Molecular Genetic Pathology Review Course

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Identity Testing

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National Institute of Standards and Technology

Expertise that advances patient care through education, innovation, and advocacy.

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Topics Covered in This Presentation

- Identity Testing Use
- NIST and our Role in Identity Testing
- Genetic Markers and Techniques Used
  - Short Tandem Repeat (STR) Analysis
  - PCR, fluorescence detection, instrumentation, etc.
- Issues with STR Data Interpretation (e.g., stutter artifacts)
- Applications

Where is Identity Testing Used?

- Cell-line authentication
- Specimen ID and contamination checks (tissue ID testing)
- Bone marrow transplant evaluation
- Linkage analysis for tracing genetic diseases in families
- Parentage & relationship testing (molar pregnancies, twins)
- Forensic testing (crime solving, missing persons ID)

National Institute of Standards and Technology (NIST)

- Started in 1901 with roots back to the Constitution
- Name changed to **National Institute of Standards and Technology (NIST)** from National Bureau of Standards in 1988
- Primary campus in Gaithersburg, Maryland (just outside of Washington, D.C.)
- Part of the U.S. Department of Commerce
- >3,000 employees and >2,000 associates
- Supply >1300 reference materials
- Defines official time for the U.S.

DNA reference materials can help calibrate laboratory results and enable traceability to a common standard

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Types of Standards

physical (measurement) standards

Certified reference material to aid with calibration of measurements

http://www.nist.gov/srm/

documentary (technical) standards

INTERNATIONAL STANDARD

ISO/IEC 17025

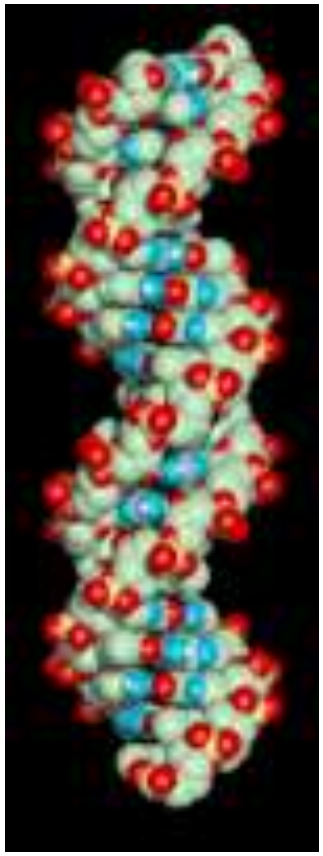
Second edition
2005-05-15

General requirements for the competence of testing and calibration laboratories

Exigences générales concernant la compétence des laboratoires d'étalonnages et d'essais

Specific requirements for the operation of a laboratory related to management system and competence

Characteristics of DNA



- Each person has a unique DNA profile (except identical twins).
- Each person's DNA is the same in every cell.
- An individual’s DNA profile remains the same throughout life.
- Half of your DNA comes from your mother and half from your father.

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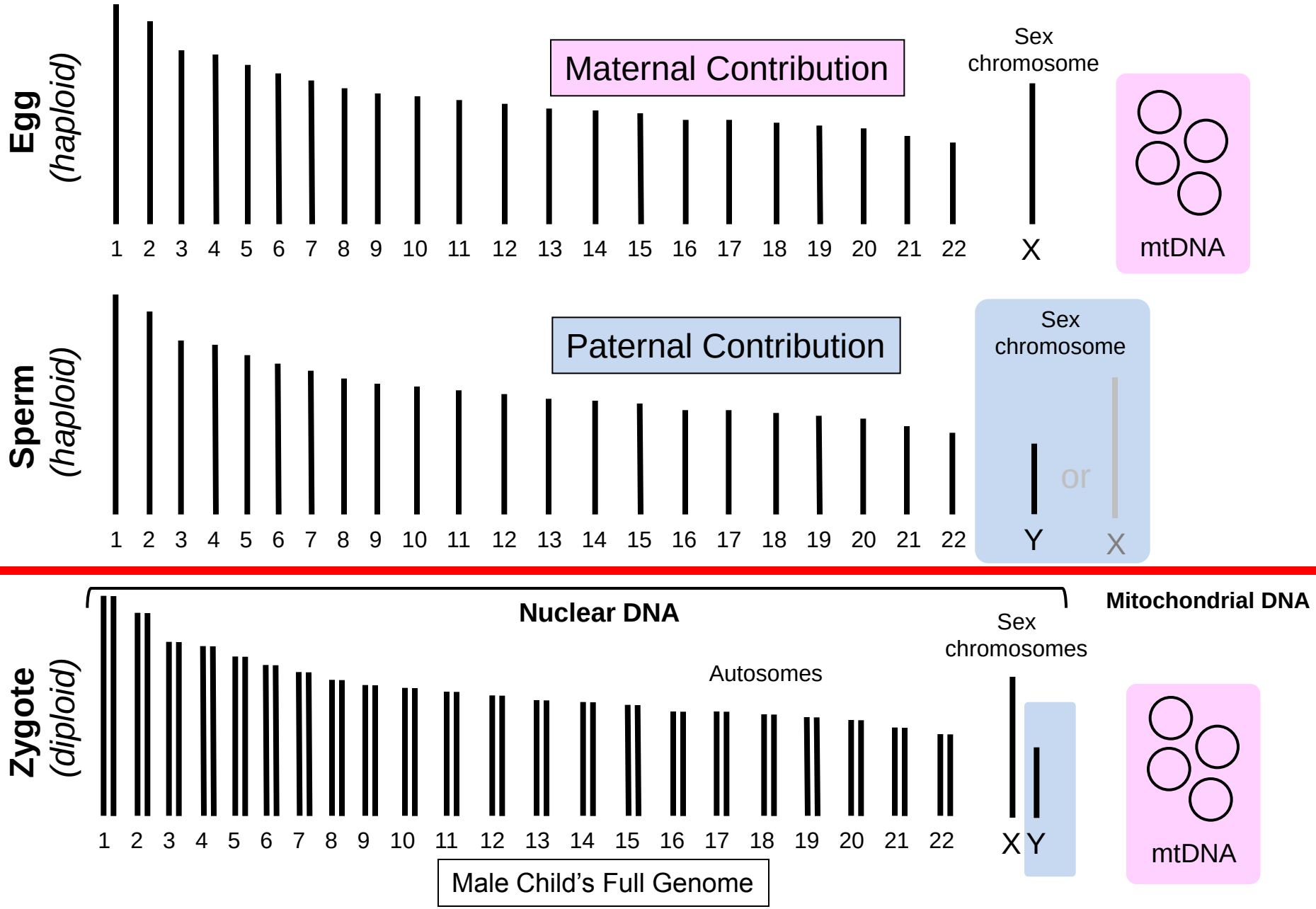
Human Genome and Inheritance

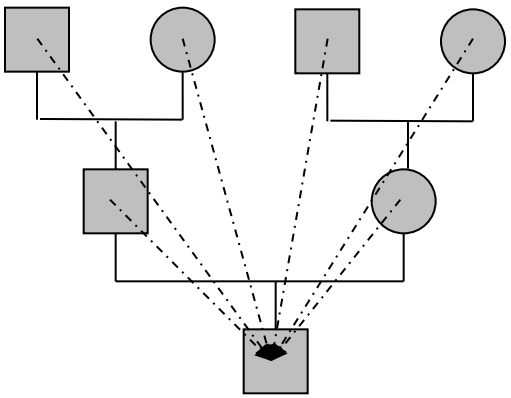


John M. Butler (2010) *Fundamentals of Forensic DNA Typing*, Figure 2.7

Different Inheritance Patterns

Autosomal Markers

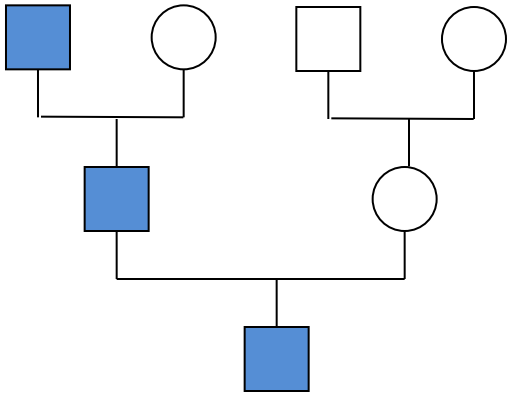
Autosomal STR Loci



22 pairs of autosomes
(passed on in part,
from all ancestors)

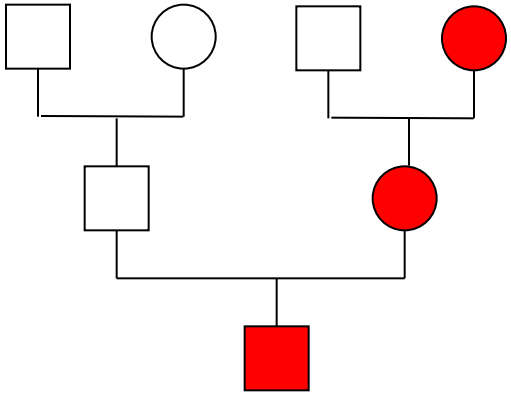
Lineage Markers

17, 23, or 27 Y-STRs



Y-Chromosome
(passed on complete,
but only by sons)

mtDNA control region



Mitochondrial
(passed on complete,
but only by daughters)

From Figure 15.1 in Butler, J.M. (2015) *Advanced Topics in Forensic DNA Typing: Interpretation*
Elsevier Academic Press: San Diego

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Stages of Forensic DNA Progression

Stages	Time Frame	Description
Exploration	1985 - 1995	Beginnings, different methods tried (RFLP and early PCR)
Stabilization	1995 - 2005	Standardization to STRs, selection of core loci, implementation of Quality Assurance Standards
Growth	2005 - 2015	Rapid growth of DNA databases, extended applications pursued
Sophistication	*2015 to 2025 and beyond*	*Expanding tools available,* ***confronting privacy concerns***

Table 1 from J.M. Butler (2015) The future of forensic DNA analysis. *Phil. Trans. R. Soc. B* 370: 20140252

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Genomic Research Enables Identity Testing and Potentially Impacts Privacy

Lowrance, W.W., & Collins, F.S. Identifiability in genomic research. *Science* (3 August 2007) 317:600-602

POLICYFORUM

"A proper balance between encouraging genomic research and protecting privacy and confidentiality of research participants will not be easily achieved."

ETHICS

Identifiability in Genomic Research

Genomic data are unique to the individual and must be managed with care to maintain public trust.

William W. Lowrance and Francis S. Collins

Genomic research can now readily generate data that cover significant portions of the human genome at levels of detail unique to individuals. Data can now be categorized with respect to disease-related genes and linked to clinical, family, and social data. Identifiability, the potential for such data to be associated with specific individuals, is therefore a pivotal concern. Research, health care, police, military, and other DNA and genotype reference collections are growing. Members of the pub-

of privacy was among the issues examined by the National Institutes of Health (NIH) in a recent public consultation (*6*).

New Modes of Data Flow

Until recently, most genomic research used data and biospecimens obtained fairly directly, from the data subjects themselves or clinical repositories or specialized research collections. This will continue, as it has many

Wellcome Trust Case Control Consortium do and U.K. Biobank will) (*7*). Among the design and governance issues are whether and how to de-identify the data and at what stages to conduct scientific and ethics review.

These new data flows, genomewide analyses, and novel arrangements such as the Informed Cohort scheme recently proposed by Kohane *et al*. (*8*) are relatively uncharted territory with respect to human subjects and privacy considerations. Precedent doesn't provide sufficient guidance.

