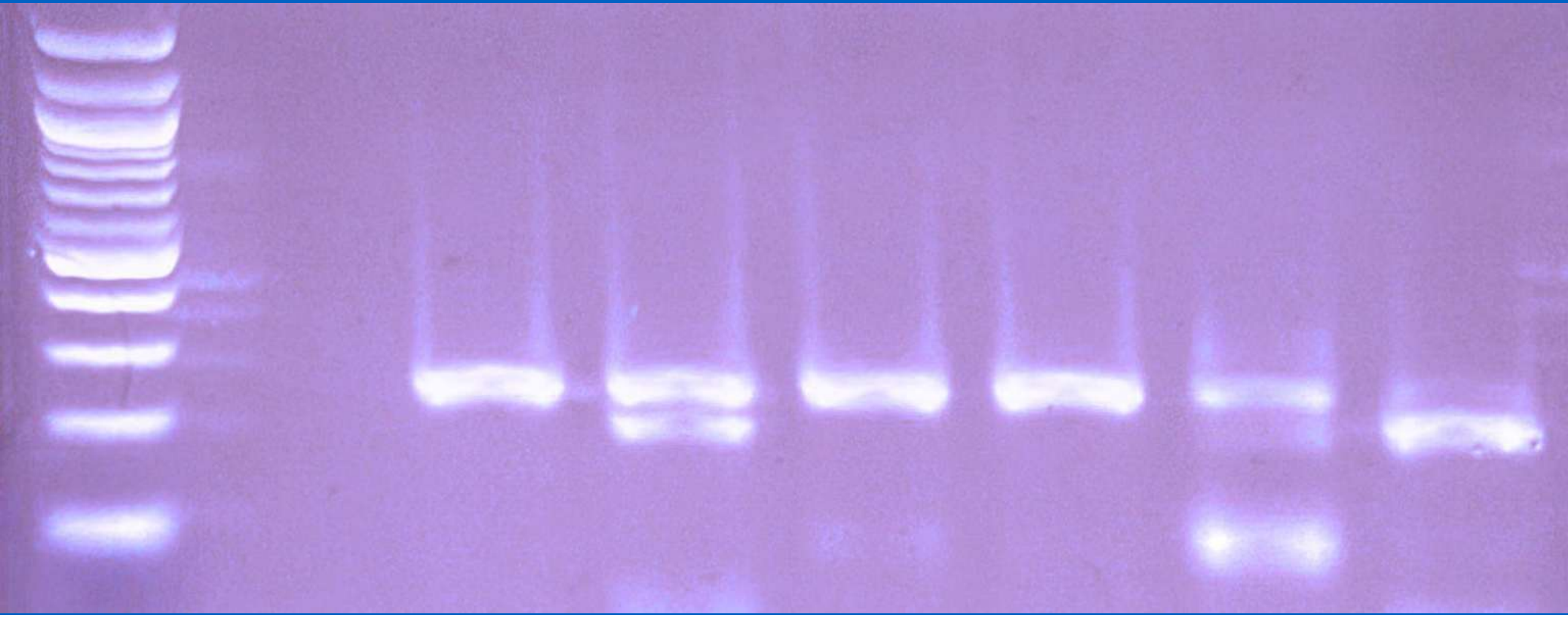
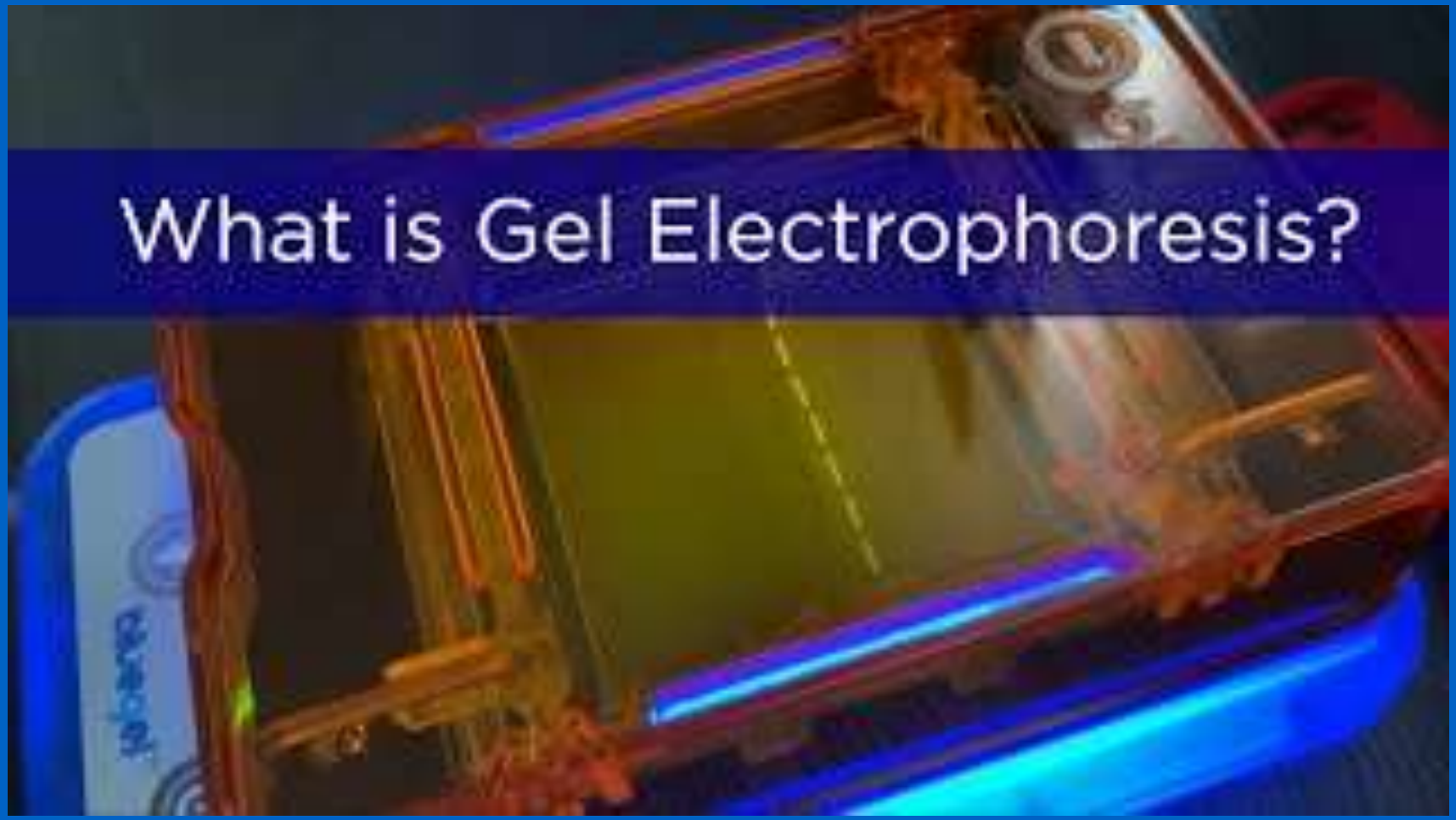
Exploring Precision Medicine

