

CHM 109 Introduction

I. PKU illustrates the relevance of chemistry to human health

Why is chemistry important in human health?

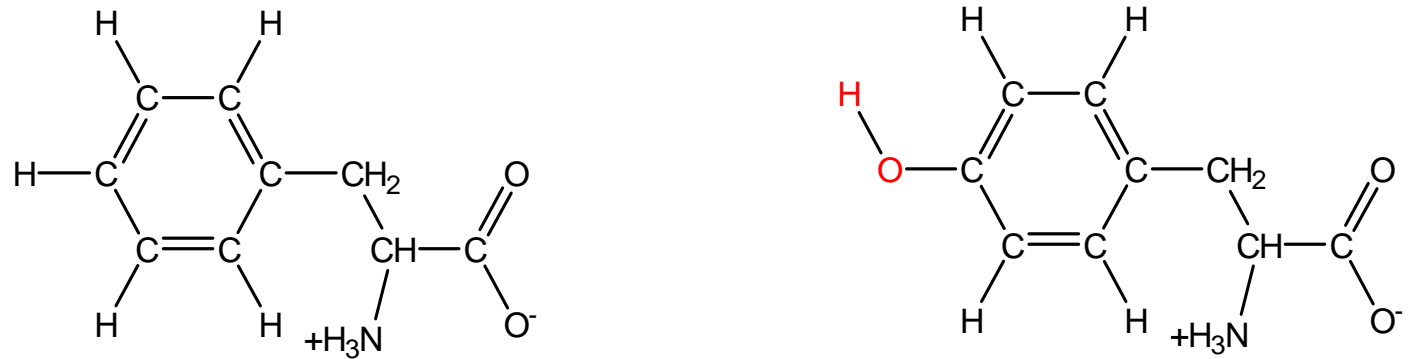
Ex.: PKU (phenylketonuria) ref. Matalon, KM *Top Clin Nutr* 16(4):41-50 (2001)

A. We are constantly being tested (from birth).

- 1) Why? Test newborns to check for congenital health problems.
- 2) What does congenital **mean**? _____

B. What is PKU? A genetic disease caused by insufficient *phenylalanine hydroxylase* (PAH) activity.

1) PAH rxn.: phenylalanine + oxidant $\xrightarrow{\text{PAH}}$ tyrosine



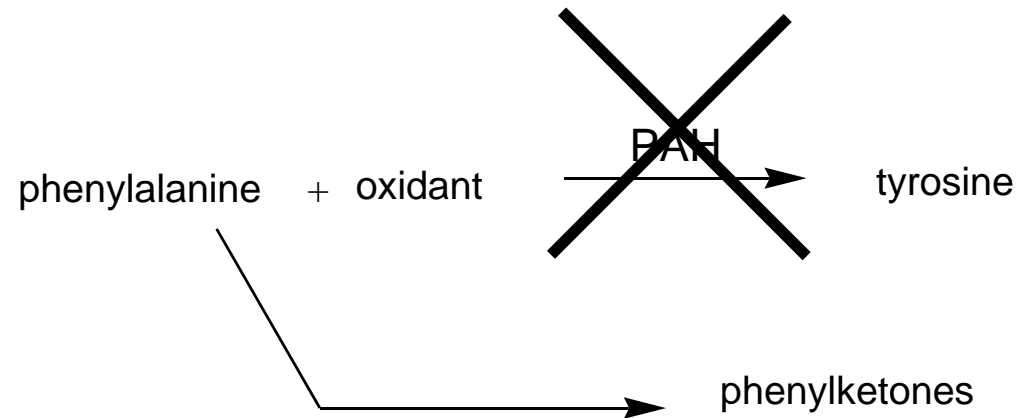
2) PAH is an enzyme. (means? _____)

3) The PAH of PKU patients is absent or doesn't work as well as normal PAH because its structure is different from normal, wild type (means? _____), PAH.

This is 1 of $\sim 10^4$ jobs you must do to stay alive, healthy.

C. Why does lack of PAH activity cause problems in PKU ?

- 1) Phenylalanine (Phe) levels increase. Some of this Phe is converted to phenylketones (excreted in urine).