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Genetic Markers Used in Identity Testing

- **VNTRs** (RFLP – hybridization, length measurement)
- **STRs** (PCR – length measurement)
- **SNPs** (PCR – hybridization, color measurement)
- **InDels** (PCR – length measurement)
- **mtDNA control region** (DNA sequence analysis)
- **Genome sequencing** (DNA sequence analysis)

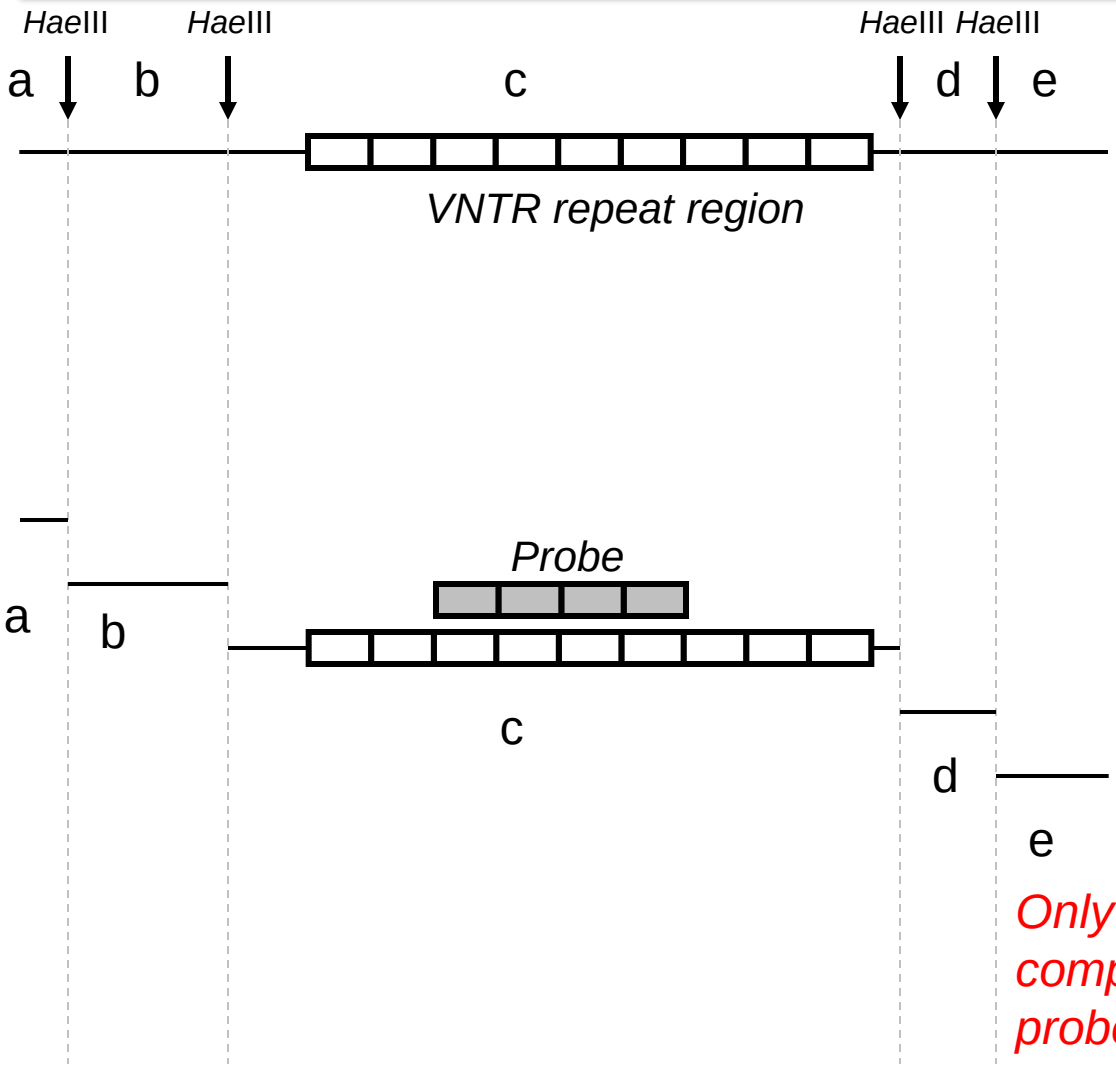
Historical Methods for DNA Testing

- RFLP
  - Multi-locus probes
  - Single-locus probes
- PCR based sequence polymorphisms
  - HLA-DQ alpha, PM + DQA1
- AmpFLPs
  - D1S80
- Silver-stained STRs
- Fluorescently detected STRs **(commercial kits)**
- SNP typing (single base extension) and InDel assays
- Microarray SNP assays
- Massively parallel sequencing (MPS)

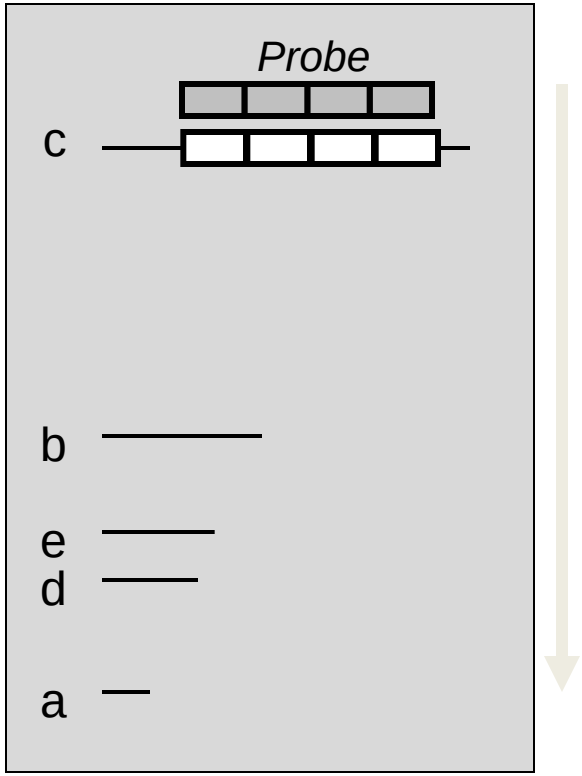
Principles of RFLP Testing

- Cut the DNA with “biological scissors” (Restriction enzymes)
- Separate Fragments of differing Length by gel electrophoresis
- Detect length-based differences (Polymorphisms) in DNA fragments of interest

Variable Number of Tandem Repeats (VNTRs)



Size Separation on Gel



Only DNA fragments containing a complementary sequence to the probe are detected

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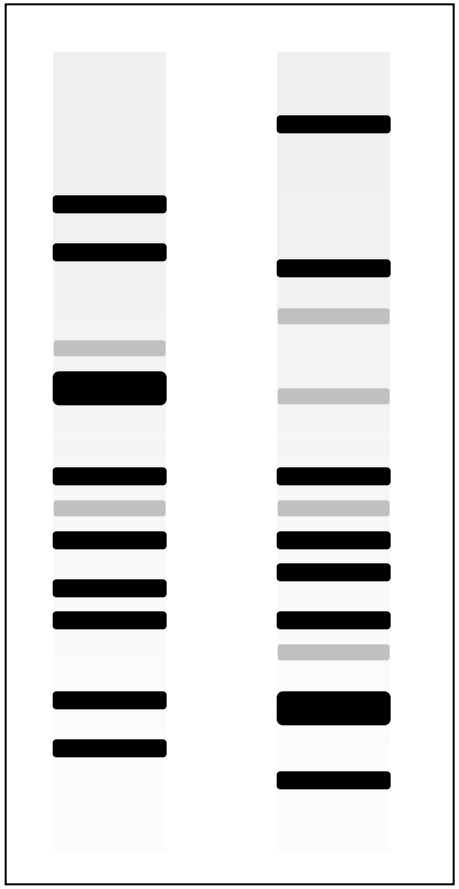
John M. Butler (2009) *Fundamentals of Forensic DNA Typing*, Figure 3.3

Multi-Locus Probe

Originally developed by Alec Jeffreys

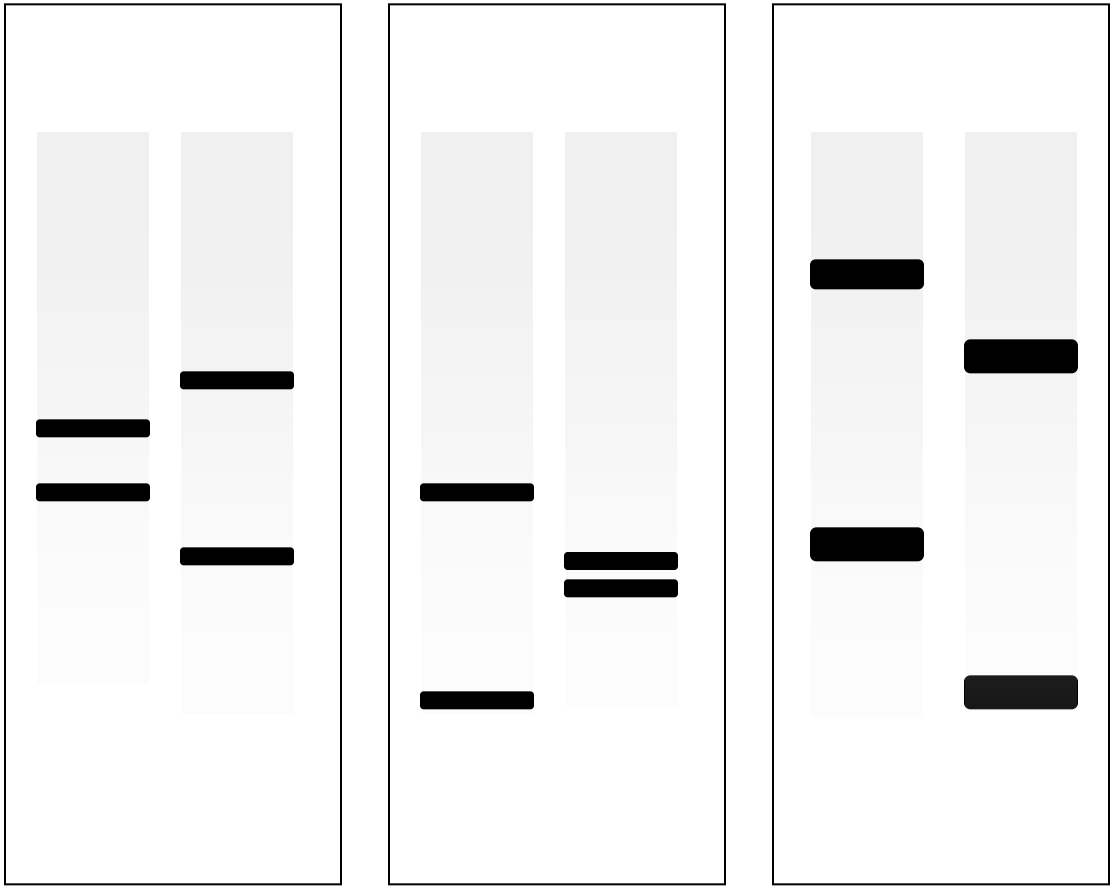


Probe 33.6

Complex patterns

Single-Locus Probe

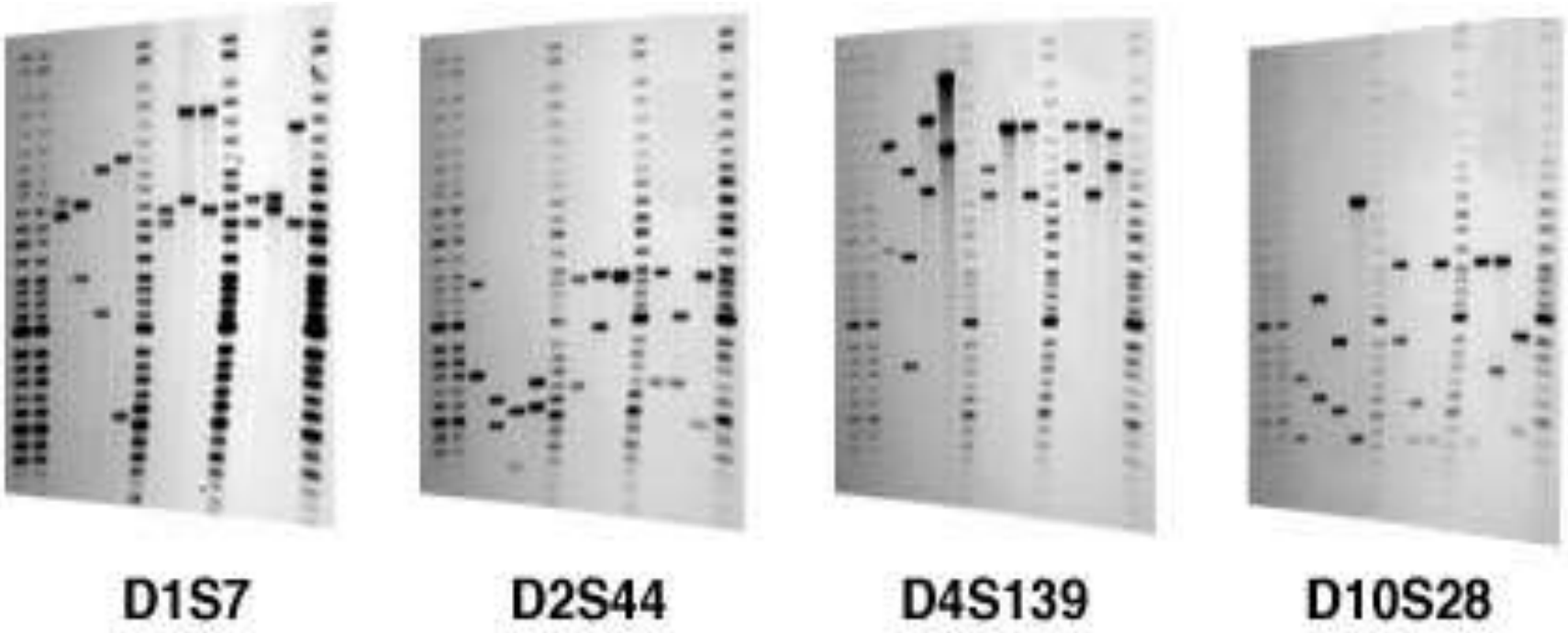
Probe 1 **Probe 2** **Probe 3**



D1S7 **D2S44** **D4S139**

Better for forensic samples containing mixtures

Repeated Probing of Same Membrane to Yield a Series of Autoradiograms



Sequential Detection of RFLP Single Locus Probes

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Restriction Fragment Length Polymorphism (RFLP) with single locus VNTR probes

Advantages	Limitations
1. Excellent powers of discrimination (≈1 in millions or greater with four loci). 2. Large number of alleles (20 to 30 bins) at each locus which facilitates mixed-sample analysis.	1. Limited sensitivity (>50 ng to 500 ng required). 2. Time-consuming process (days to weeks) that cannot be automated. 3. Not suitable with degraded DNA samples due to high molecular weight needed. 4. Essentially continuous allele sizes which requires grouping alleles into bins. Binning introduces statistical complications and sometimes difficulties of interpretation. 5. Limited number of validated loci (4 to 6 loci commonly used) which meant that these VNTRs were of limited value in distinguishing between siblings.