- Chapter 1: What's the Right Medicine?
- Chapter 2: Is My Sense of Taste Controlled by my Genes?
- Chapter 3: Exploring Our DNA
- Chapter 4: How Is DNA Sequenced, and What Can We Learn?
- Chapter 5: Restriction Enzyme Digestion of TAS2R38 PCR Products
- Chapter 6: Gel Electrophoresis and Genotyping
- Chapter 7: SNPs and Drug Metabolism

Chapter 6: Gel Electrophoresis and Genotyping



Video: *What Is Gel Electrophoresis?*



Exploring Precision Medicine: Activities

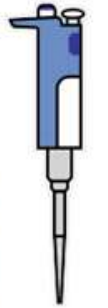
AMGEN Biotech Experience
Scientific Discovery for the Classroom

Sample Our Own DNA

Take a sample of cheek cells, isolate DNA, and amplify a short sequence of the bitter taste gene.

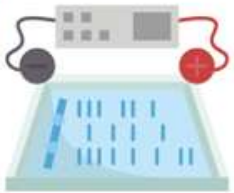
Sequence Analysis

Use bioinformatics software to explore the bitter taste gene and how genotypes can be distinguished.



Restriction Enzyme Digest

Use restriction enzyme digestion to prepare to determine our bitter taste genotypes.



Gel Electrophoresis

Use gel electrophoresis to determine our bitter taste genotypes.

Investigate Genetics of Drug Metabolism

Investigate the genetics of drug metabolism and consider how genotyping can aid medical treatment.

Medical Mystery

Explore the idea that people respond differently to medications and consider the possible reasons.

Is Taste Genetic?

Begin to explore a trait (taste) and investigate whether people experience it differently.

UNDERSTANDING PRECISION MEDICINE

In this module, we explore the genetics of the ability to taste bitter substances. It turns out that even small differences in our DNA—our genotype—can lead to major differences in traits—our phenotype. All of our genes have such individual differences, and some lead to changes in medically important traits. Advances in DNA sequencing and bioinformatics have made it much easier to discover these differences. Similarly, understanding how each of us metabolizes medications differently allows doctors to practice precision medicine—medicine based on each individual's genotype.