- 2) Part of the PKU pathology (**means?** _____) appears to be caused by elevated Phe. How Phe does this is not completely clear, (ex. :see Shefer, *et al.*, *J Neurosci Res.* 61(5):549-63., 2000).
- 3) Tyrosine (Tyr) is not formed via the PAH pathway in PKU patients, so Tyr is an *essential amino acid* for them (dietary supplements needed!).

D. Back to “Why test newborns?” **PKU can be treated!**

See: Irene, spouse, sister, (& Stephanie) (Pheno, Genotypes?)

<http://www.pahdb.mcgill.ca/?Topic=Information&Section=Clinical&Page=1>



Put on your detective/diagnostician hat. What can you tell me about these 3 people?

Note: The pictures below and on the previous page are from *The Montreal Children's Hospital Hyperphenylalaninemia (PKU) Resource Booklet for Families*, by Peter M. Nowacki at The Biochemical Genetics Unit; updated by Annie Capua, Margaret Lilly, David Cé, Manyphong Phommarinh and Shannon Ryan. Used with permission, Dr. C. Scriver.

1. Set diet with low levels of Phe
2. Supplement w/ Tyr, which leads to healthy Irene & eventually to healthy 2 yr old Stephanie, →

E. What happens to PKU patients that are not treated or are not compliant with their treatment? *i.e.*, What is the pathology? See Irene's sister, above.

1. Mental retardation
2. Microencephaly (means? _____)
3. Congenital heart disease



F. Genetics *“Loss of function” genetic diseases & diploidy.*

0. A linear sequence of bases in your DNA that codes for a specific function is called a *gene*.

1. Genotype vs. phenotype (Look up if unfamiliar.)
genotype _____
phenotype _____

2. Why doesn't genotype = phenotype? Ploidy!!!
 - a) Are you haploid or diploid?
 - b) Better:
 - i) Which of your cells are haploid? _____
 - ii) Which of your cells are diploid? _____
 - c) Now, are you haploid or diploid? This likely needs a longer answer.

3. What can you say re. genes of a PKU patient?

Nice web site (from McGill Univ.) with lots of information about specific PKU mutations: <http://www.pahdb.mcgill.ca/>

also see: <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd>

4. What can you say re. genes of parents of a PKU patient?

G. Like many medical/biological problems, the problem often gets complicated because *the PAH gene is complex*. It can “go wrong,” in many ways. (See figs & mutation map on following pages.) Remember **major theme for this course:**