John M. Butler (2010) *Fundamentals of Forensic DNA Typing*, Table 3.6

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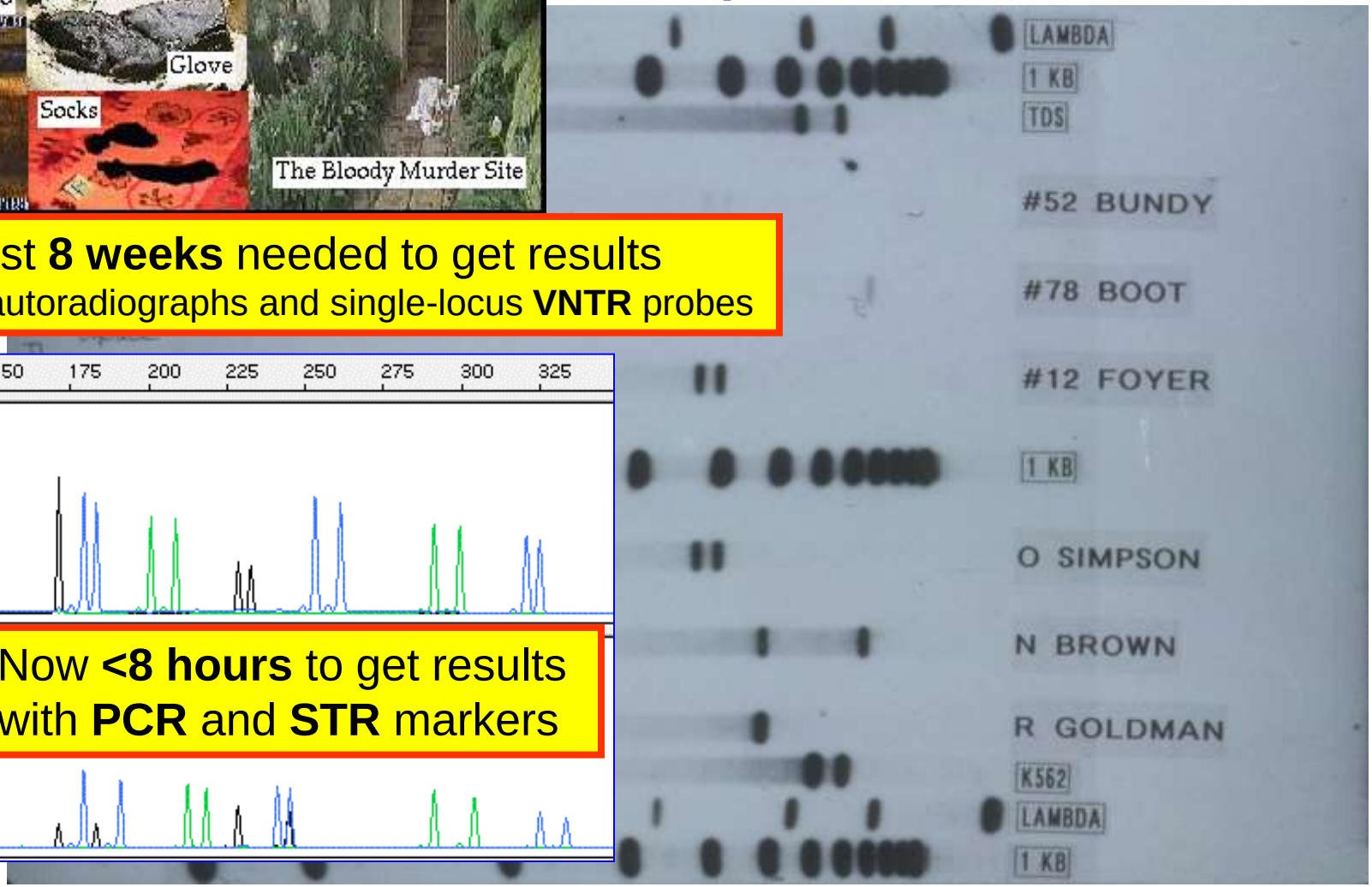
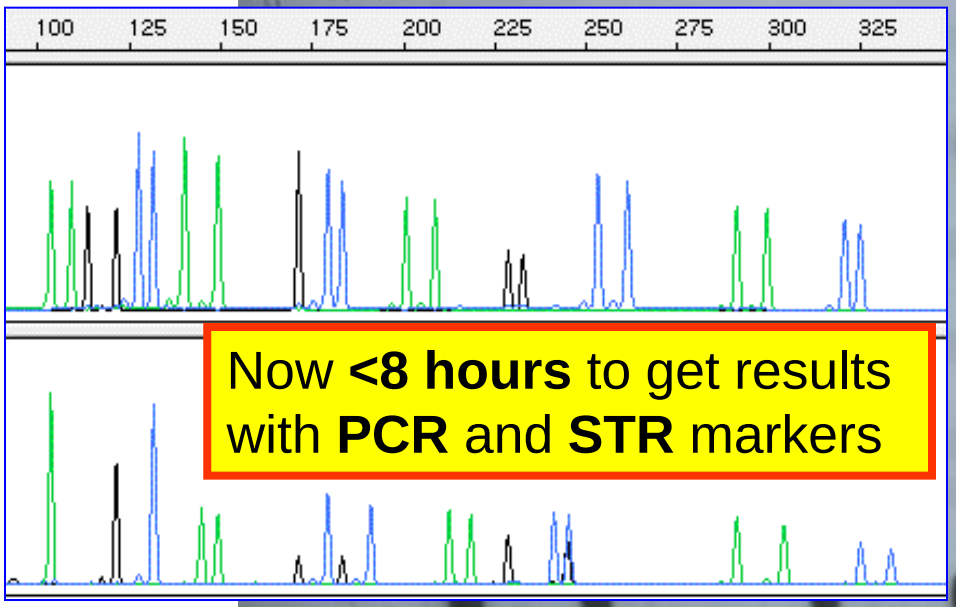
Progress Since 1995…

O.J. Simpson DNA testing was performed with RFLP



Almost **8 weeks** needed to get results
with **RFLP** autoradiographs and single-locus **VNTR** probes



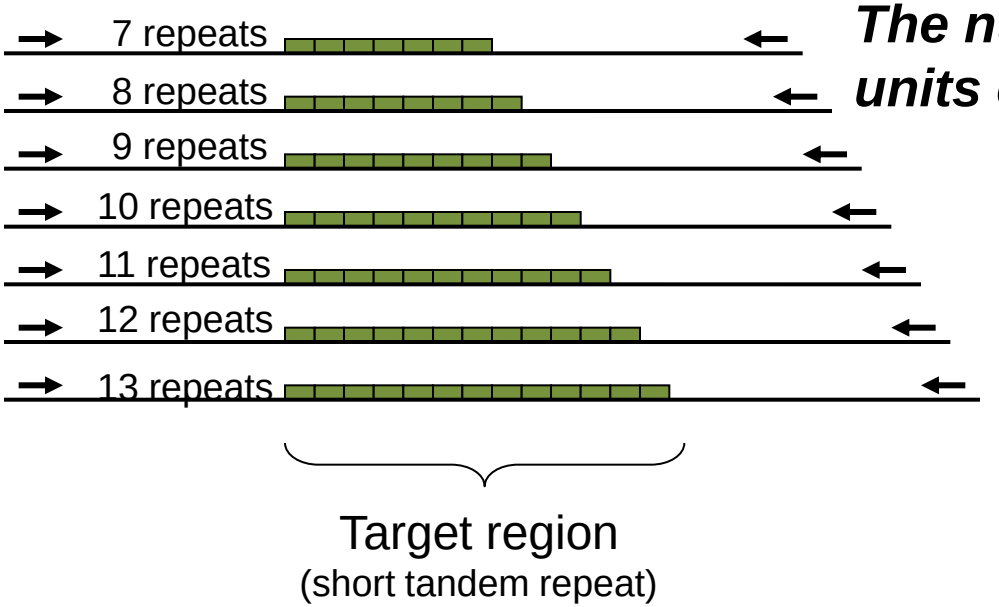
Now **<8 hours** to get results
with **PCR** and **STR** markers

Short Tandem Repeat (STR) Markers

An accordion-like DNA sequence that occurs between genes

TCCCAAGCTCTTCCTCTTCCCTAGATCAATACAGACAGAAGACA
GGTG**GATAGATAGATAGATAGATAGATAGATAGATAGATAGATA**
GATATCATTGAAAGACAAAACAGAGATGGATGATAGATACATGCT
TACAGATGCACAC

= 11 GATA repeats ("11" is all that is reported)



The number of consecutive repeat units can vary between people

In 1997, the FBI selected **13 core STR loci** that must be run in all DNA tests in order to provide a common currency with DNA profiles; in 2017, this was increased to **20 core loci**

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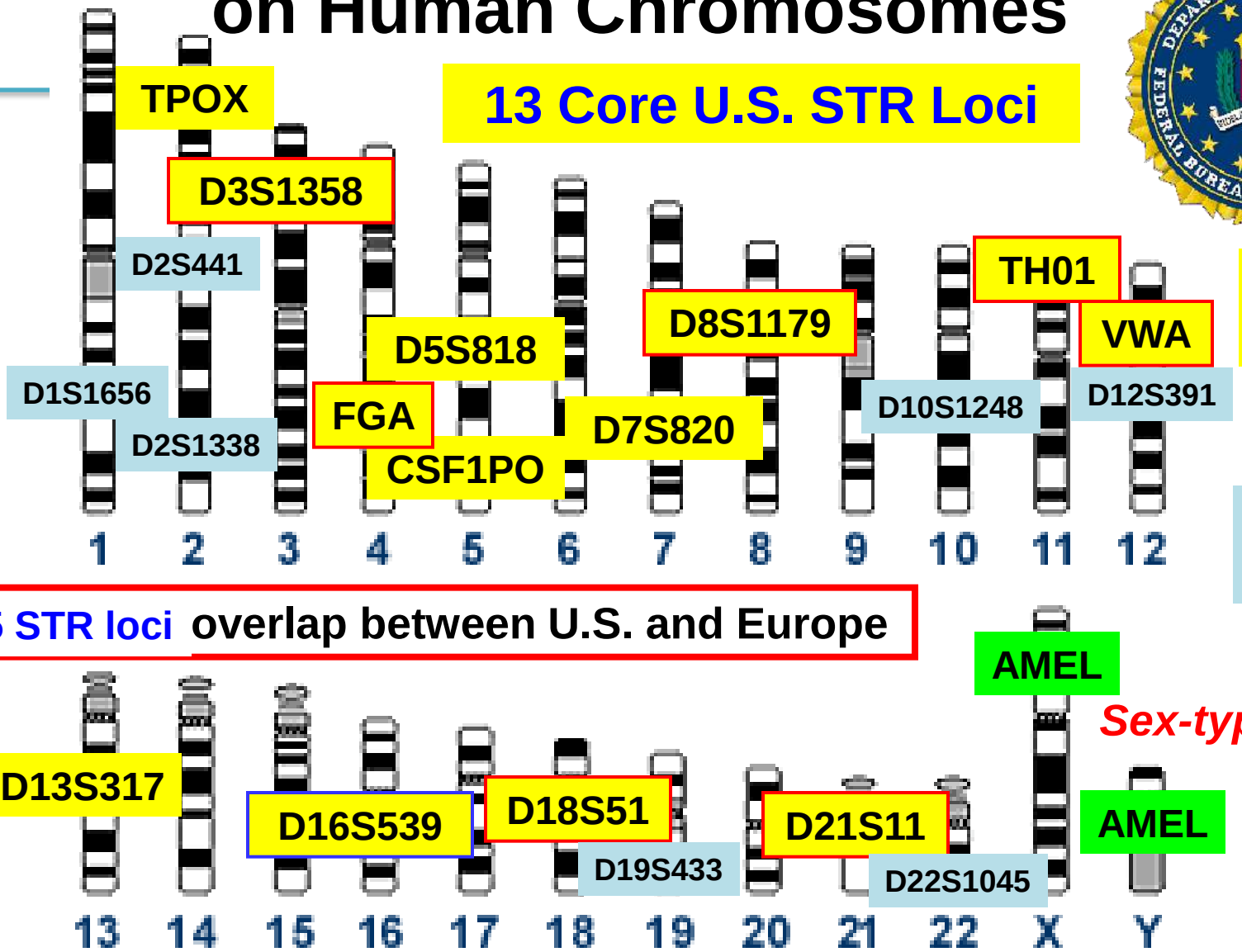
Advantages for STR Markers