Load and run your gels following the lab directions

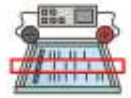
MATERIALS

For each student:

A pair of gloves

RM 6.2: Gel Electrophoresis of TAS2R38 Recording Sheet

1 lane of an agarose gel



Student restriction enzyme digest

For each team:

1 electrophoresis chamber and power supply

Gel running buffer

P-20 micropipette and tips

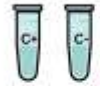
10 µL 100-bp ladder (M)

Waste container

Microfuge tube rack

For the class:

Control restriction enzyme digests, plus extra positive control digests as needed

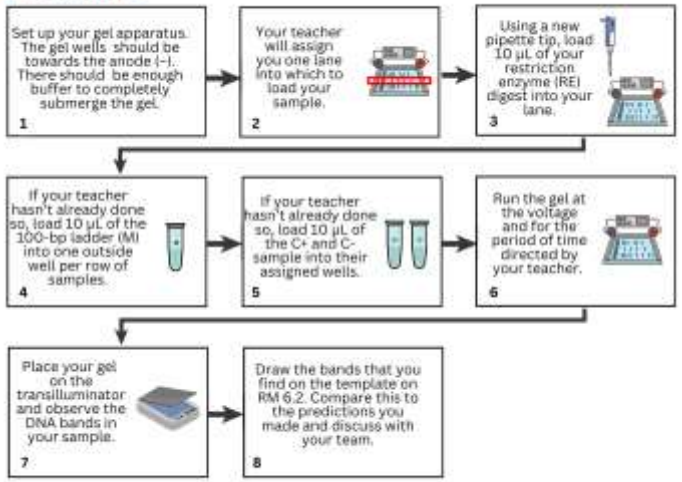


2 lanes of one agarose gel to run the controls

For every additional gel, 1 lane to run additional positive controls

Transilluminator

PROCEDURE



Reading: “Genes Give Africans a Better Sense of Taste”

NewScientist

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Life

Genes give Africans a better sense of taste

By Ewen Callaway

2 January 2009

(Image: Krzysztof Miller/Gazeta/Agence Vu)

Some put forward France's decadent sauces or Spain's creative tapas as evidence of Europeans' delicate taste for food, while Asian gourmands would sing the praises of sushi.

But they might all be wrong. New research suggests that Africans have more sensitive palates than Europeans and Asians – at least for bitter tastes.

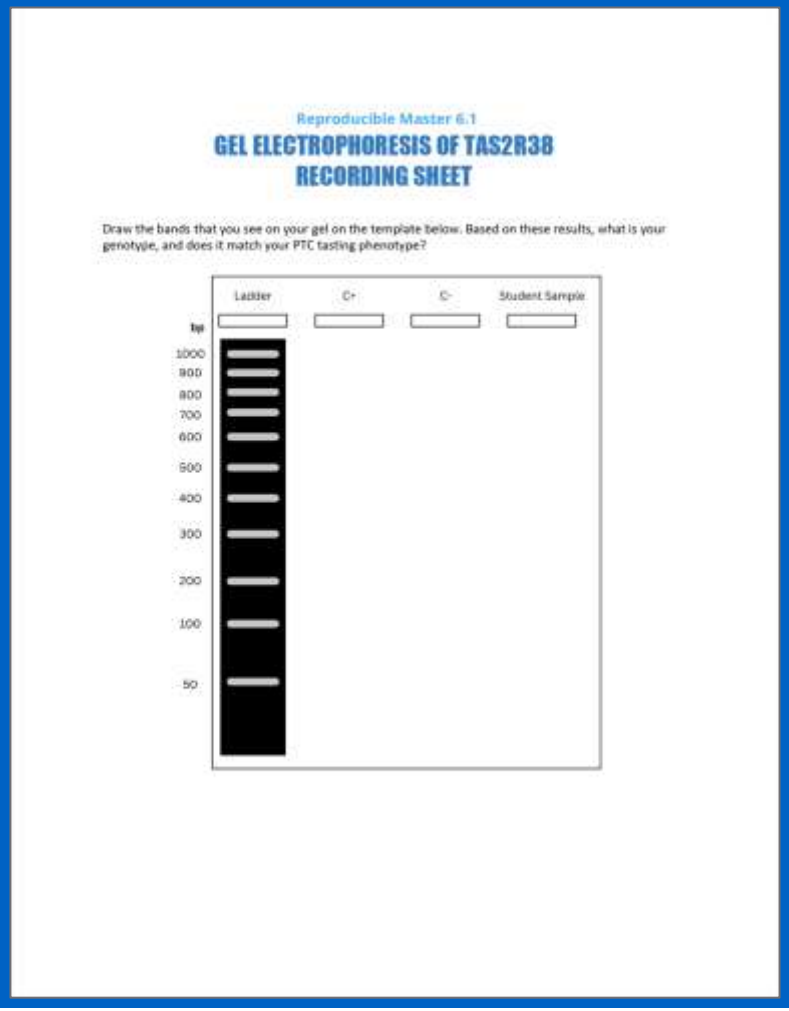
A survey of numerous African populations in Kenya and Cameroon found a striking amount of diversity in a gene responsible for sensing bitter tastes.

