2

13327 is in the ND5 gene, with the A>G SNP causing a non-syn change from T>A

No known disease state associated with the change

… are differentiating sites of heteroplasmy due to background noise or error in the MPS process, or to numts, especially with low-level heteroplasmy??

“Noise” in the System

“Noise” in the System

A.

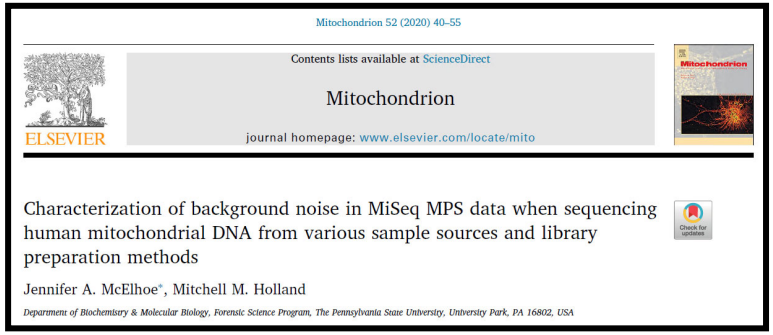
	Metals-Power	Hair-Power	Blood/Buccal-Power	LowTemp-Power	LowTemp-Next	Buccal-Next
Total error	0.485±0.0049	0.325±0.1005	0.231±0.0663	0.297±0.0694	0.205±0.0021	0.182±0.0645
A error	0.118±0.0009	0.100±0.0417	0.052±0.0230	0.048±0.0035	0.070±0.0476	0.037±0.0121
C error	0.121±0.0006	0.085±0.0280	0.080±0.0191	0.069±0.0189	0.079±0.0297	0.060±0.0205
G error	0.131±0.0033	0.048±0.0227	0.044±0.0097	0.059±0.0013	0.061±0.0023	0.047±0.0204
T error	0.115±0.0038	0.091±0.0261	0.053±0.0145	0.049±0.0110	0.065±0.0243	0.039±0.0139

B.

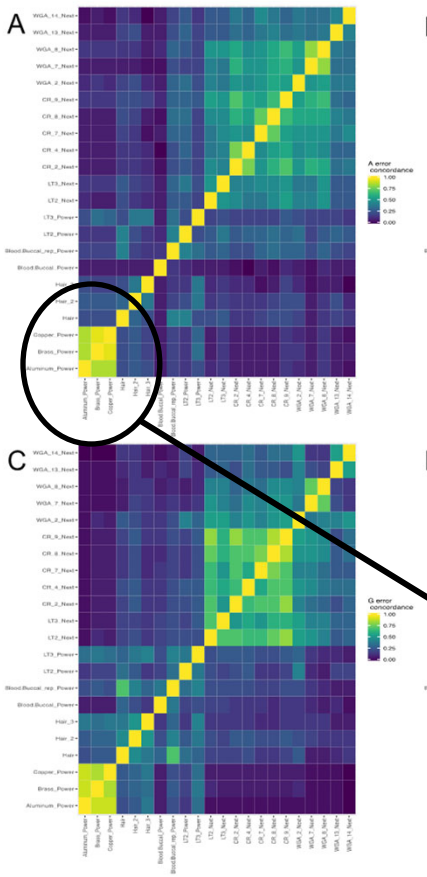
	Buccal-Next CR	Buccal-Next mtgenome
Total error	0.158±0.0720	0.166±0.0745
A error	0.032±0.0148	0.036±0.0164
C error	0.057±0.0273	0.063±0.0292
G error	0.036±0.0180	0.036±0.0171
T error	0.032±0.0126	0.030±0.0124

Background noise or error ranged from 0.030% to 0.131% across the four nucleotides.

Samples with increasing DNA damage saw increases in error.



420+ million reads of data



Forensic Science International: Genetics 39 (2019) 86–96

Contents lists available at ScienceDirect

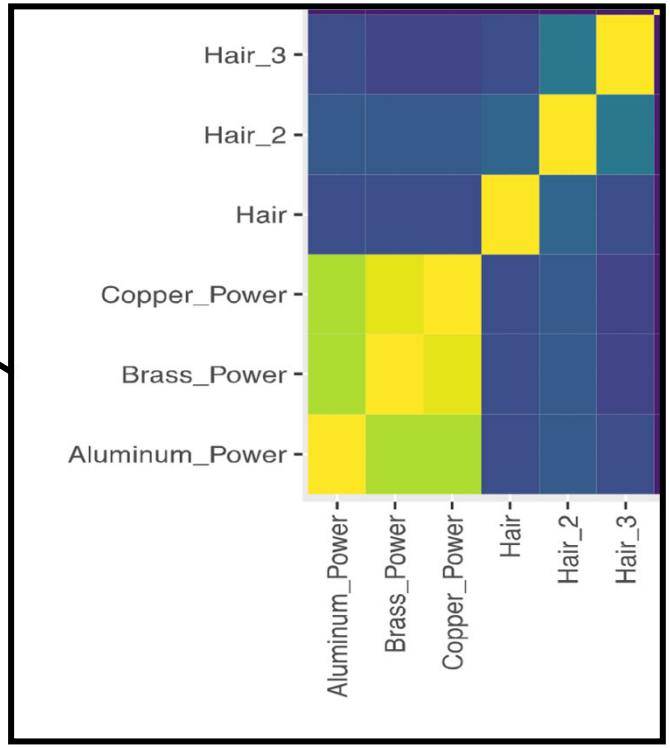
Forensic Science International: Genetics

journal homepage: www.elsevier.com/locate/fsigen

Recovery of mtDNA from unfired metallic ammunition components with an assessment of sequence profile quality and DNA damage through MPS analysis

Mitchell M. Holland, Rachel M. Bonds, Charity A. Holland, Jennifer A. McElhoe

Forensic Science Program, Department of Biochemistry and Molecular Biology, The Pennsylvania State University, 014 Thomas Building, University Park, PA, 16802, United States