- Small product sizes are generally **compatible with degraded DNA** and PCR enables recovery of information from **small amounts of material**
- Numerous alleles per locus aid **mixture interpretation**
- Multiplex amplification with fluorescence detection enables **high power of discrimination** in a single test
- Commercially available in an **easy to use kit format**
- Uniform set of **core STR loci** provide capability for national (and international) sharing of criminal DNA profiles

Position of Forensic STR Markers on Human Chromosomes

Core STR Loci for the United States



1997 (13 loci)

⇩

2017 (20 loci)

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U.S. has moved to 20 core loci

Locus
CSF1PO
D3S1358
D5S818
D7S820
D8S1179
D13S317
D16S539
D18S51
D21S11
FGA
TH01
TPOX
vWA
D1S1656
D2S441
D2S1338
D10S1248
D12S391
D19S433
D22S1045

Red is for original CODIS Core 13 Loci.
Blue is for new additional CODIS Core Loci.

Forensic Science International: Genetics 17 (2015) 33–34

Contents lists available at ScienceDirect

Forensic Science International: Genetics

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

Letter to the Editor

Required in U.S. starting January 1, 2017

Selection and implementation of expanded CODIS core loci in the United States

"The CODIS Core Loci Working Group selected a consortium of 11 CODIS laboratories…these laboratories performed validation experiments…

With the assistance of the National Institute of Standards and Technology (NIST), the data generated through these validation studies were compiled, reviewed and analyzed."

Hares, D.R. (2015) Selection and implementation of expanded CODIS core loci in the United States. *Forensic Sci. Int. Genet.* 17:33-34

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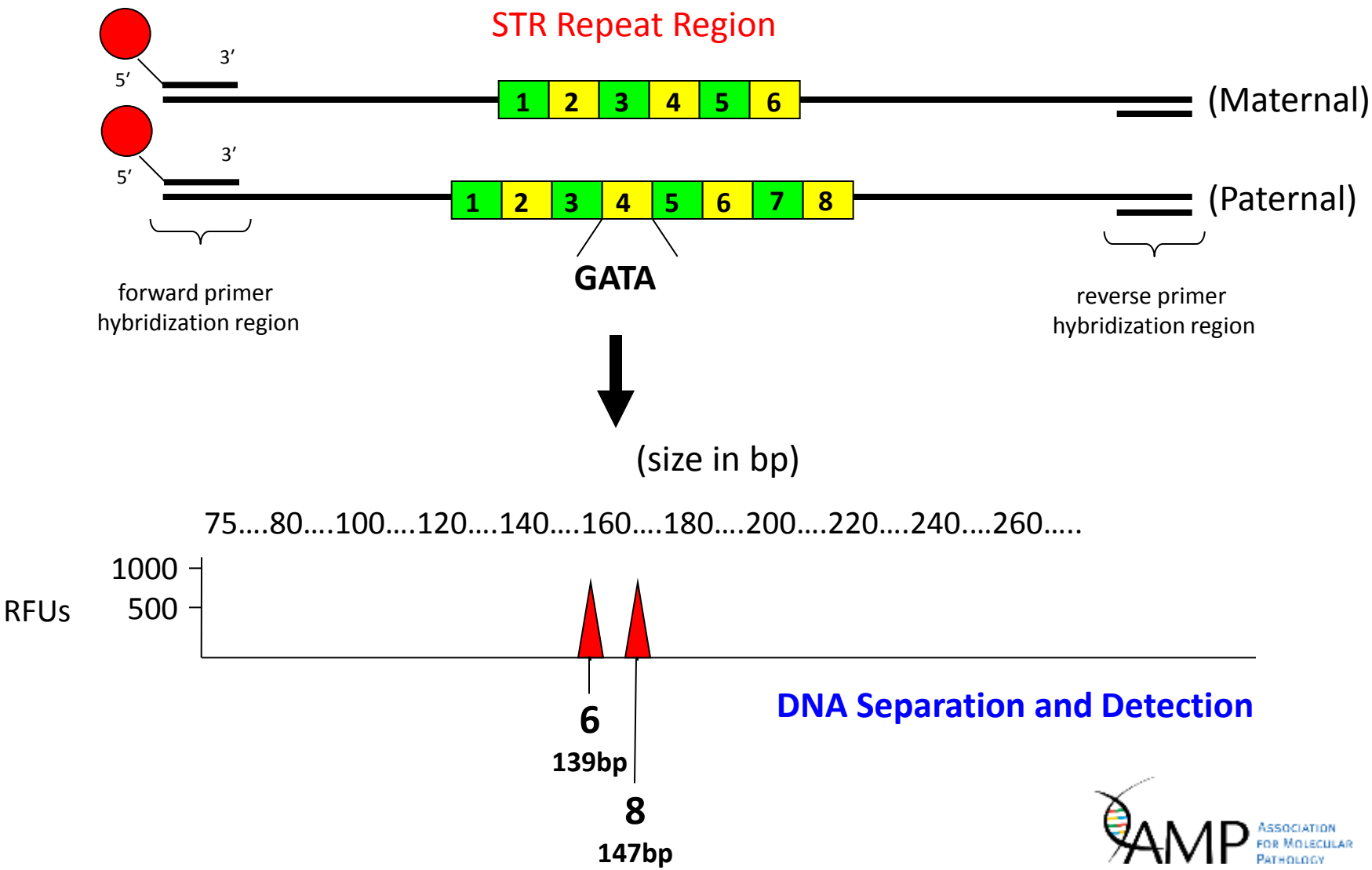
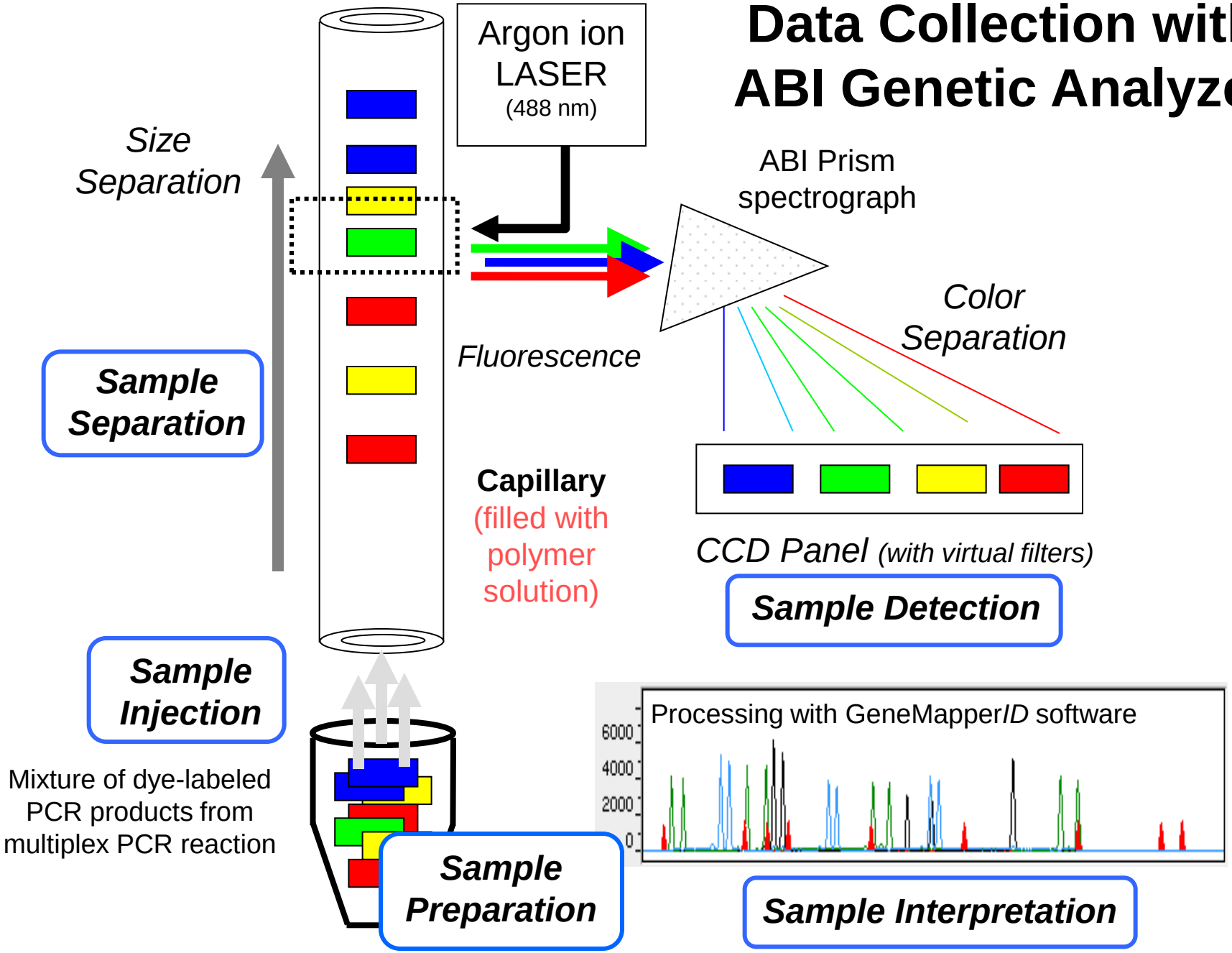
Short Tandem Repeat (STR) Typing