Answer the questions on **RM 6.1** for class discussion

Discussion: “Genes Give Africans a Better Sense of Taste”

- How were Kenyans’ and Cameroonians’ TAS2R38 genes different from those of Europeans and Asians?
  - They had additional genetic variants.
- One scientist speculated that iodine might play a role in natural selection of this gene. What did they suggest?
  - Maybe access to iodine protected the thyroid from toxic compounds in bitter foods?
- What is another reason that Africans have more genetic diversity than Europeans?
  - Human migration from Africa to Asia caused a genetic “bottleneck.”

Once you have your gel image, complete RM 6.2.



Reproducible Master 6.1

GEL ELECTROPHORESIS OF TAS2R38
RECORDING SHEET

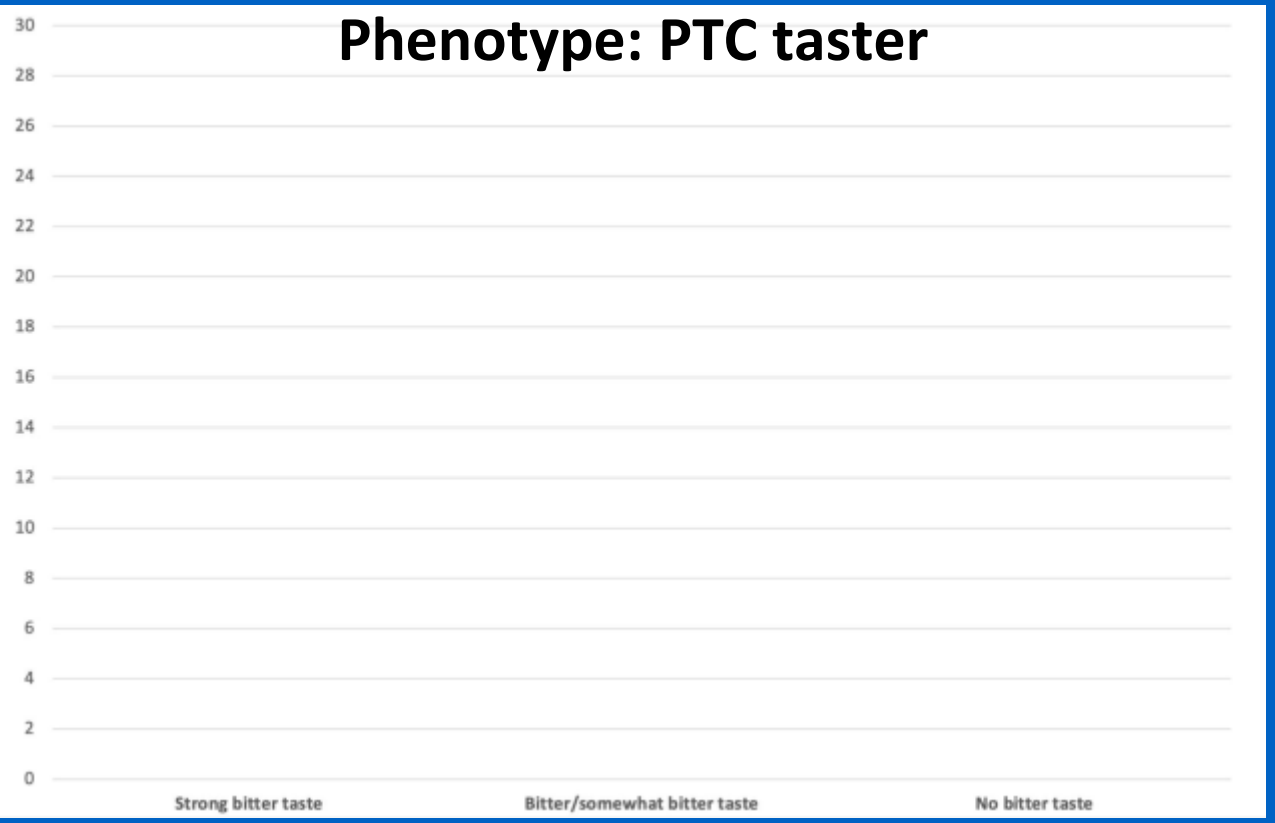
Draw the bands that you see on your gel on the template below. Based on these results, what is your genotype, and does it match your PTC tasting phenotype?