DNA → RNA → Protein

H. Human haploid genome, chromosome 12, PAH gene.

http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?taxid=9606

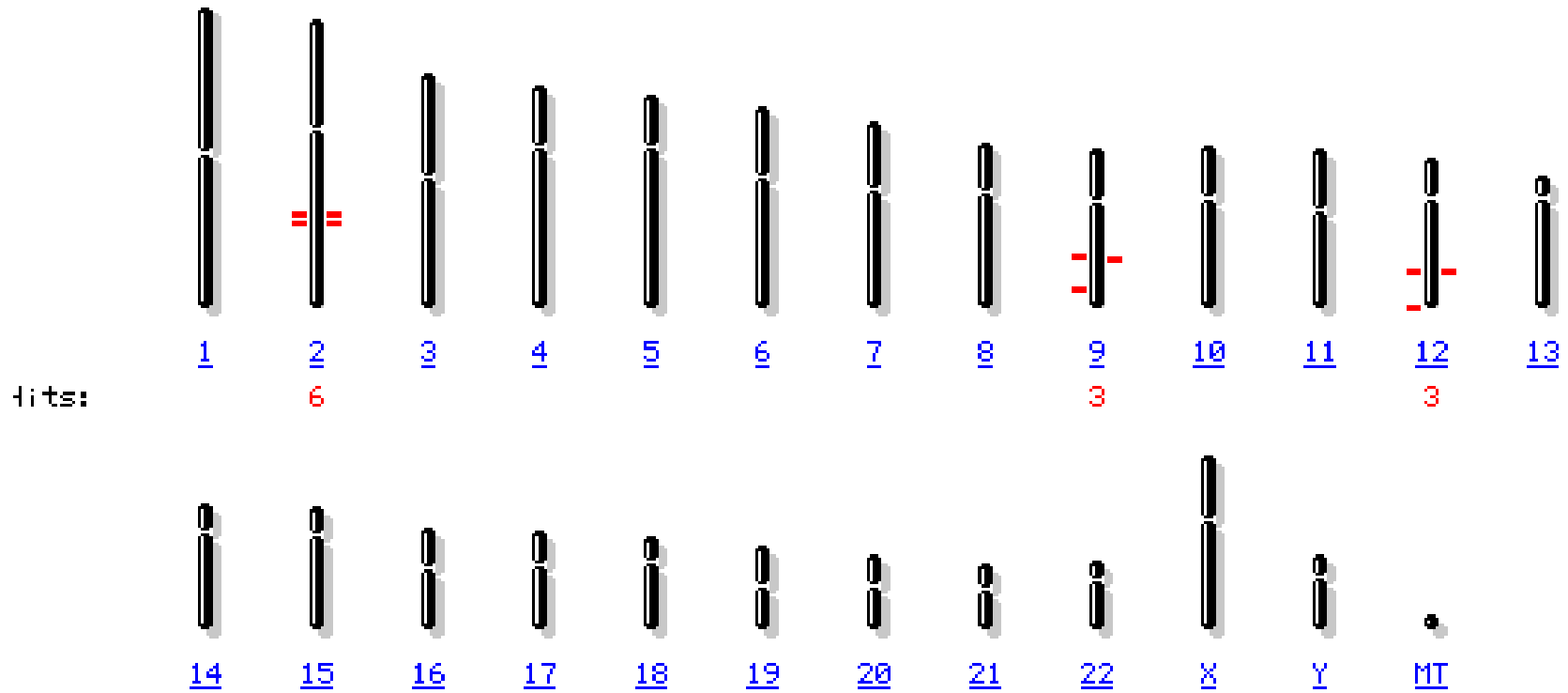
1. The Human Genome Project

The screenshot displays the NCBI Map Viewer interface. At the top left is the NCBI logo. To its right is a compass icon and the text "NCBI Map Viewer". Below this is a navigation bar with tabs for "PubMed", "Nucleotide", "Protein", "Genome", "Gene", and "Structure". The "Genome" tab is selected. A search bar contains the text "pku" and "on chromosome(s)", followed by an "assembly" dropdown menu set to "All" and a "Find" button. On the left side, there is a vertical menu with links for "Map Viewer", "Map Viewer Home", "Map Viewer Help", "Human Maps Help", "Release Notes", "NCBI Resources", "Genome Project", "TaxPlot", "Consensus Coding Sequence (CCDS)", "Human Genome Resources", "NCBI Handbook", "RefSeq", and "Trace Archive". The main content area shows the "Homo sapiens (human) genome view" for "Build 36.3", with links for "statistics" and "Switch to previous build". Below this is a karyotype of human chromosomes, with chromosome 12 highlighted in blue. The chromosomes are arranged in two rows: the first row contains chromosomes 1 through 13, and the second row contains chromosomes 14 through 22, X, Y, and MT. At the bottom, a blue box contains the text: "Lineage: [Eukaryota](#); [Metazoa](#); [Chordata](#); [Craniata](#); [Vertebrata](#); [Euteleostomi](#); [Mammalia](#); [Eutheria](#); [Homo sapiens](#)".