Data Collection with ABI Genetic Analyzer



STR Kits and Dye Sets Used

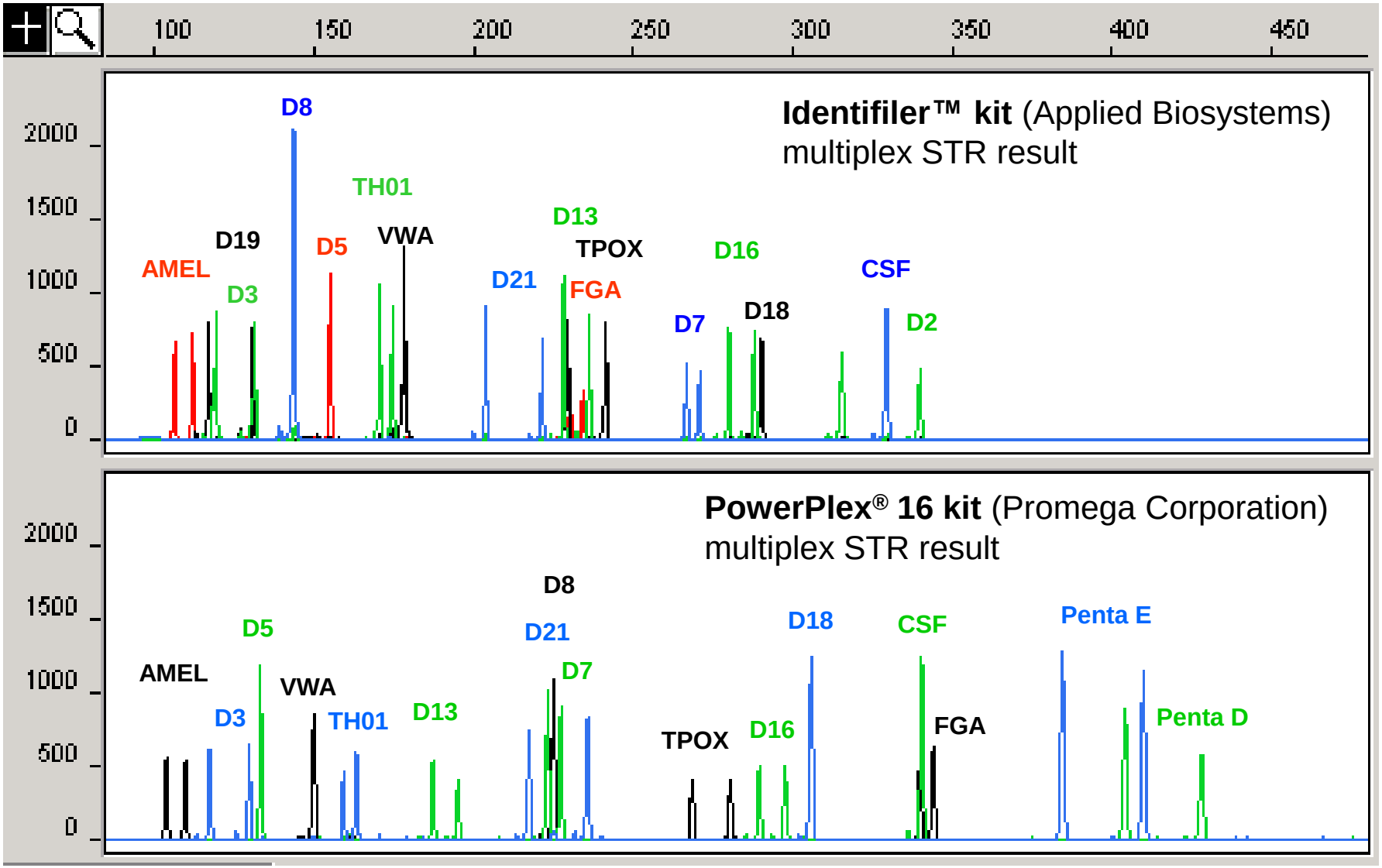
Sets virtual filter

Example STR Kits	Dye Labels	Dye Set
Profiler Plus, SGM Plus, COfiler, Profiler	**5-FAM, JOE, NED, ROX**	F
Identifiler, MiniFiler, NGM, NGM SElect	**6-FAM, VIC, NED, PET, LIZ**	G5
GlobalFiler	**6-FAM, VIC, NED, TAZ, SID, LIZ**	J6 (3500)
PowerPlex 16, 16HS	**FL, JOE, TMR, CXR**	F
PowerPlex ESI 16/17, ESX 16/17, 18D, 21, Fusion	**FL, JOE, TMR-ET, CXR-ET, CC5**	G5
Qiagen Investigator Kits	**B, G, Y, R, O**	G5
Research assays	**6-FAM, TET, HEX, ROX**	C

J.M. Butler (2015) *Advanced Topics in Forensic DNA Typing: Interpretation*, **Table 5.1**, p. 111

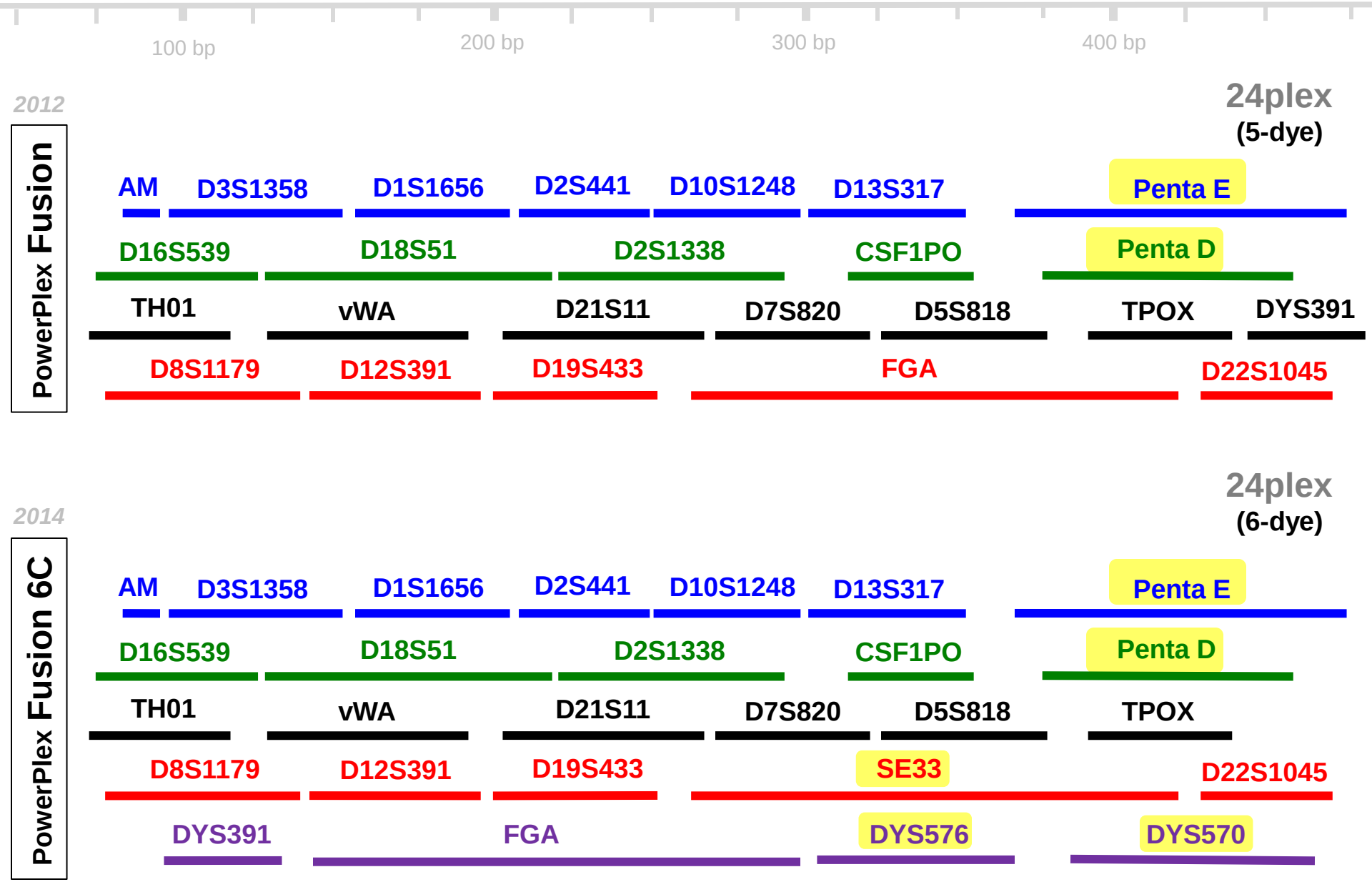
Commercial STR 16plex Kits

SRM 2391b component 1



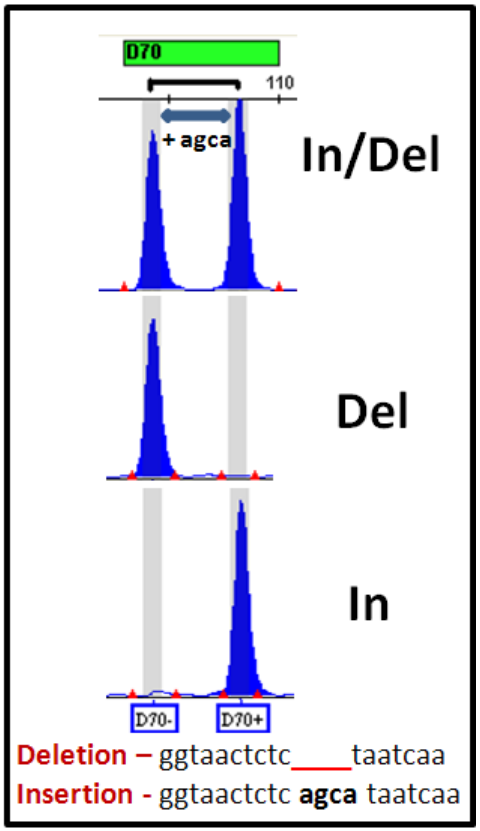
From Butler, J.M. (2005) Constructing STR multiplex assays. *Methods in Molecular Biology: Forensic DNA Typing Protocols* (Carracedo, A., ed.), Humana Press: Totowa, New Jersey, *297: 53-66.*

STR Marker Layouts for New U.S. Kits



Insertion/Deletion (InDel) Markers

- InDels (insertion-deletion) or DIPs (deletion-insertion polymorphisms) are short length polymorphisms, consisting of the presence or absence of a short (typically 1-50 bp) sequence
- Like SNPs, InDels have low mutation rate (value to kinship analysis), small amplicon target sizes (value with degraded DNA), and can be highly multiplexed
- Can be analyzed on CE instruments like STRs
- We have studied **commercial 30plex** (Qiagen DIPlex) and a **home-brew 38plex** in U.S. population samples



See Fondevila, M., et al. (2012) Forensic performance of two insertion-deletion marker assays. *Int. J. Legal Med.* 126: 725-737.

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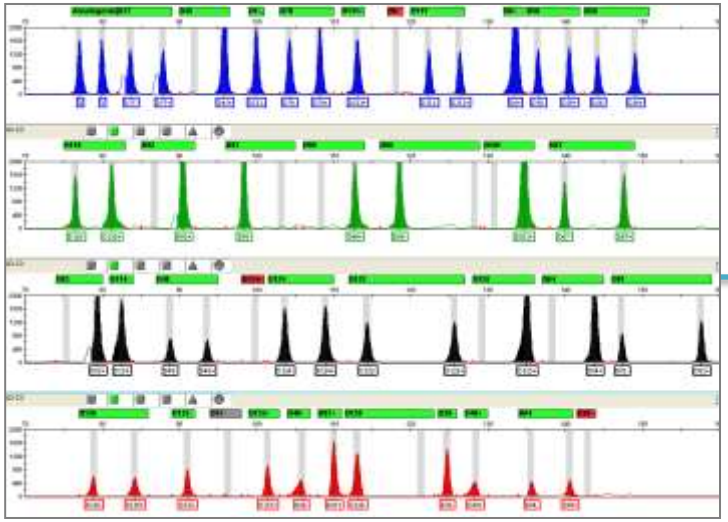
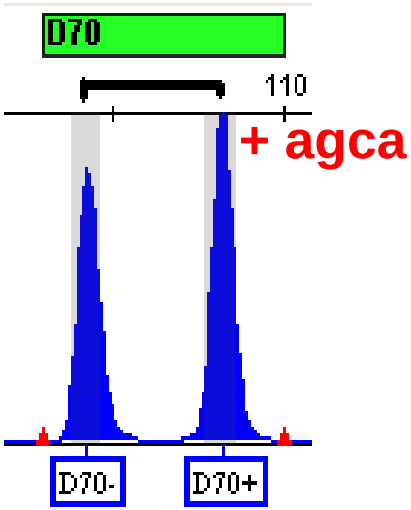
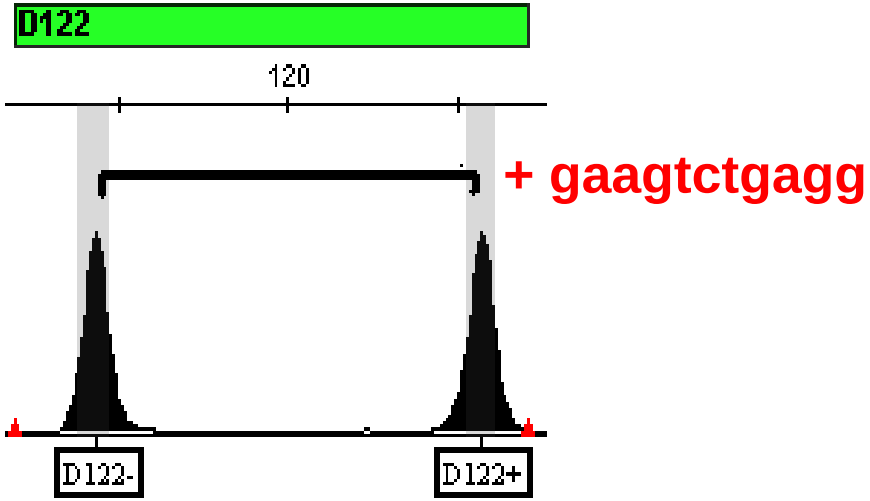


InDel Assays





Heterozygous alleles with different insertion lengths

Work performed by Manuel **Fonde**vila Alvarez (Santiago de Compostela, SPAIN), guest researcher at NIST

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Genetic Markers and Methods

STRs	InDels	SNPs
PCR	PCR	PCR
		EXO-SAP clean up
		SNaPshot
		SAP clean up
Capillary electrophoresis	Capillary electrophoresis	Capillary electrophoresis
Data analysis	Data analysis	Data analysis

As length polymorphisms, InDels can be typed with a simple direct PCR-to-CE genotyping strategy, using a single multiplexed PCR with dyed-linked primers immediately followed by capillary electrophoresis.