Discussion: Your Taster Genotype

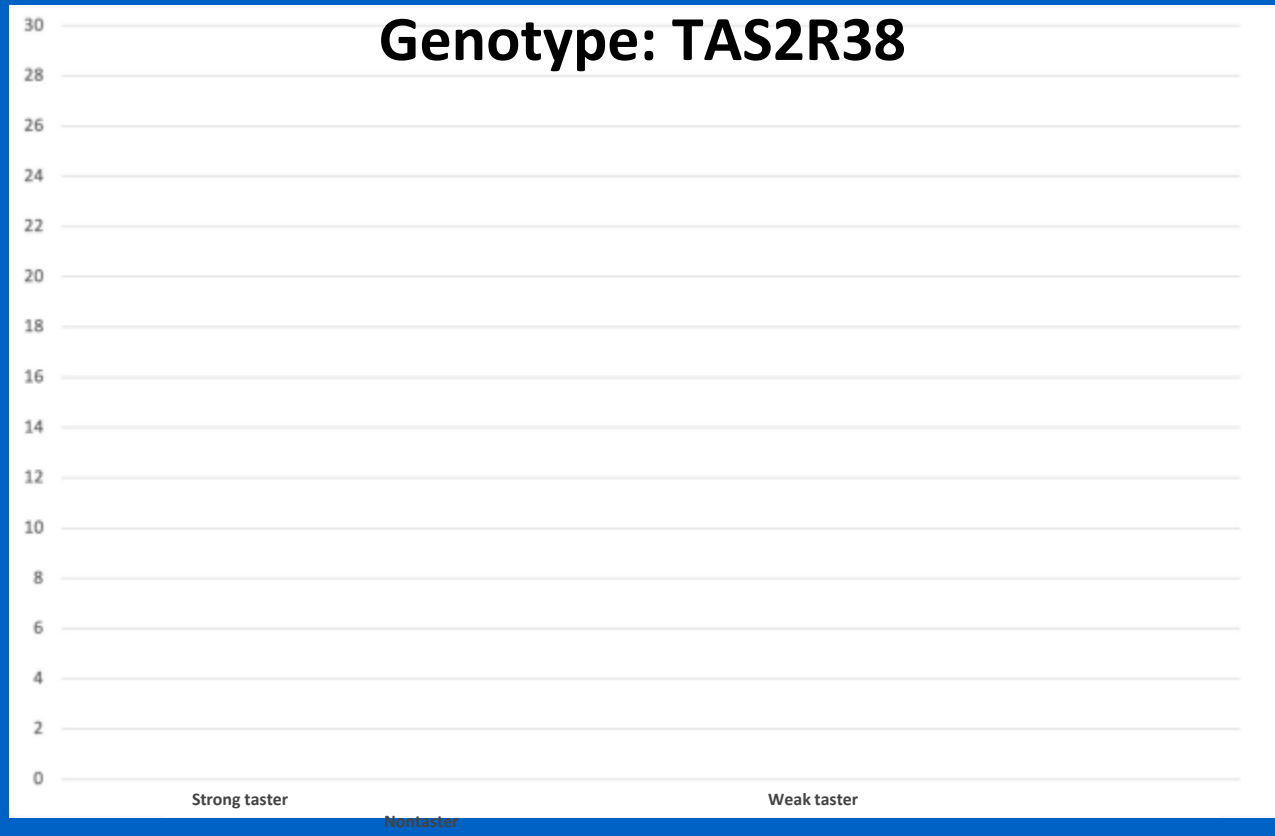
- Did your genotype and phenotype match?
- If not, where could experimental error have occurred?

Did your phenotype and genotype match?