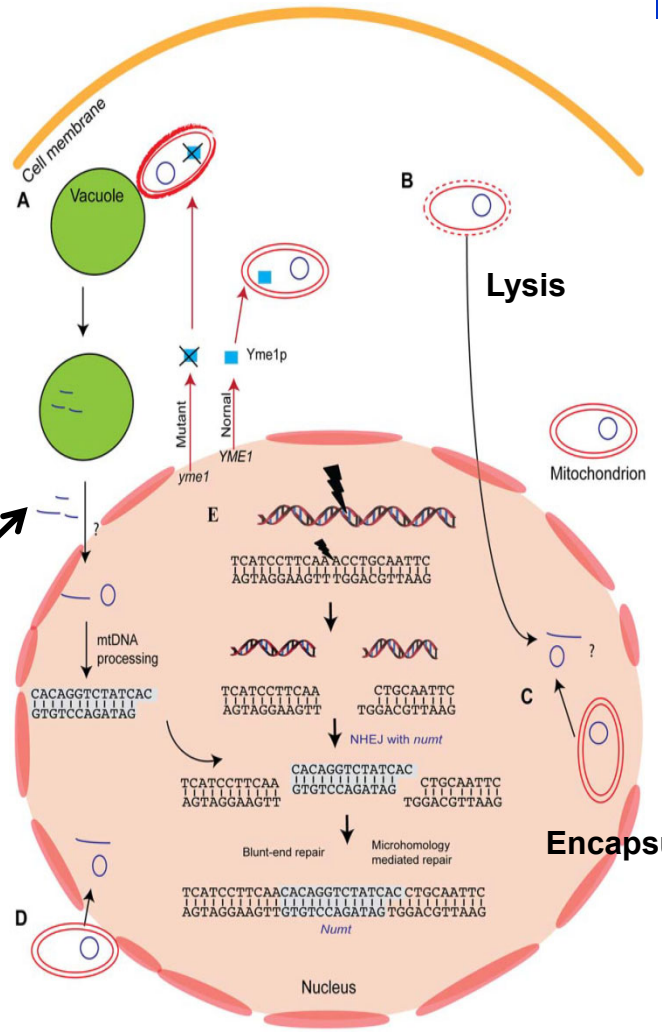
DNA recovered from the surface of ammunition components (Holland et al., FSIG 2019) gave the highest level of concordance

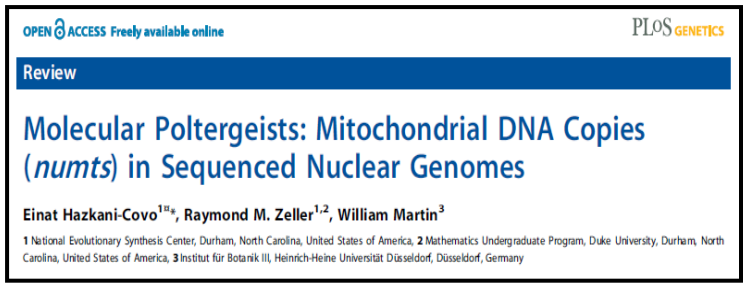
NUMTs

= nuclear mitochondrial DNA segments *
= nuclear mitochondrial sequences
= nuclear mitochondrial segments
= nuclear mitochondrial insertions

Estimate that ~750 NUMTs can be found in the nugenome, including some entirely intact mitogenomes, with ~4 unique NUMTs per individual

Most supported pathway is degradation of abnormal mitochondria




OPEN ACCESS Freely available online

PLoS GENETICS

Review

Molecular Poltergeists: Mitochondrial DNA Copies (*numts*) in Sequenced Nuclear Genomes

Einat Hazkani-Covo[1¤*], Raymond M. Zeller[1,2], William Martin[3]

1 National Evolutionary Synthesis Center, Durham, North Carolina, United States of America, 2 Mathematics Undergraduate Program, Duke University, Durham, North Carolina, United States of America, 3 Institut für Botanik III, Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany

Mitochondrion 46 (2019) 302–306

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Short communication

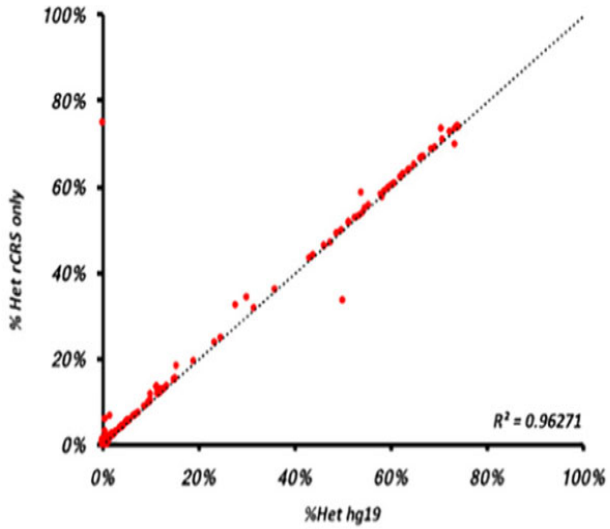
Assessing mitochondrial heteroplasmy using next generation sequencing: A note of caution

Mauro Santibanez-Koref[a], Helen Griffin[a], Douglass M. Turnbull[b], Patrick F. Chinnery[c], Mary Herbert[b,d], Gavin Hudson[a,b,*]

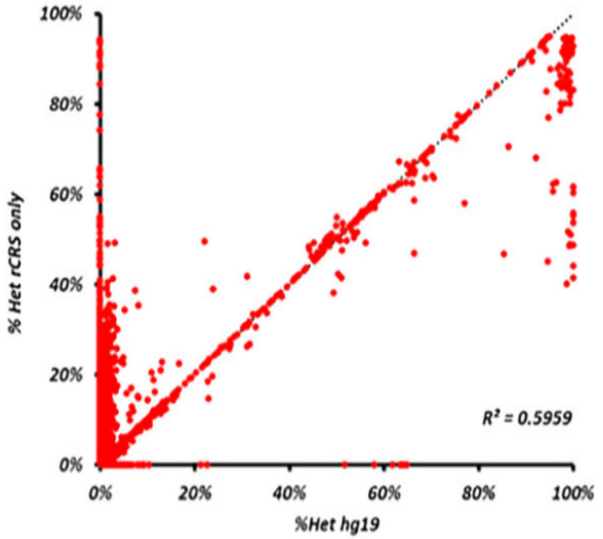
[a] Institute of Genetic Medicine, International Centre for Life, Central Parkway, Newcastle upon Tyne NE1 3BZ, UK
[b] The Wellcome Centre for Mitochondrial Research, Newcastle University, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK
[c] MRC Mitochondrial Biology Unit, Wellcome Trust/MRC Building, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0XY, UK
[d] Newcastle Fertility Centre, International Centre for Life, Central Parkway, Newcastle upon Tyne NE1 3BZ, UK

Heteroplasmy observed in whole mtgenome MPS data is dependent on enrichment method

The impact is mitigated when nucDNA is depleted



2 amplicon approach



180 amplicon approach

As amplicon size decreases, the number of minor variants with discrepant frequencies can increase, with the majority of variant frequencies increasing when aligned to the rCRS only

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ORIGINAL ARTICLE

Damage patterns observed in mtDNA control region MPS data for a range of template concentrations and when using different amplification approaches

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If we're going to consider low-level heteroplasmy (2-5% of the minor variant):

What's the potential impact of DNA damage on the interpretation of MPS data when dealing with low-template samples?