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Massively Parallel Sequencing (MPS)

- **Higher information content** with sequence data
  - Expanded number of STR loci and other genetic markers such as SNPs and InDels
    - New markers may enable additional applications (e.g., biogeographical ancestry and phenotypic prediction)
  - **Deeper depth of information on STR alleles**
    - For example, eight different sequence versions of D12S391 alleles among 197 samples examined (Gelardi et al. 2014)

- **Significant challenges with BIG data**
  - STR allele nomenclature issues (ISFG DNA Commission - Parson et al. 2016)
  - Data storage (do you retain terabytes of data?)
  - Data analysis time will increase…
  - Privacy concerns with additional genomic information

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Potential Pitfalls with PCR Methods

1. The target DNA template may not amplify due to the presence of **PCR inhibitors** in the extracted DNA.

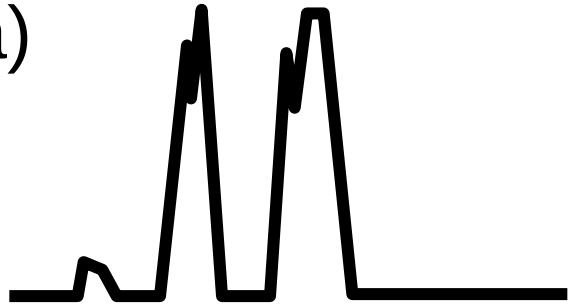
2. Amplification may fail due to sequence **mutations in the primer-binding region** of the genomic DNA template – something often referred to as a 'null allele.'

3. **Contamination** from other human DNA sources besides the forensic evidence at hand or previously amplified DNA samples is possible without the use of careful laboratory technique and validated protocols.

STR Typing Works Best in a Narrow Window of DNA Template Amounts

Off-scale data with flat-topped peaks

(a)

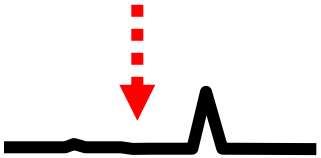


Too much DNA amplified

Or injected onto CE

Allele dropout due to stochastic effects

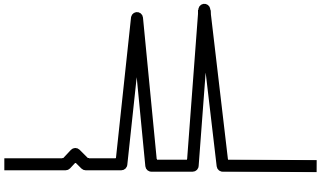
(b)



Too little DNA amplified

"Just right"

(c)

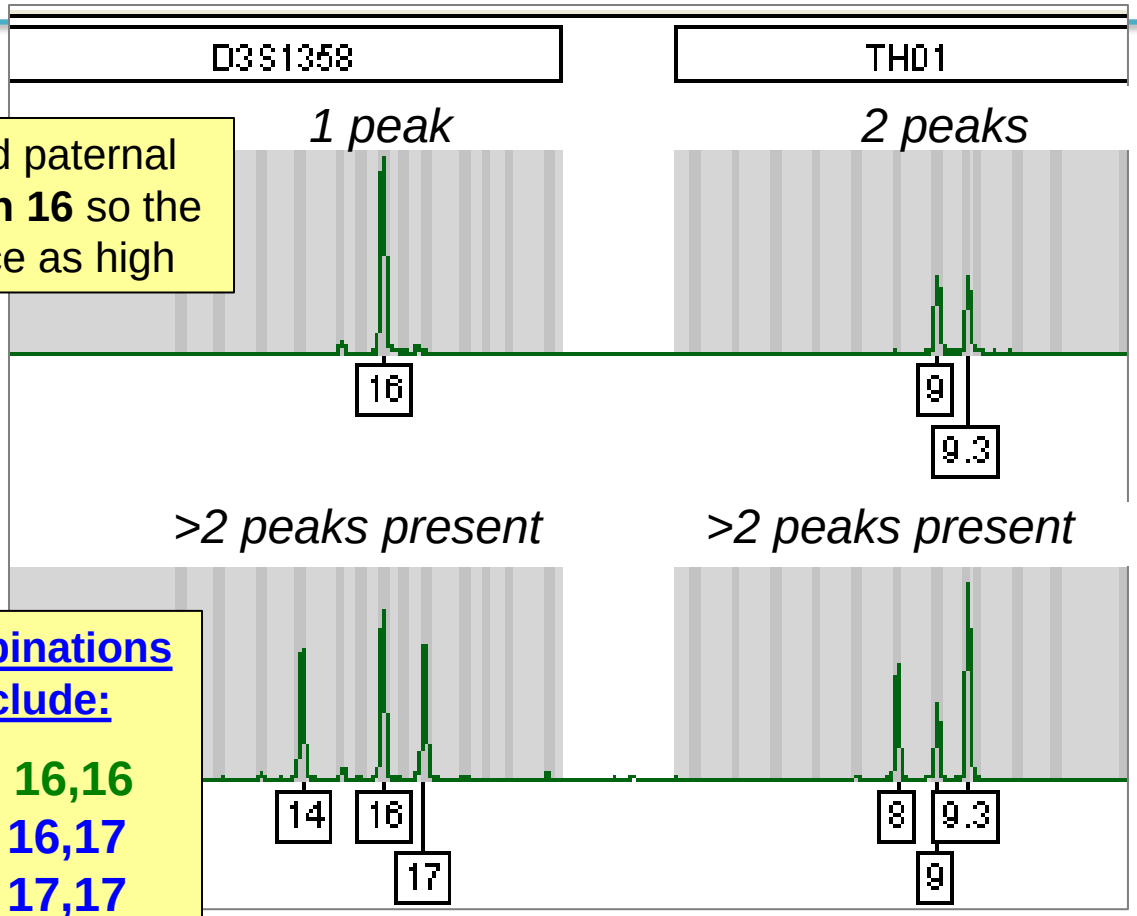


Within optimal range

Typically best results are seen in the 0.5 ng to 1.5 ng range for most STR kits

Single-Source Sample vs Mixture Results

Maternal and paternal allele are **both 16** so the signal is twice as high



Single-Source

Mixture

Possible combinations at D3S1358 include:

14, 17 with 16,16
14,14 with 16,17
14,16 with 17,17

Multiple possible combinations could have given rise to the mixture observed here

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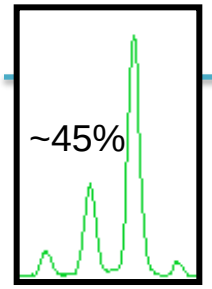
Types of STR Repeat Units

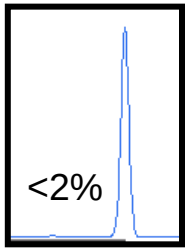
YCAII



High stutter

Low stutter

DYS448



Requires size based DNA separation to resolve different alleles from one another

- **Di**nucleotide (CA)(CA)(CA)(CA)
- **Tri**nucleotide (GCC)(GCC)(GCC)
- **Tetra**nucleotide (AATG)(AATG)(AATG)
- **Penta**nucleotide (AGAAA)(AGAAA)
- **Hexa**nucleotide (AGTACA)(AGTACA)

Short tandem repeat (STR) = microsatellite = simple sequence repeat (SSR)

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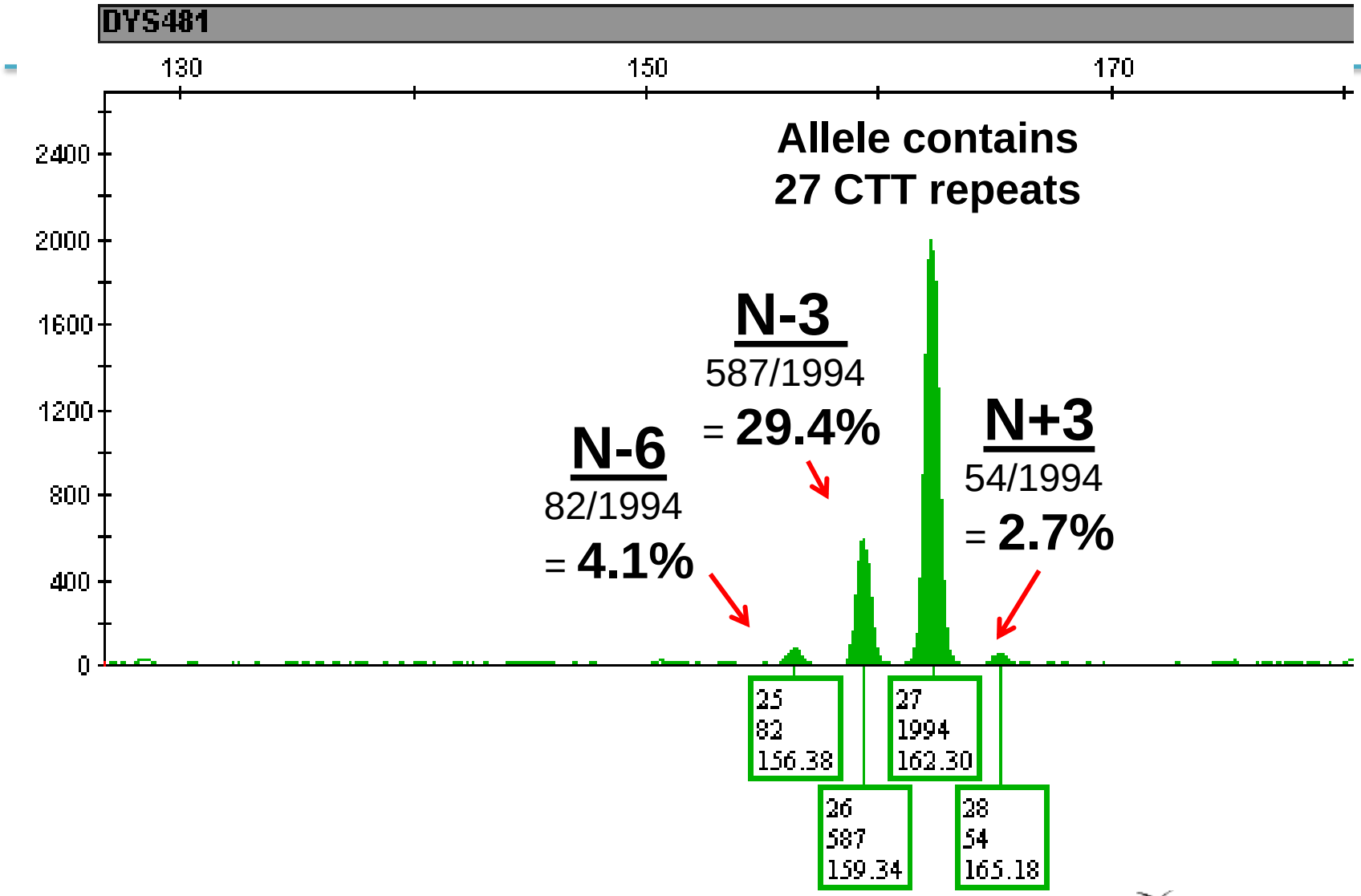
Stutter Artifacts Complicate Interpretation of STR Results