Phenotype: PTC taster



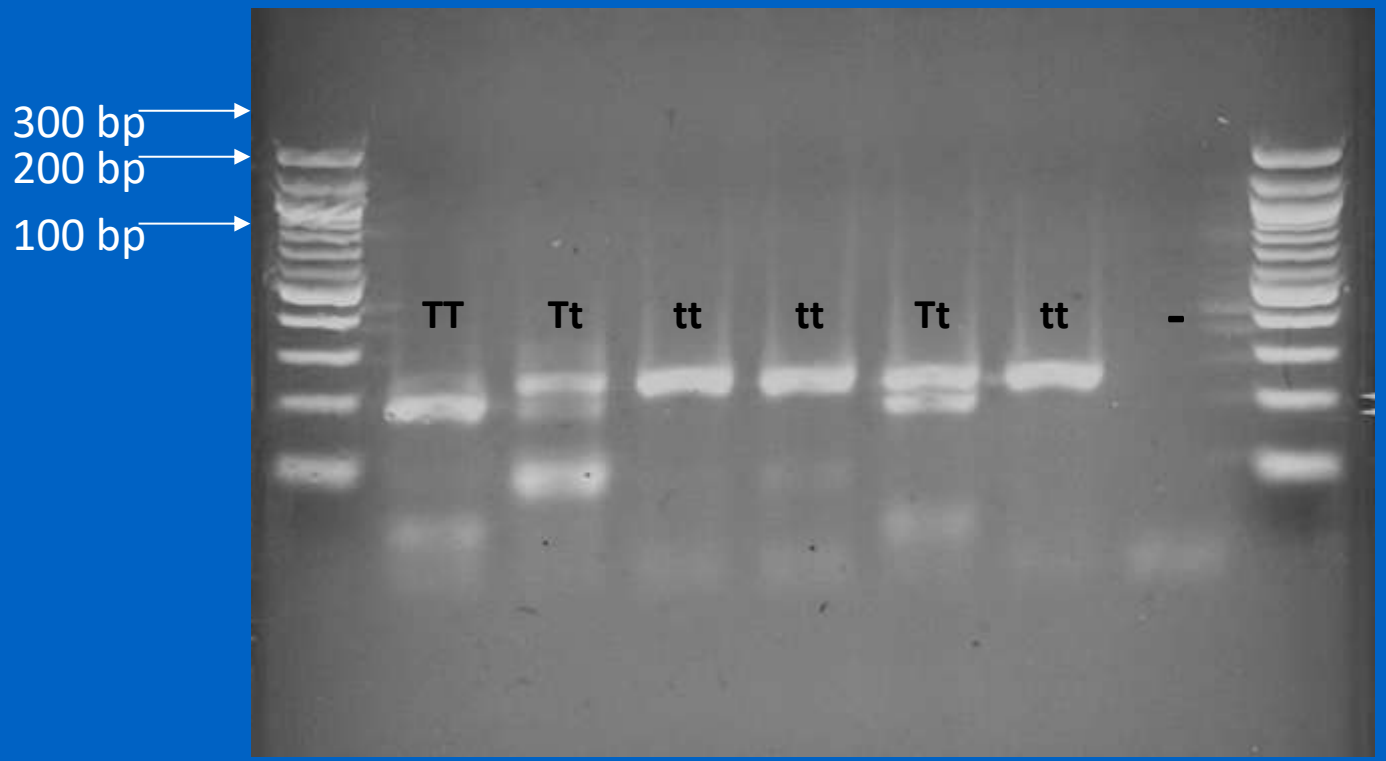
Genotype: TAS2R38



Based on your gel, what do you think the C+ genotype is?

- Heterozygous (weak taster)

An example of various taster genotypes



Homozygous nontaster:
1 band (240 bp)

Heterozygous weak taster: *3 bands (44 bp, 196 bp, 240 bp)*

Homozygous strong taster: *2 bands (44 bp, 196 bp)*

Were your phenotype and genotype *perfect* matches?

- How did your rate broccoli bitterness?
- Did that match your PTC taste test?
  - Did *that* match your TAS2R38 genotype?
- Did you find PTC bitter, but not broccoli? Why?