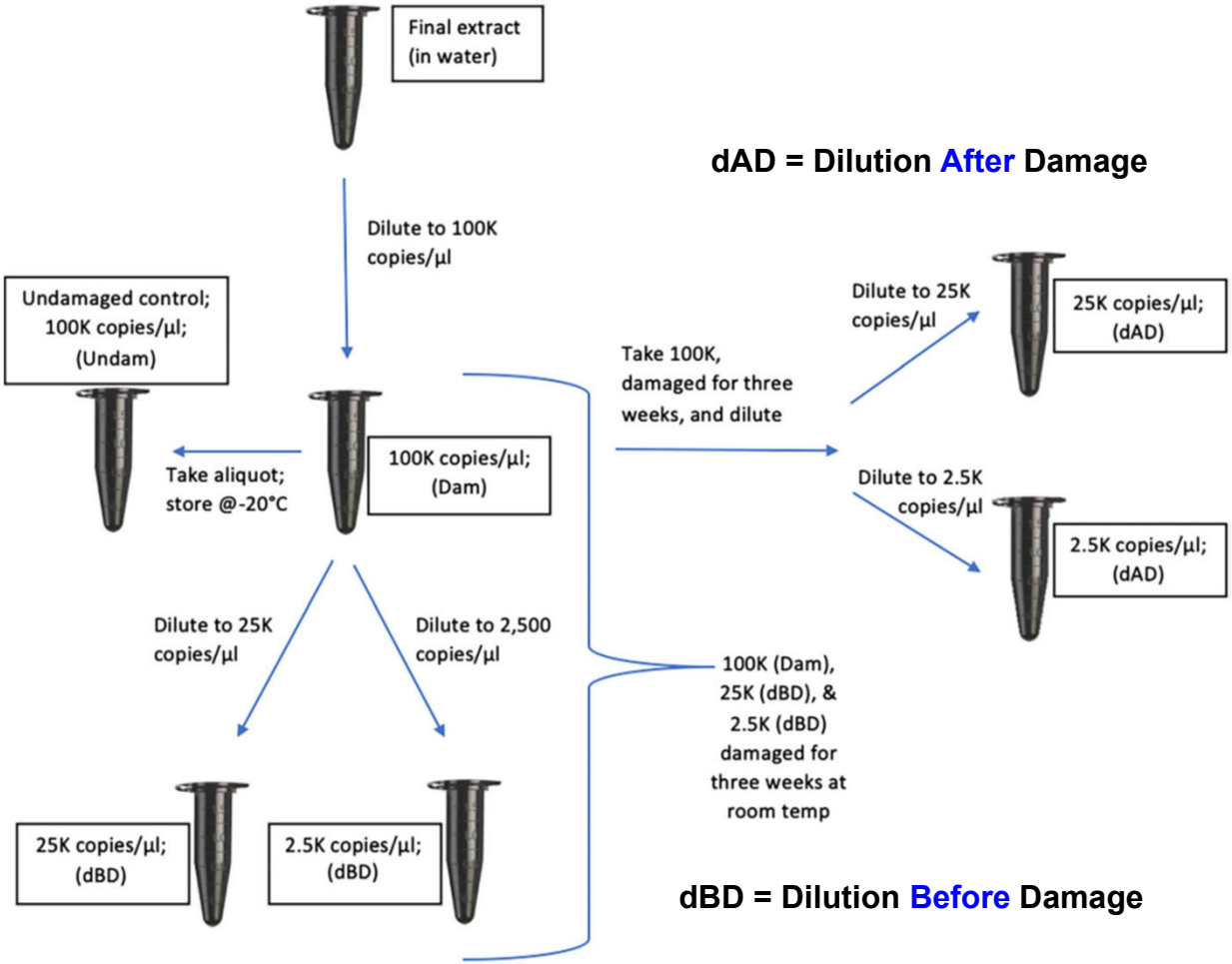
Most importantly, what's the impact on reporting thresholds?

Buccal cells collected from donors, DNA extracted, and mtDNA quantified using a custom mtqPCR assay (Gallimore et al., 2018)

Experimental Design:

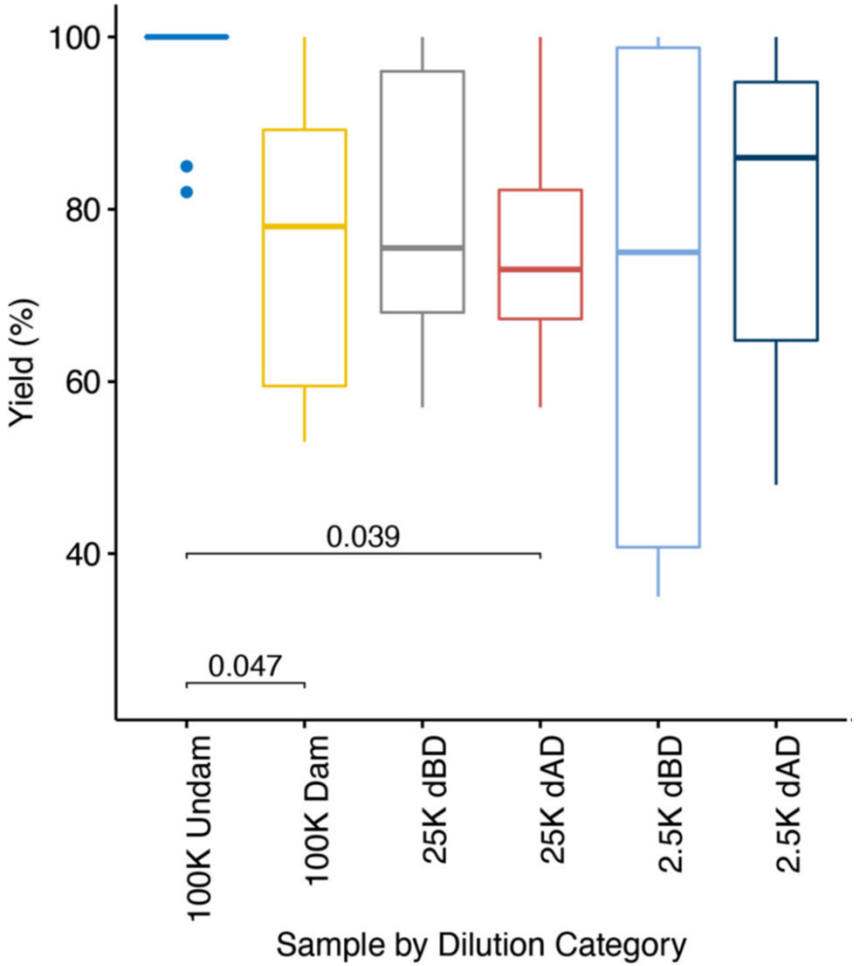
Control sample at 100k copies/uL of mtDNA stored at -20C

Dilutions made to 25k and 2.5k copies/uL before or after damage for three weeks at RT