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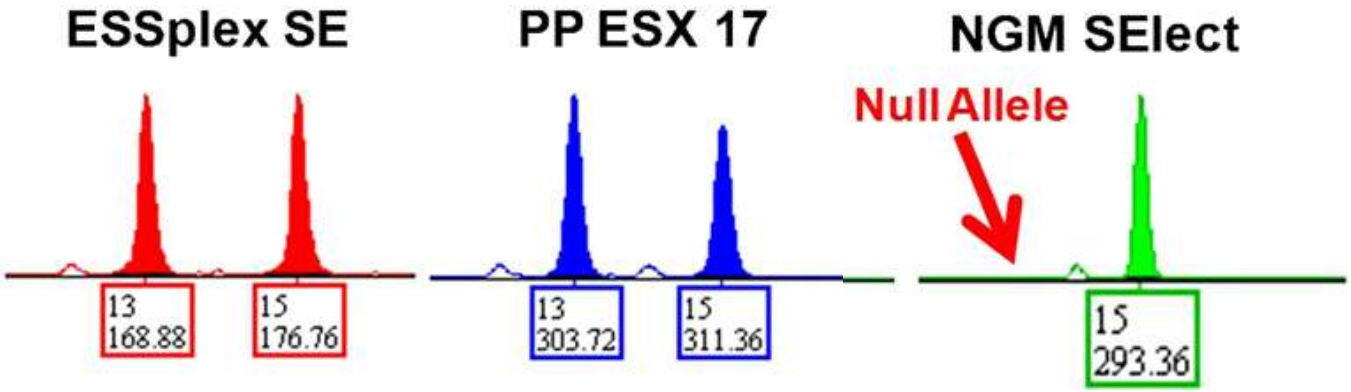
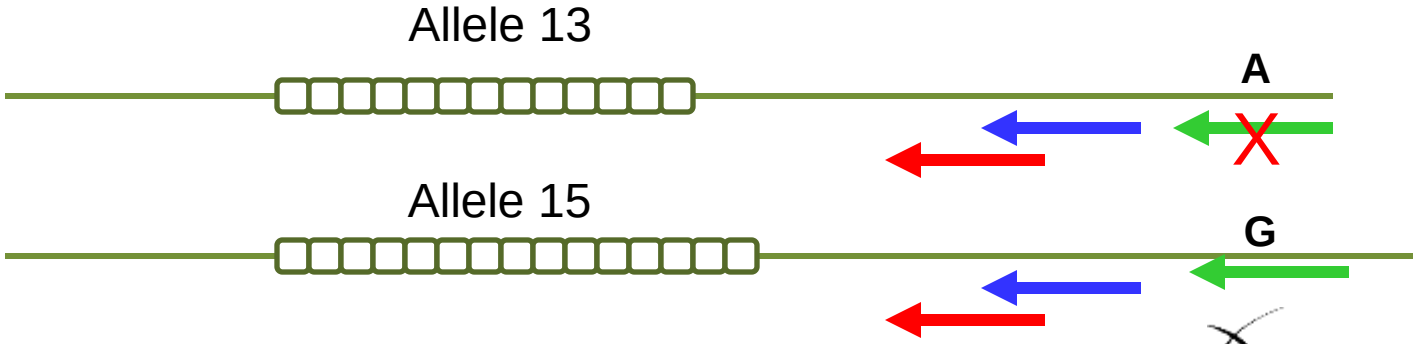
Primer Binding Site Mutations can lead to “null alleles” that are not detected

(a)



Concordance testing (involving DNA testing with different primer sets) reveals a missing “null” allele with one of the DNA tests

(b)



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Information that goes into a DNA rarity estimate (i.e., where errors can occur)

3

Estimates are derived from testing a small subsection of a population

Population allele frequencies

1

Evidentiary DNA Profile
(with specific alleles/genotypes)

Rarity estimate of DNA profile
(e.g., RMP or LR)

The risk of error goes up with complexity of the DNA profile (e.g., >2 person mixture or low-quality, low-template DNA sample)

Genetic formulas and assumptions made

"All models are wrong – but some are useful" (George Box, 1979)

2

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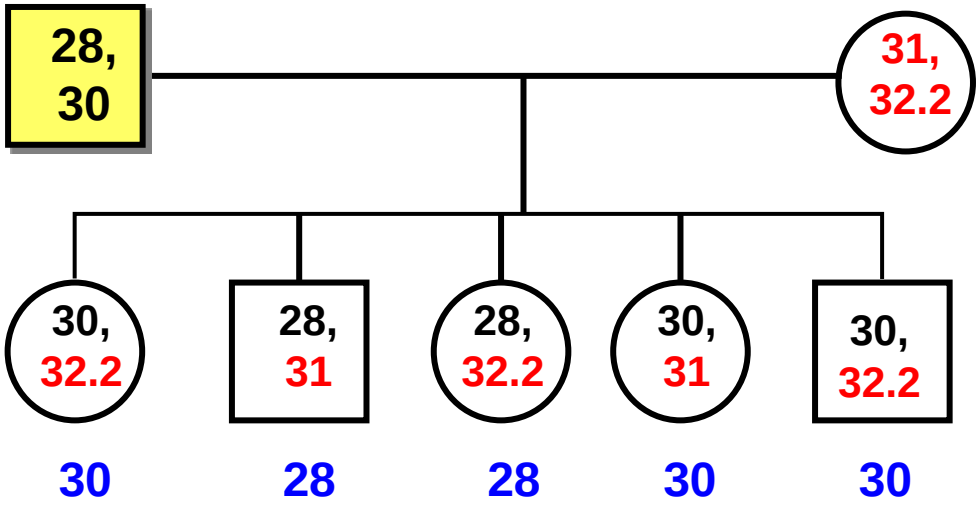
Parentage or Relationship Testing

Example Pedigree: STR Marker D21S11



Obligate paternal allele

From Figure 14.2(b) in Butler, J.M. (2015) *Advanced Topics in Forensic DNA Typing: Interpretation* Elsevier Academic Press: San Diego

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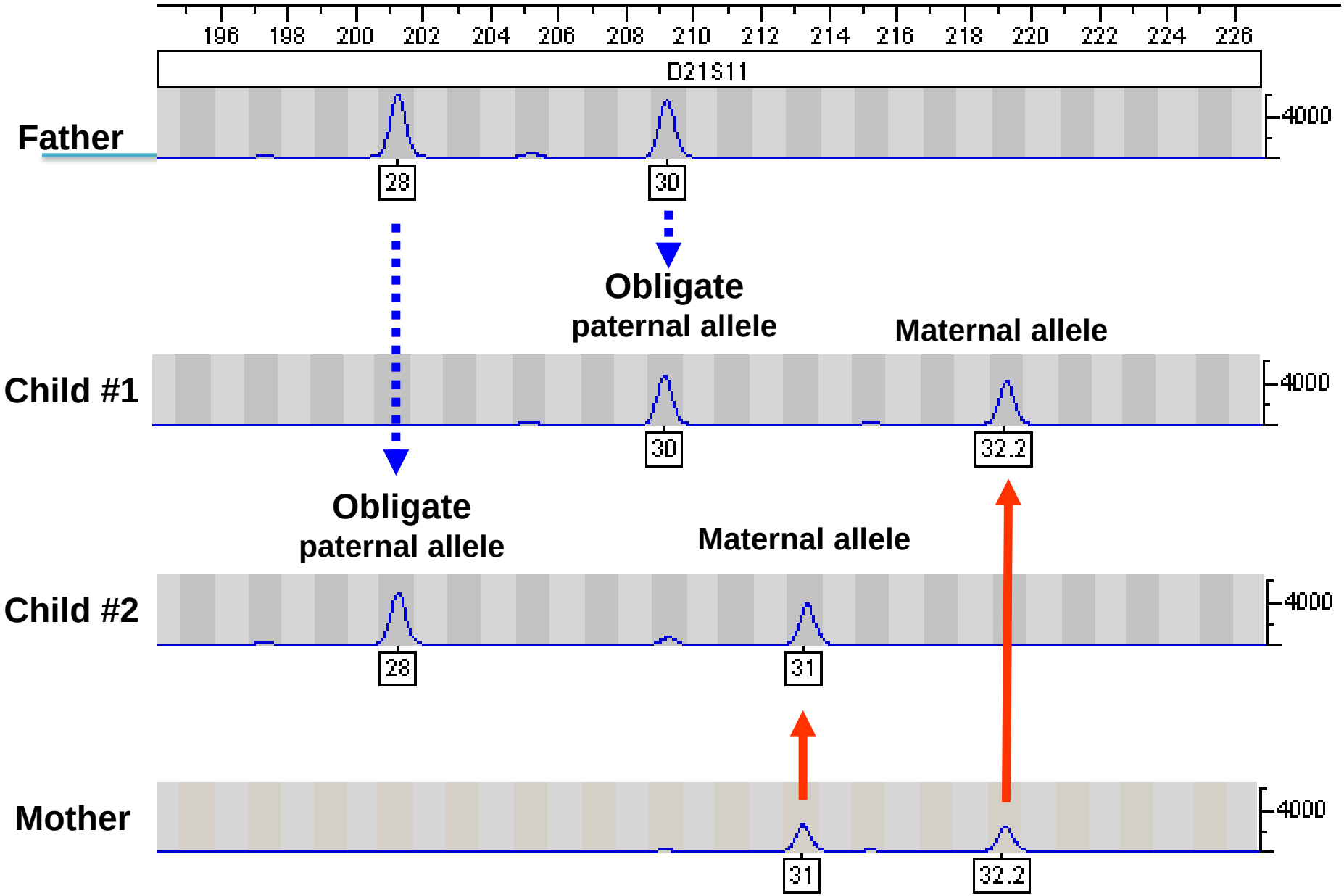

From Figure 14.2(c) in Butler, J.M. (2015) *Advanced Topics in Forensic DNA Typing: Interpretation* Elsevier Academic Press: San Diego

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STRs are the Dominant Genetic Markers Used in Paternity Testing

Latest available report (2013):
http://www.aabb.org/sa/facilities/Documents/2013-relationship-testing-summary-report.pdf

Table 4. The Technology Used in Cases Reported in 2013

Technology	Number of Cases	Utilization (%)
STR	368357	99.84
RFLP	48	0.01
HLA Class II Molecular	1	0.0003
Y Chromosome	489	0.13
HLA Class 1 Molecular	46	0.01
SNP	0	0.00
Total of All Technologies	368941	100

*Note that some cases used more than one technology.

Table 5. Sample Source in 2013.

Sample	Number	Percent
Buccal Swabs	892256	99.5051
Blood	1458	0.1626
Blood Spot Cards	1356	0.1512
Amniotic Fluid	463	0.0516
Misc. Tissues	314	0.0350
Paraffin Blocks	67	0.0075
Hair	364	0.0406
CVS	385	0.0429
Bone	31	0.0035
Total	896694	100.00

http://www.aabb.org/sa/facilities/Pages/relationshipreports.aspx

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Aiding Cell Line Authentication

Katsnelson, A. (2010) *Nature News*, 465: 537 (3 June 2010)

Biologists tackle cells' identity crisis

DNA fingerprinting scheme aims to make sure researchers are working on the right cells.

Ever since biologists learned how to grow human cells in culture half a century ago, the cells have been plagued by a problem of identity: many commonly used cell lines are not actually what researchers think they are.

Cell-line misidentification has led to mistakes in the literature, misguided research based on those results and millions wasted in grant money. Last year, *Nature* described the situation as a scandal[1].

But a universal system for determining the identity of cell lines may now be in view. Next month, a working group led by the American Type Culture Collection (ATCC), a nonprofit biological repository based in Manassas, Virginia, that stores 3,600 cell lines from more than 150 species, plans to unveil standard-

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Designation: ASN-0002

Authentication of Human Cell Lines: Standardization of STR Profiling

The working group, composed of representatives from academia, government and industry,

a universally accepted approach will allow different facilities to compare their cell lines with each other, he adds.