Extend Your Findings to Precision Medicine

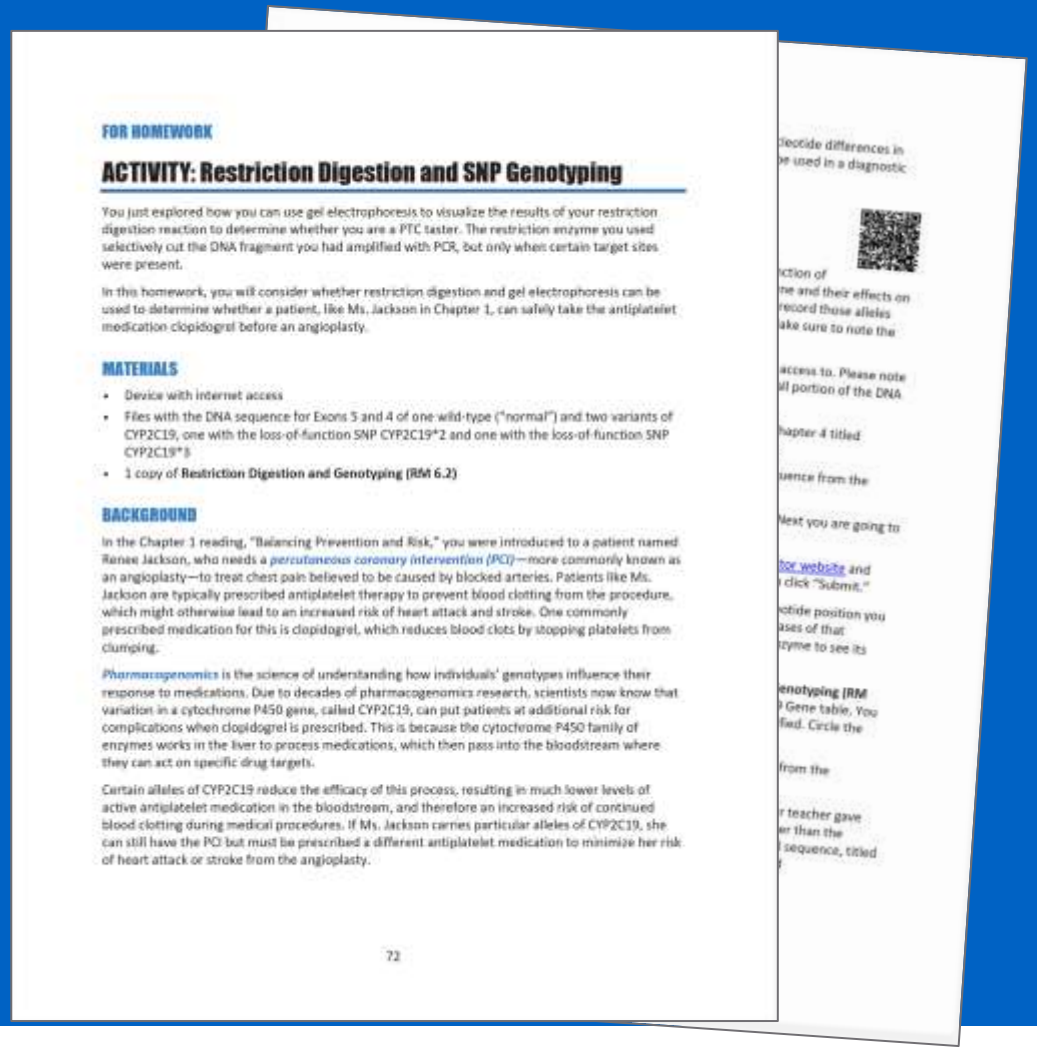
- PTC taste testing is not really medically relevant . . .
- . . . but can you name some other genetic tests which *are* important to patient health?

Hypothesize: What use are bitter-taste receptors?

- Why do you think genes encoding receptors like TAS2R38 would have persisted through human evolution?

bitter melon

Carry out the activity “Restriction Digestion and SNP Genotyping”



FOR HOMEWORK

ACTIVITY: Restriction Digestion and SNP Genotyping

You just explored how you can use gel electrophoresis to visualize the results of your restriction digestion reaction to determine whether you are a PTC taster. The restriction enzyme you used selectively cut the DNA fragment you had amplified with PCR, but only when certain target sites were present.

In this homework, you will consider whether restriction digestion and gel electrophoresis can be used to determine whether a patient, like Ms. Jackson in Chapter 1, can safely take the antiplatelet medication clopidogrel before an angioplasty.

MATERIALS

- Device with internet access
- Files with the DNA sequence for Exons 5 and 4 of one wild-type (“normal”) and two variants of CYP2C19, one with the loss-of-function SNP CYP2C19*2 and one with the loss-of-function SNP CYP2C19*3
- 1 copy of **Restriction Digestion and Genotyping (RM 6.2)**

BACKGROUND

In the Chapter 1 reading, “Balancing Prevention and Risk,” you were introduced to a patient named Renee Jackson, who needs a *percutaneous coronary intervention (PCI)*—more commonly known as an angioplasty—to treat chest pain believed to be caused by blocked arteries. Patients like Ms. Jackson are typically prescribed antiplatelet therapy to prevent blood clotting from the procedure, which might otherwise lead to an increased risk of heart attack and stroke. One commonly prescribed medication for this is clopidogrel, which reduces blood clots by stopping platelets from clumping.

Pharmacogenomics is the science of understanding how individuals’ genotypes influence their response to medications. Due to decades of pharmacogenomics research, scientists now know that variation in a cytochrome P450 gene, called CYP2C19, can put patients at additional risk for complications when clopidogrel is prescribed. This is because the cytochrome P450 family of enzymes works in the liver to process medications, which then pass into the bloodstream where they can act on specific drug targets.