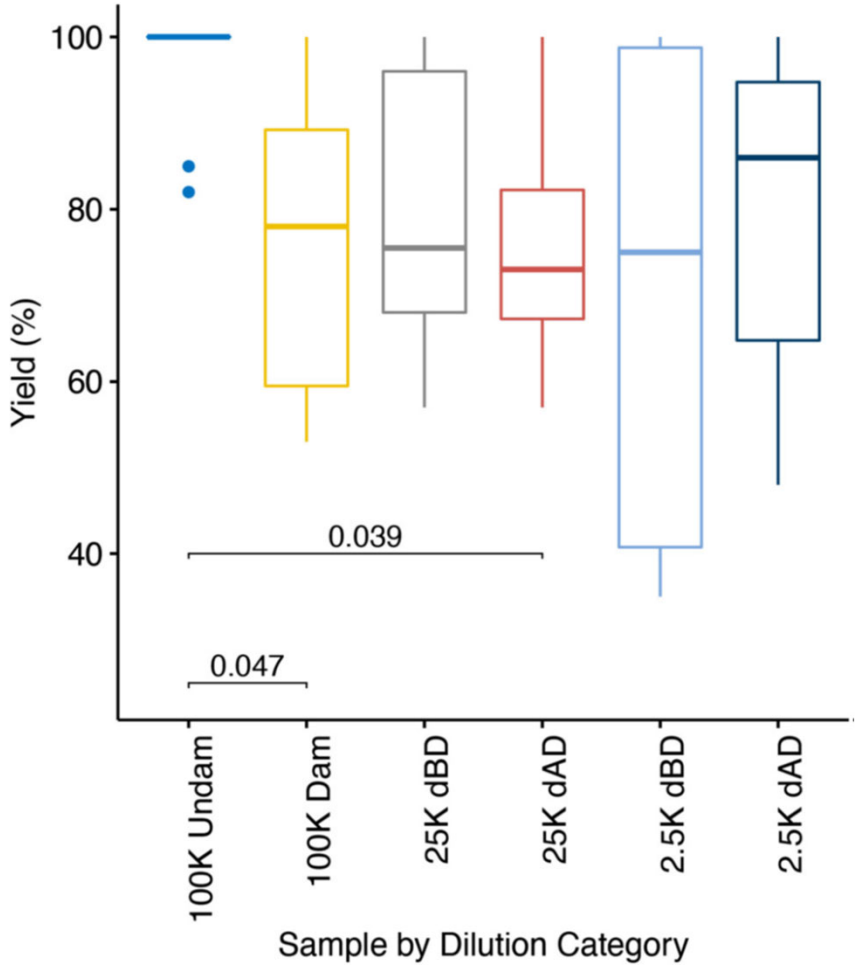
Control sample yields are high, reflecting that storage at -20C is effective, even when stored in water

Storage in water at RT results in lower yields across the data set



Box and whisker plot depicting mtqPCR results as percent yield (observed/expected) for each dilution category (**n = 20 per category**) after exposure to DNA damage. Two outliers were observed for the 100 K Undam category (82% and 85%). Median values are depicted by lines within box plots. Kruskal-Wallis test (with Benjamini-Hochberg correction for multiple testing) p values are given in the bottom portion of the figure with the ends of the brackets denoting which datasets are being compared.

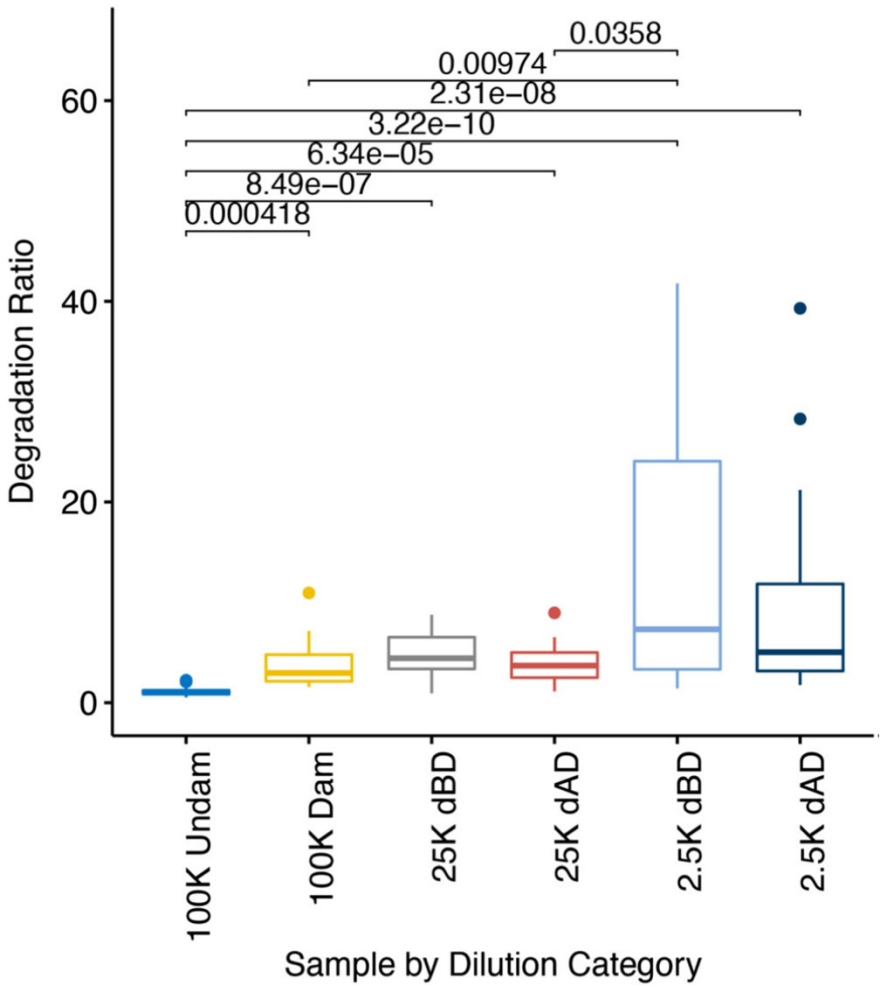
Dilutions made before damage (dBD) result in the lowest yields for the 2.5k samples



Box and whisker plot depicting mtqPCR results as percent yield (observed/expected) for each dilution category (**n = 20 per category**) after exposure to DNA damage. Two outliers were observed for the 100 K Undam category (82% and 85%). Median values are depicted by lines within box plots. Kruskal-Wallis test (with Benjamini-Hochberg correction for multiple testing) p values are given in the bottom portion of the figure with the ends of the brackets denoting which datasets are being compared.

Control sample degradation is low, again, reflecting that storage at -20C is effective

Dilutions before damage (dBD) result in higher degradation for both the 2.5k & 25k samples



Box and whisker plot depicting mtqPCR results as degradation ratios (**mtcopies of 69 bp target/mtcopies of 283 bp target**) for each dilution category after exposure to DNA damage. The following outliers were removed from the figure: 2.1 (100 K Undam), 11 (100 K Dam), 145 and 349 (2.5 K dBD), and 28 and 39 (2.5 K dAD). Median values are depicted by lines within box plots. Kruskal-Wallis test (with Benjamini-Hochberg correction for multiple testing) p values are given in the top portion of the figure with the ends of the brackets denoting which datasets are being compared.