2. Now search “PKU”

Homo sapiens (human) genome view

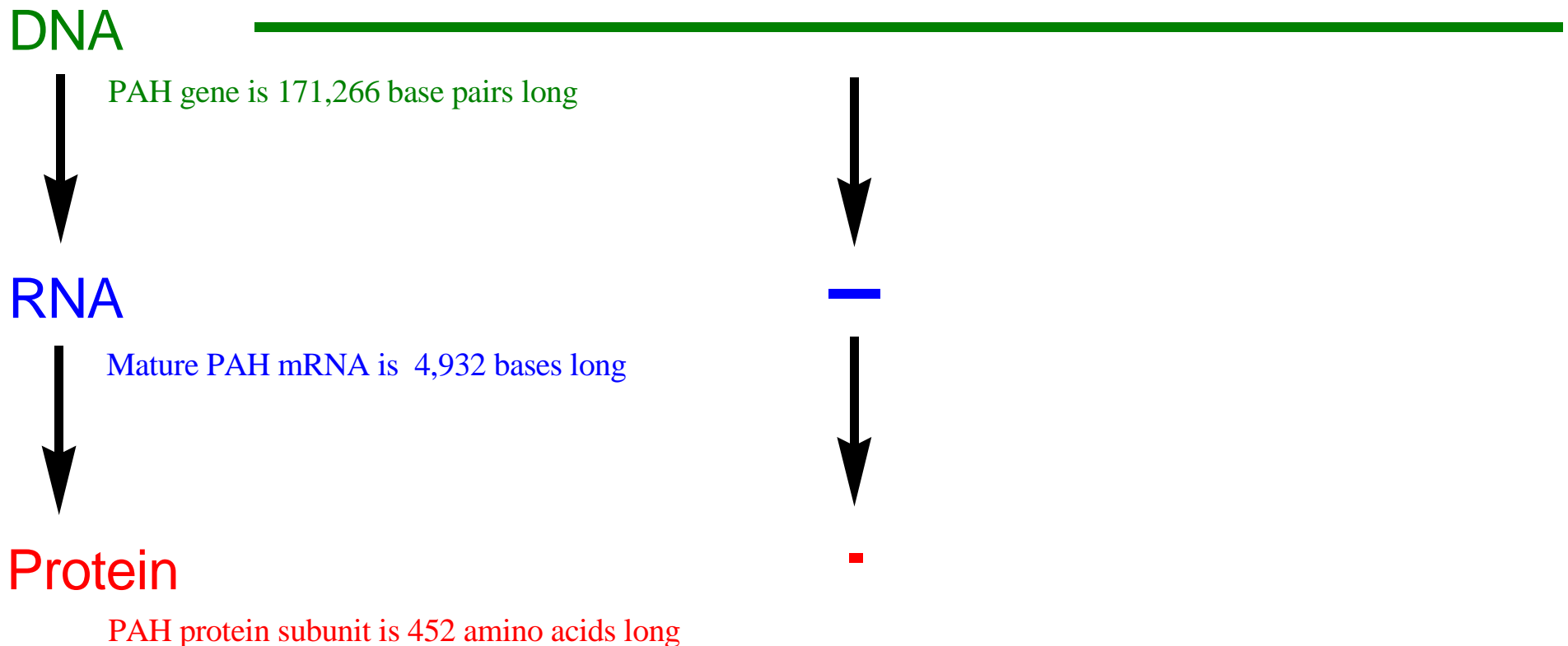
Build 36.3 statistics [Switch to previous build](#)



It looks like there are different ways (mechanisms) to get PKU (**important re. treatment strategies!**). The gene that codes for PAH is on **chromosome #12**.

3. Gene: a linear sequence of bases in DNA that codes (information) for a specific function (job). Fig. below based on: Dr. C. Scriver, *Human Mutation* 28(9): 831-45 (2007).

PAH gene expression



4,932 is ~ 2.9% of 171,266! Why have the extra 97%?

4. The thin vertical lines in the mutation map (see link) (<http://www.pahdb.mcgill.ca/?Topic=Information&Section=MutationMap&Page=0>) are put together to form the mature mRNA (**short for?** _____). The open blocks labeled 1-12 are spliced out (& degraded?).
5. View the PAH gene like a paper you have written that has 171, 266 letters. (Spelling errors possible?). Spelling error \approx a mutation (DNA sequence change).
 - a) Clearly a spelling error could result in less effective communication. (like a harmful mutation)
 - b) Can you imagine a spelling error resulting in more effective communication. (a helpful mutation?)
6. 528 different mutations (as of 1-08-07)! *PAHdb website*, Dr. C. Scriver

II. Administrative items

A. Syllabus (posted on web <http://faculty.uscupstate.edu/rkrueger/>) /course structure

0. Introductions

1. Lecture (75% of grade) & lab/recitation (25%)

2. Attendance

3. Grading (what to do to succeed in CHM 109)

4. Civility

B. Pace

1. Outside reading usually *before* lecture

2. Exams

3. Math issues (See web page!)

4. Calculators for exams

C. Re. CHM 109, Fall 2008

1. Attendance
2. Deal w/ problems we have identified... *before* exams.
3. Your expectations *vs.* your ability & effort.

*If you have problems, are uncertain, etc.,
please see me!!!! Efficiently!*