Certain alleles of CYP2C19 reduce the efficacy of this process, resulting in much lower levels of active antiplatelet medication in the bloodstream, and therefore an increased risk of continued blood clotting during medical procedures. If Ms. Jackson carries particular alleles of CYP2C19, she can still have the PCI but must be prescribed a different antiplatelet medication to minimize her risk of heart attack or stroke from the angioplasty.

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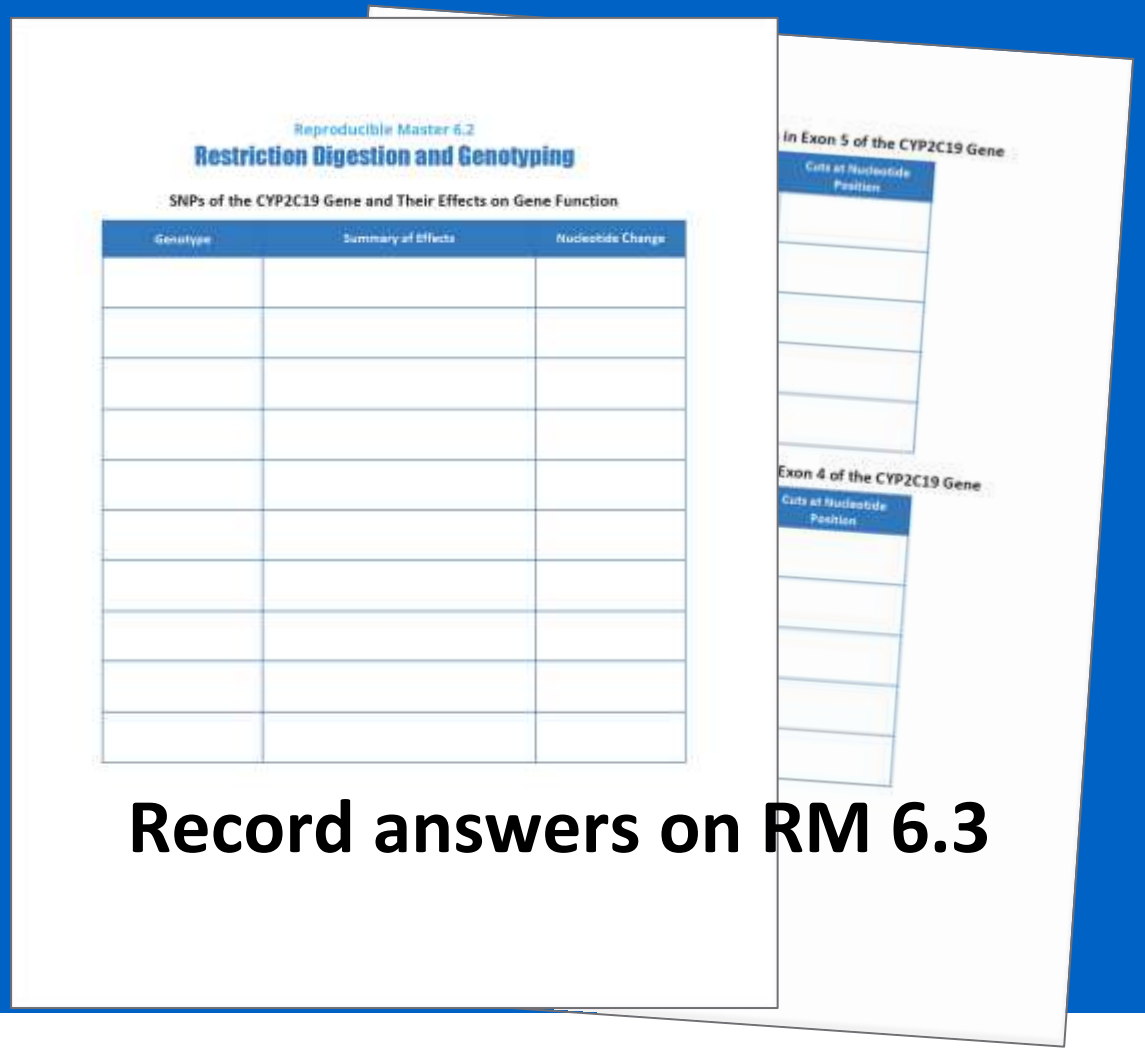

Reproducible Master 6.2

Restriction Digestion and Genotyping

SNPs of the CYP2C19 Gene and Their Effects on Gene Function

Genotype	Summary of Effects	Nucleotide Change

in Exon 5 of the CYP2C19 Gene

Cuts at Nucleotide Position

Exon 4 of the CYP2C19 Gene

Cuts at Nucleotide Position

Record answers on RM 6.3

An Example of Various Taster Genotypes