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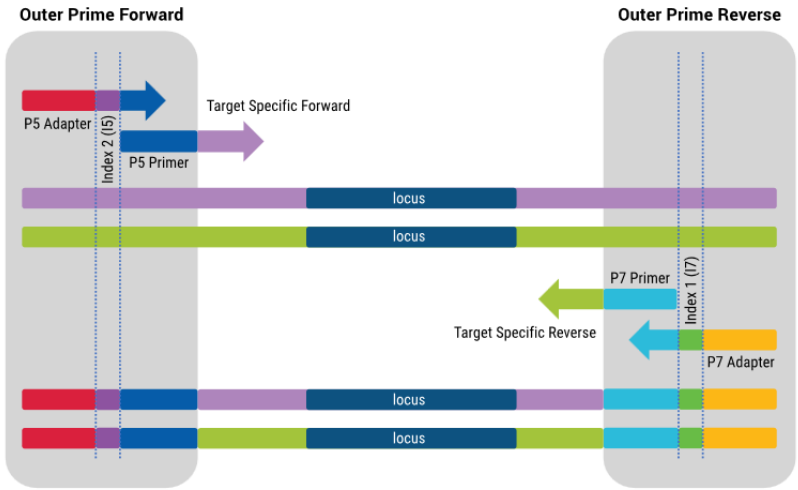


Adapted from Lange *et al.* (2014) *BMC Genomics* **15**, 63.

144-237 bps = **"10-Plex" a**pproach

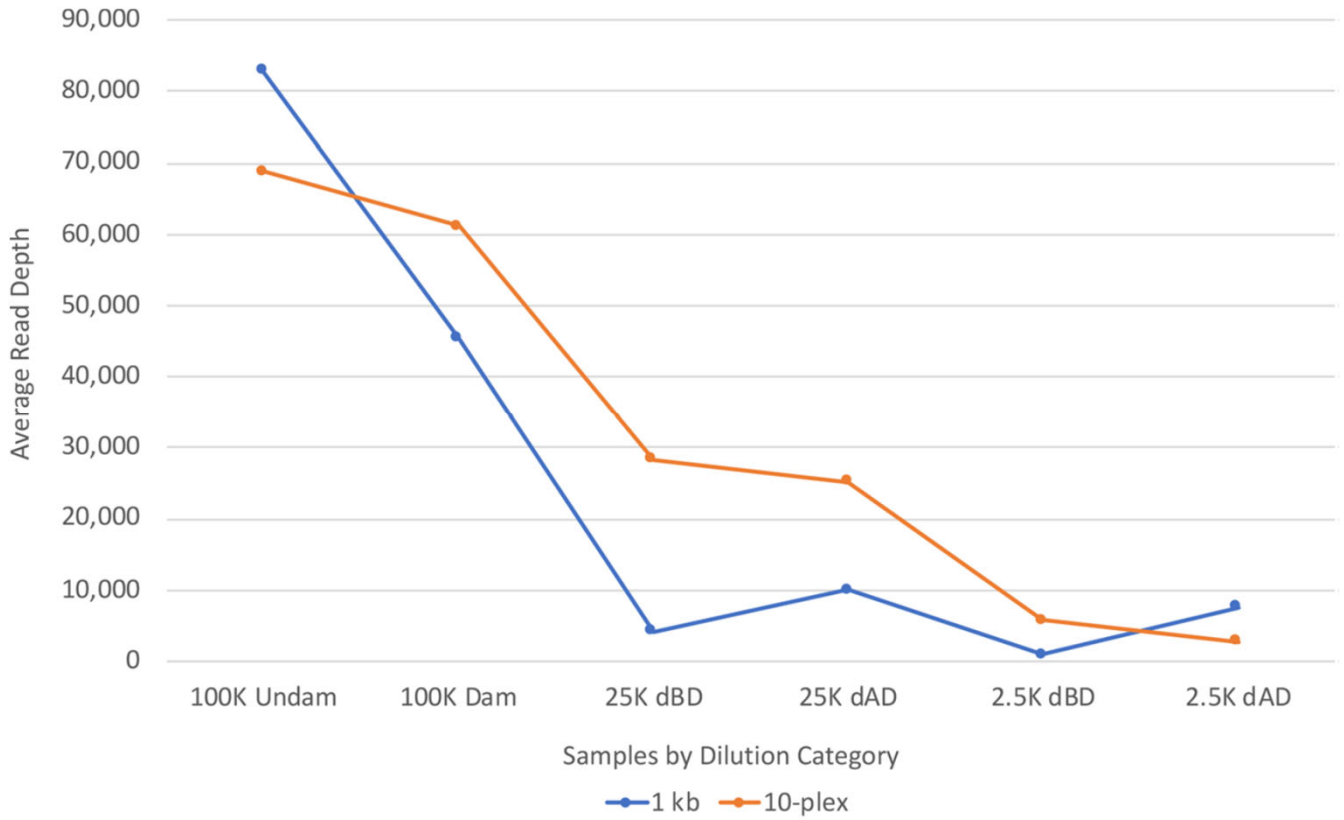
versus

Amplification of the entire CR (1.16kb amplicon) referred to as the **"1 kb"** approach with adapters on the primers for library preparation

NexteraXT library preparation

Libraries run on a MiSeq with a 600-cycle v3 kit (10-Plex) versus 300-cycle v2 kit (1 kb)