Fingerprinting has its limits, cautions Michael Johnson, a cancer researcher at Georgetown University in Washington DC. "Just because a cell fingerprints out as the same [as another cell] doesn't mean they will behave the same," he says, noting that a cell's properties can also be affected by the way it has been grown, the number of times it has been cultured anew and small genetic changes that wouldn't show up in a fingerprint test. One classic example, he notes, is an immortalized breast cell line called MCF10A, which can form organized hollow structures similar to those found in mammary tissue; MCF10A cells currently distributed by

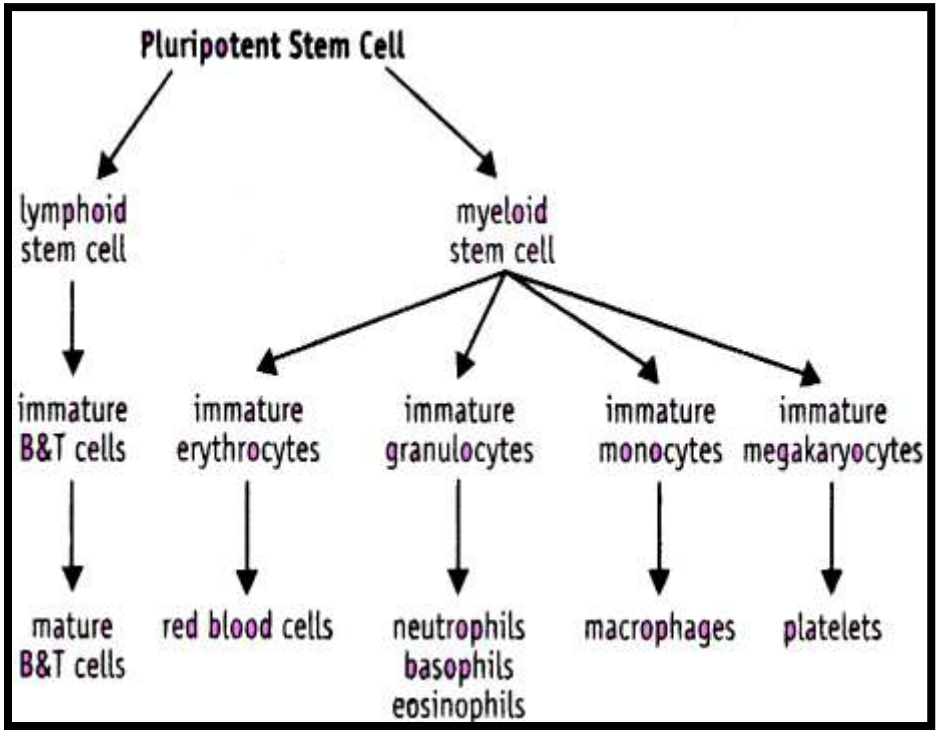
http://www.nature.com/news/2010/100602/pdf/465537a.pdf

Bone Marrow Transplant Engraftment Analysis

- Autologous Transplant
- Allogeneic Transplant
  - Cells used: bone marrow, hematopoietic stem cells (cord blood), peripheral blood
  - Relationship of donor and recipient
    - Matched sibling
    - Matched, unrelated individual
    - Partially matched, related
  - Conditioning of recipient prior to transplant
    - Myeloablative
    - Non-myeloablative

Slide courtesy of Prof. Greg Tsongalis, Dartmouth Hitchcock Medical Center

Examination of peripheral blood, both unfractionated and ficoll separated (PMN's and Mononuclear), and bone marrow DNA for assessment of engraftment



- **METHODS:** Peripheral blood lymphocytes were fractionated using a Ficoll/Hypaque gradient prior to analysis. Purity of the fractions was determined by flow cytometry. The mononuclear fraction was 98% pure and the PMN fraction was 95% pure.

SAMPLES:

1. 03/21/2008 - peripheral blood, unfractionated [08-0201]
2. 03/21/2008 - peripheral blood, mononuclear fraction [08-0202]
3. 03/21/2008 - peripheral blood, PMN fraction [08-0203]
4. 03/21/2008 - bone marrow, [08-0204]

} **Myeloid vs Lymphoid lineages**

Data courtesy of Prof. Greg Tsongalis, Dartmouth Hitchcock Medical Center

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Bone Marrow Transplant Engraftment Analysis
(using SNP markers with only 2 or 3 possible alleles)

	Female	Male Recipient			
Marker	**Donor**	**Buccal**	**1st**	**2nd**	**3rd**
LDLR	AA	AB	AB	AB	AA
GYPA	AB	BB	BB(A)	BB(A)	AB
HBGG	AB	AB	AB	AB	AB
D7S8	AB	AB	AB	AB	AB
GC	AC	AC	AC	AC	AC
Y1	Neg	Pos	ND	ND	Neg
N1	Neg	Pos	ND	ND	Neg

Donor and recipient have indistinguishable genotypes

Data courtesy of Prof. Greg Tsongalis, Dartmouth Hitchcock Medical Center

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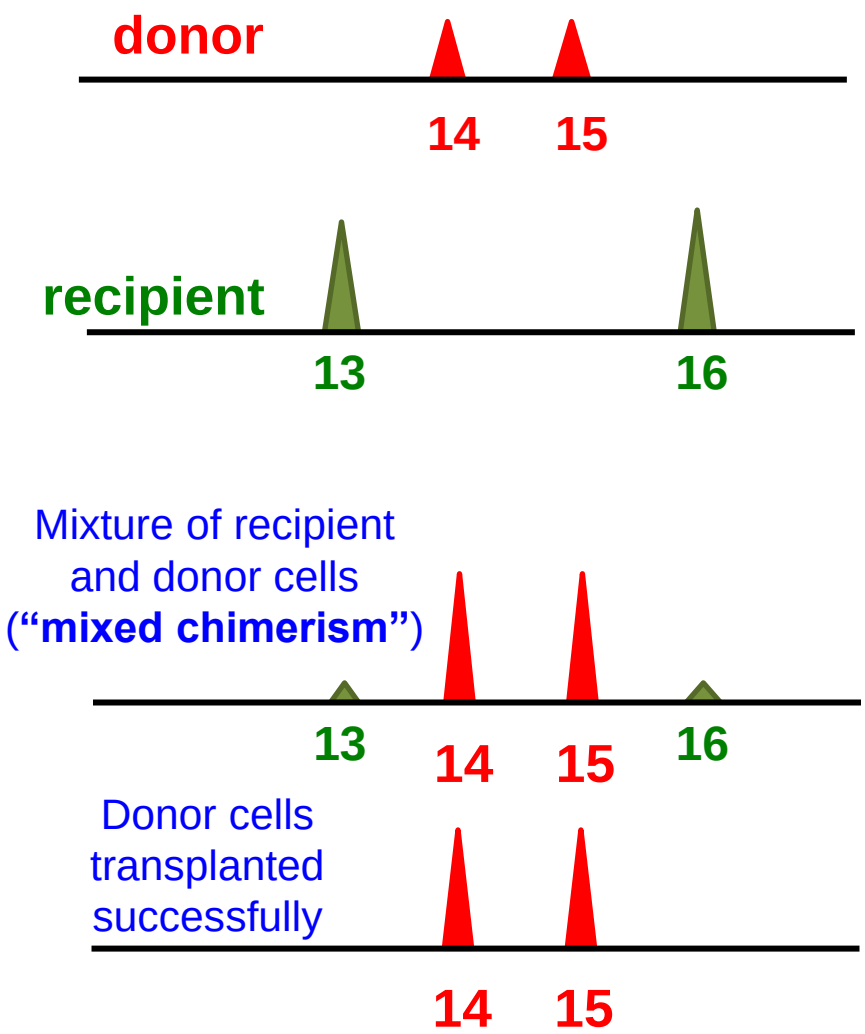
Bone Marrow Transplant Monitoring:
Easier with STRs that possess many alleles



- When there are different STR genotypes between donors and recipients at the tested loci, it is possible to evaluate the degree of donor transplantation
- STR analysis enables monitoring the persistence of recipient cells

Antin, J.H. et al. (2001) Establishment of complete and mixed donor chimerism after allogeneic lymphohematopoietic transplantation: recommendations from a workshop at the 2001 tandem meetings. *Biology of Blood and Marrow Transplantation* 7: 473-485

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Method for Assessment of Bone Marrow Engraftment by STRs

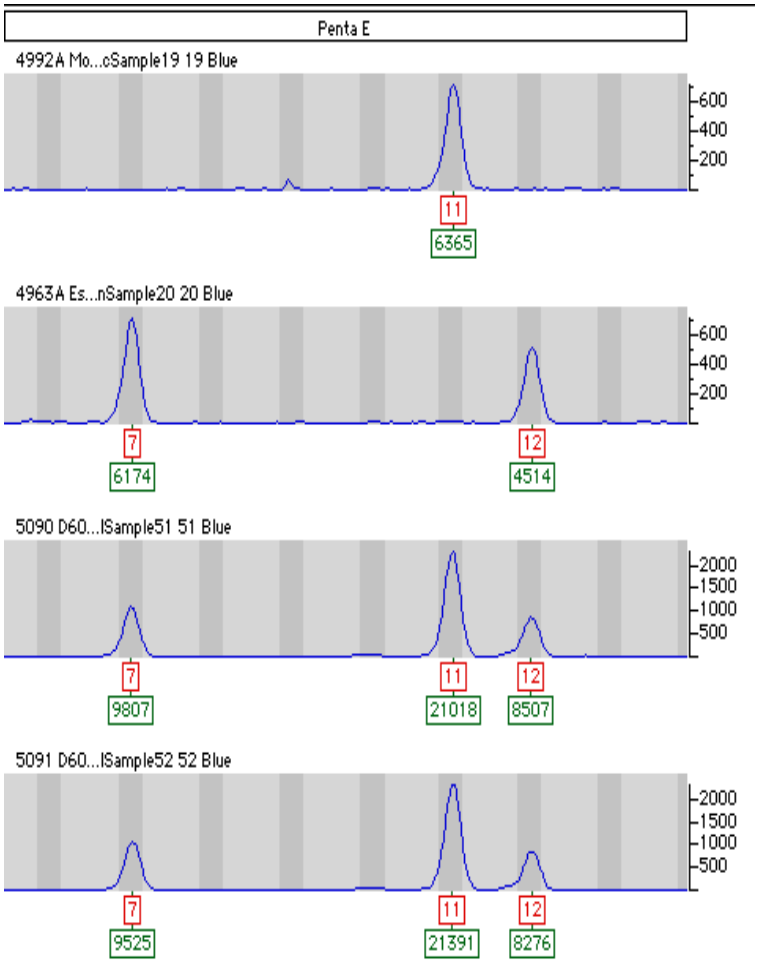
- PCR was performed with fluorescently labelled primer sets directed at the following microsatellite loci: D3S1358, TH01, D13S317, D8S1179, D7S820, TPOX, D16S539, D18S51, CSF1PO, Penta D and **Penta E**. The PCR products were separated by capillary electrophoresis and amplicons detected by laser excitation.

- **Engraftment was calculated using a ratio of the peak area for recipient specific products to the peak area of donor plus recipient products.** Control mixtures of recipient DNA in donor DNA were made to evaluate sensitivity.

Slide courtesy of Prof. Greg Tsongalis, Dartmouth Hitchcock Medical Center

Results from Penta E

(a single STR marker from multiple STRs examined)



Donor profile

Recipient profile

Profile indicates a mixture of recipient and donor cells . (**"mixed chimerism"**)

RESULTS: All samples analyzed are greater than 95% second donor engrafted *(complete data not shown)*

Data courtesy of Prof. Greg Tsongalis, Dartmouth Hitchcock Medical Center

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Possible Outcomes from Testing

INTERPRETATION: These results suggest a complete donor chimerism.

- **Full chimerism: 100% donor cells (DNA) detected; complete lymphohematopoietic replacement**
- **Mixed chimerism: donor and recipient DNA detected**
- **Split chimerism: one whole lineage is recipient and one is donor (myeloid vs T-cells)**
- **Microchimerism: <1% recipient DNA detected.**

Slide courtesy of Prof. Greg Tsongalis, Dartmouth Hitchcock Medical Center

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Current Trends in DNA Testing

- ***Faster** results:* Rapid DNA capabilities and new sample-to-answer integrated instruments
- ***Higher** sensitivity:* New assays lowering the limits of detection, which makes interpretation more challenging
- ***Higher** information content:* Next-generation sequencing (NGS) for more markers & STR allele information
- ***Stronger** conclusions:* Mixture interpretation with probabilistic genotyping models

Butler, J.M. (2015) The future of forensic DNA analysis. *Phil. Trans. R. Soc.* B 370: 20140252

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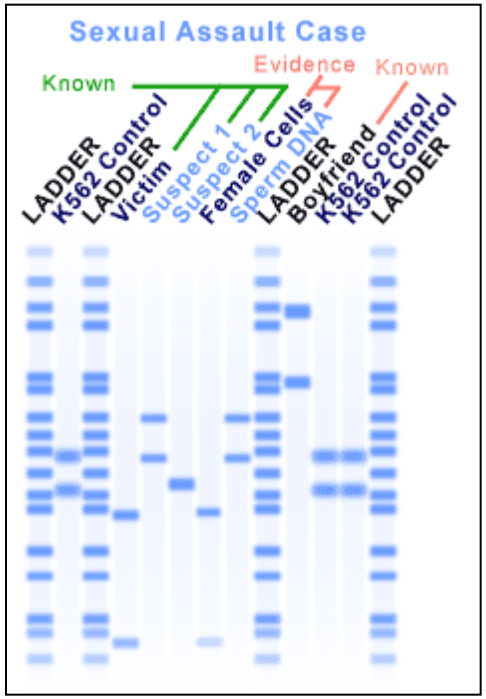
The DNA Field Moves Forward…

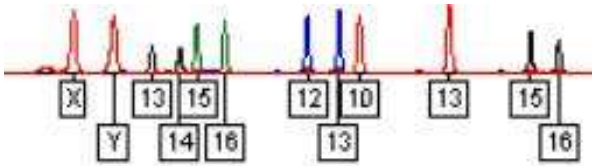
The Past



http://www.bioteach.ubc.ca/MolecularBiology/DNAfingerprint/

RFLP

The Present



STRs

The Future

http://www.manastungare.com/publications/genetic/dna.gif

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