MPS Results



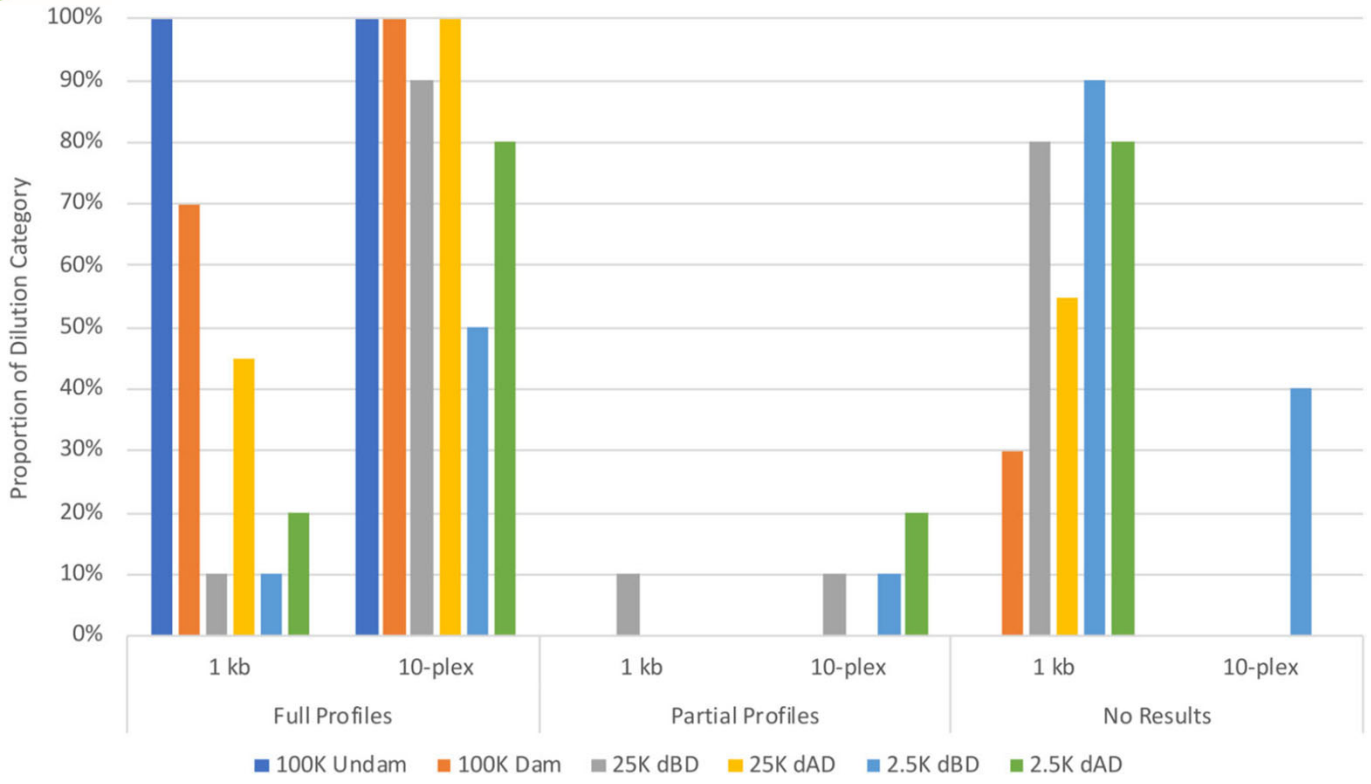
Comparison of ***normalized average*** read depths between different DNA damage dilution categories and two amplification and library prep strategies (**1 kb v. 10-plex; n = 20 per category**).

MPS Results

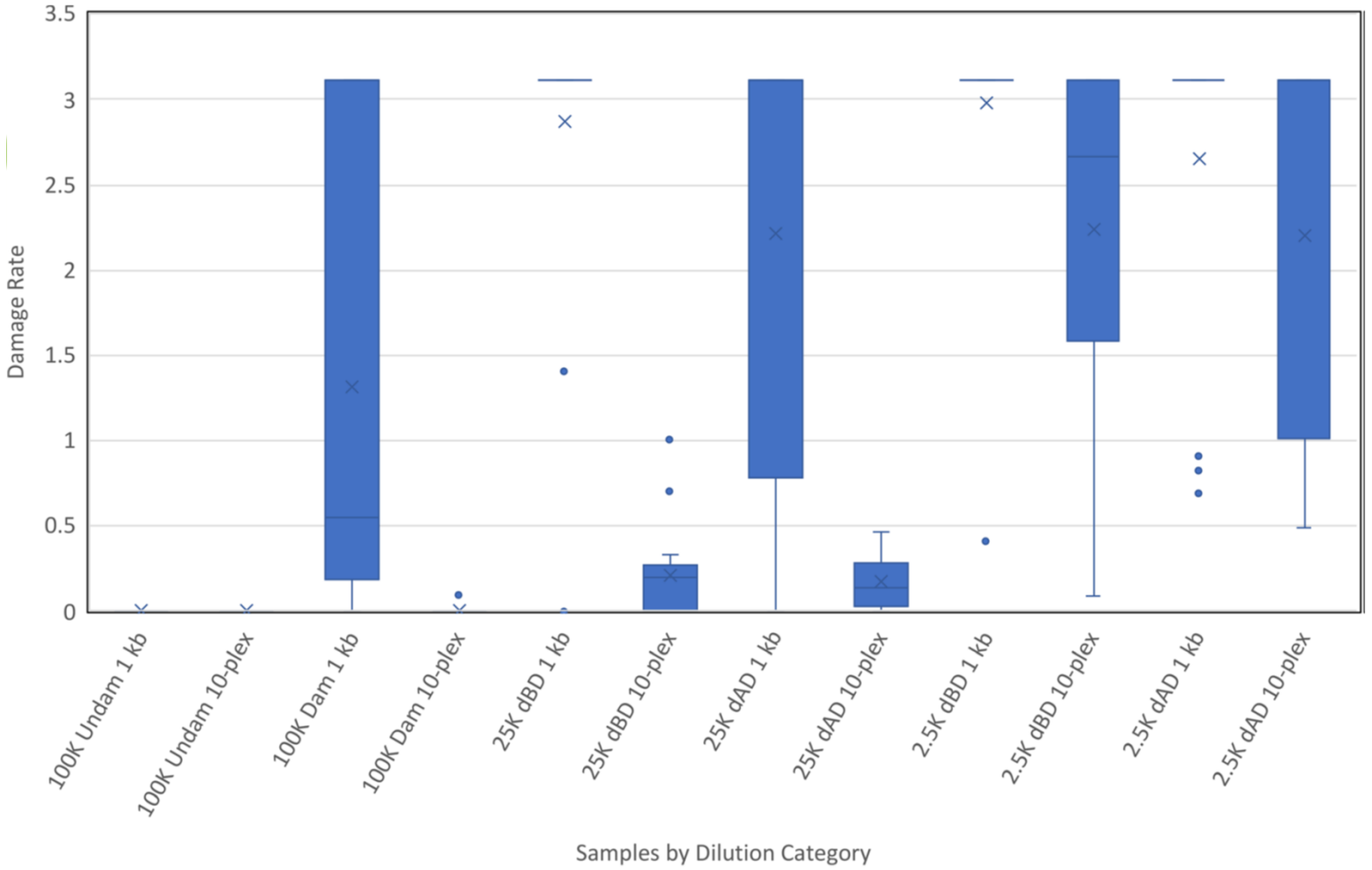
	Full Profiles		Partial Profiles		No Results	
	1 kb	10-plex	1 kb	10-plex	1 kb	10-plex
100K Undam	100%	100%	0%	0%	0%	0%
100K Dam	70%	100%	0%	0%	30%	0%
25K dBD	10%	90%	10%	10%	80%	0%
25K dAD	45%	100%	0%	0%	55%	0%
2.5K dBD	10%	50%	0%	10%	90%	40%
2.5K dAD	20%	80%	0%	20%	80%	0%

Table 1: MPS results depicted as percentages of full profiles, partial profiles, and no results across each dilution category and comparing the two amplification and library prep strategies (**1 kb v. 10-plex**), with n = 20 per category.

MPS Results



MPS results depicted as percentages of full profiles, partial profiles, and no results across each dilution category and comparing the two amplification and library prep strategies (1 kb v. 10-plex) with n = 20 per category.

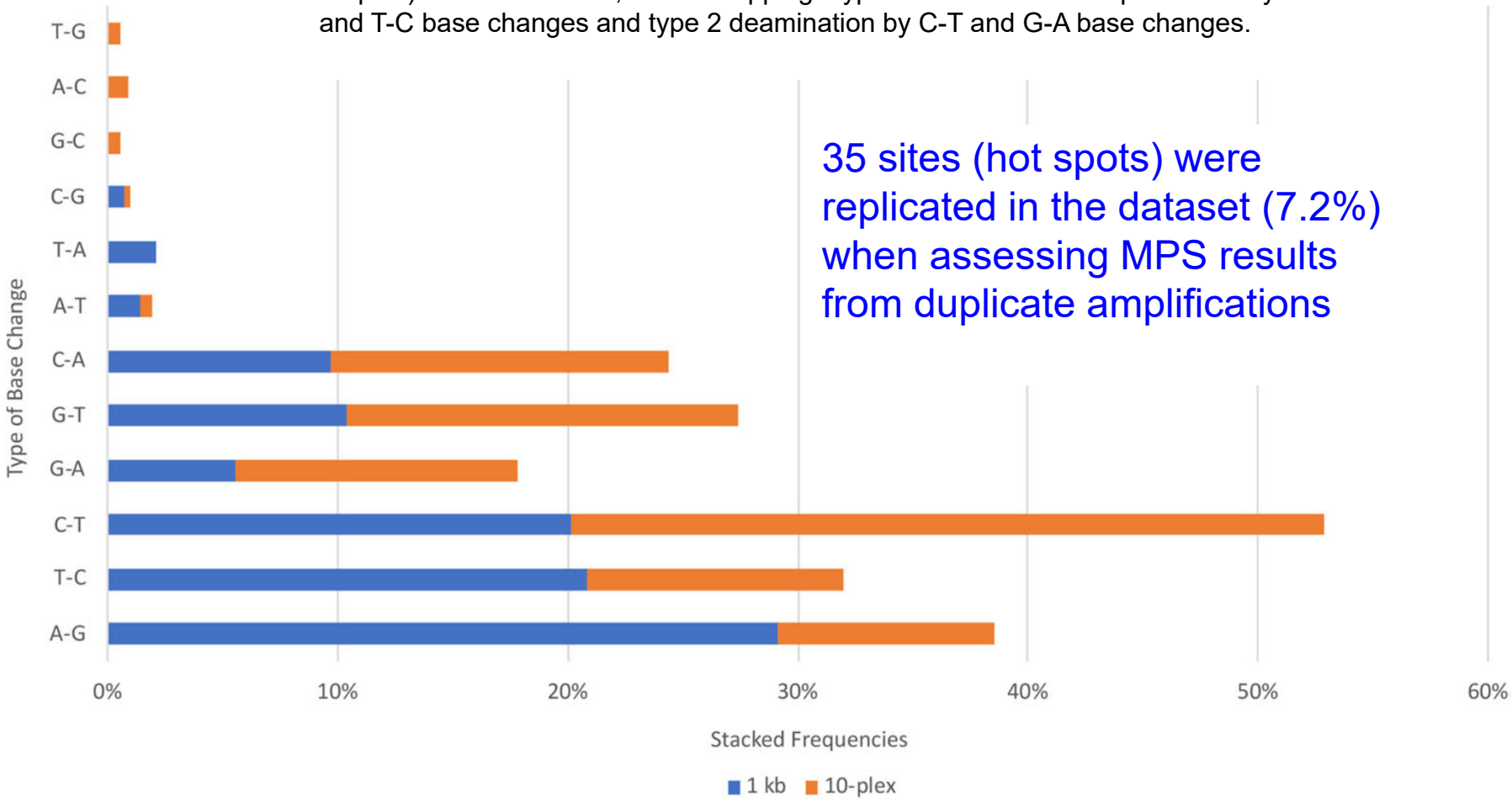


Box and whisker plot depicting damage rates (**number of damage sites/number of total sites reported × 100**) calculated across each dilution category using a 4000 read cutoff and a comparison of the 1 kb and 10-plex amplification and library prep strategies (n = 20 per category).

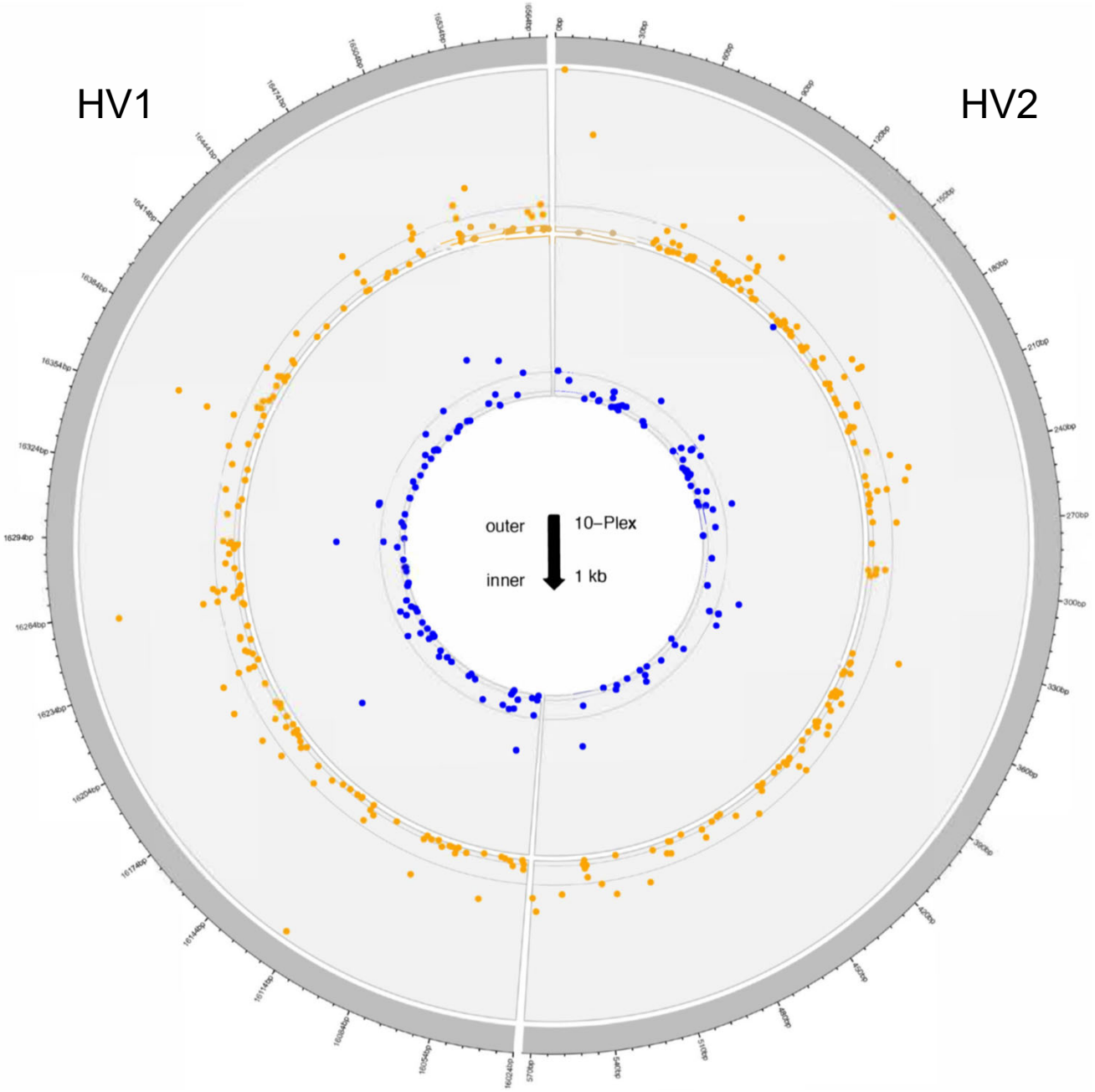
Damage Rates

Type of Base Change

Frequencies of each type of base change observed in **486 damage lesions** across all samples and comparison of two amplification and library prep strategies (1 kb v. 10-plex). Data is stacked, not overlapping. Type 1 deamination is represented by A-G and T-C base changes and type 2 deamination by C-T and G-A base changes.

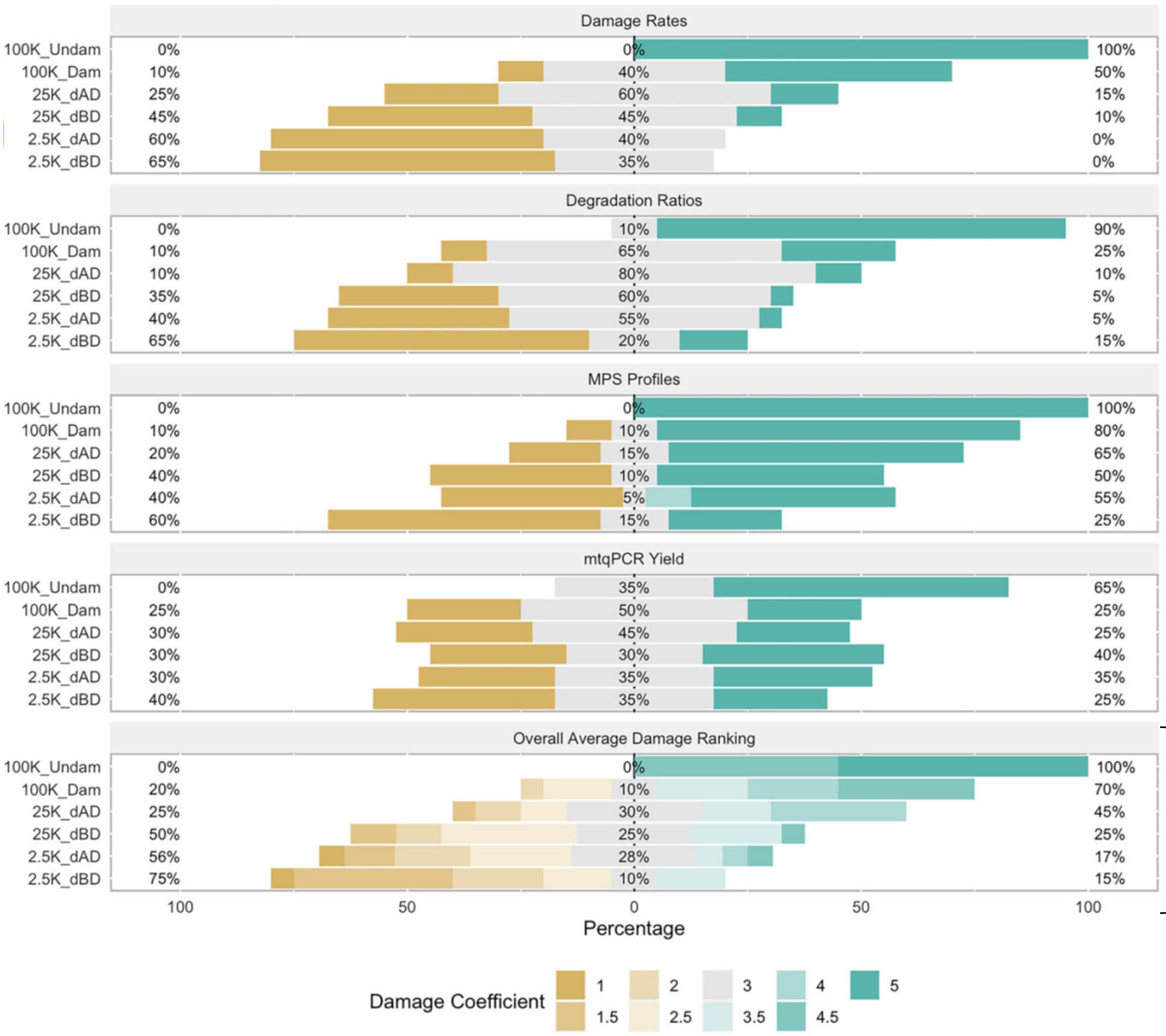


35 sites (hot spots) were replicated in the dataset (7.2%) when assessing MPS results from duplicate amplifications



Impact of Damage on Reporting Thresholds

Individual MVFs of 486 damage lesions observed across the control region for all samples (144 in the 1 kb samples and 342 in the 10-plex samples). **Proposed analytical (2%) and reporting (5%) thresholds** are marked by the first and second circles moving outward, respectively, for each dataset.



Overall damage assessment using a damage coefficient scale of 1–5 (1 = highest damage; 5 = little to no damage).

The last plot shows the overall damage assessment when averaging the damage coefficients for all four categories.

Take Home Messages

DNA damage impacts the quantity and quality of mitoMPS data when working with low-template samples.

DNA damage increases as template levels decrease, especially when the damage occurs after dilution.

Therefore, it's important to protect against further damage when working with forensic samples containing low amounts of extracted DNA.

Take Home Messages

Duplicate amplifications will mitigate the impact of the damage on interpretation of low-level heteroplasmy.

Reporting thresholds may be impacted by damage associated with low-level template samples.

The Promega 10-Plex helped to mitigate the impact of the damage, mostly likely due to the size of the amplicons being targeted.

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Therese Mandracchia (fired ammunition)
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Working Together

They Rock!!

Daisy says hello!

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