

## **Phenylketonuria: A hallmark disease for society**

### **Introduction**

“If only I had known”: Never is this phrase truer than in the case of phenylketonuria (PKU). Consider the case of two siblings. Both of them suffer from this genetic condition. The older one, an eleven-year old boy, was not diagnosed or treated and is severely affected with mental retardation. On the other hand, his younger sister was treated from early infancy with a low phenylalanine diet; both her physical and mental status developed normally<sup>1</sup> (See Appendix I). The damaging effects of this autosomal recessive trait are completely preventable. It was the first genetic disorder affecting the central nervous system that could be fully treated by changing the environment (i.e., diet)<sup>2</sup>, the first identifiable metabolic cause of mental retardation, and the first disorder to be successfully diagnosed by neonatal screening<sup>3</sup>. However, the more striking characteristic of this disease is that it constitutes a blatant example of the interaction between culture and biology. PKU demonstrates the co-evolution of culture driving biological factors, and biology forming cultural paradigms.

### **Overview of Phenylketonuria**

PKU was originally found by Dr. Asbjorn Folling in 1934<sup>4</sup>, and (if untreated) is characterized by mental retardation, microcephaly, tremors, and hyperactivity<sup>5</sup>. An inherited disorder, it occurs in approximately 1 in every 15,000 babies born in the US<sup>6</sup>. PKU appears to be distributed in an uneven manner amongst races and geographic regions, occurring most often in Europe and Asia. In the United States, PKU afflicts mainly the Caucasian population.

At birth, individuals with the genetic defect appear to develop normally for several months<sup>7</sup>, at which point they begin progressive developmental delay. It is most commonly diagnosed in newborns through newborn screening programs<sup>8</sup>.

PKU consists of a defect in the enzyme phenylalanine dehydroxylase (PAH), resulting in an impaired ability to metabolize phenylalanine<sup>9</sup>. As a result, phenylalanine accumulates in their body, and they cannot convert dietary phenylalanine to tyrosine. It leads to another clinical symptom, lighter hair and lighter coloring, because melanin is made from tyrosine, which patients cannot synthesize but must obtain from their diet<sup>10</sup>. PAH is located on chromosome 12, and has the identification 12q22–q24<sup>11</sup>, indicating that it spans the 22-24 region on the long arm of chromosome 12. It is relatively large, and spans more than 90 kb<sup>12</sup>. Up to 70 different mutations are thought to be discovered, yet four of these are found to be the most common in the Northern European population<sup>13</sup> (See Appendix II). The most common mutation in this population is the nonsense mutation, found at exon 12, which will result in a protein 52 amino acids shorter than normal<sup>14</sup>.

The wild type role of the genetic element of PKU is the function of the enzyme PAH. It functions in the processing of phenylalanine and converts it to tyrosine. Without it, phenylalanine will accumulate in the body system, and constitute the source of phenylketonuria's symptoms.

### **Module I: Heterozygote Advantage and Prevalence in Society**

Genes and culture appear to have a reciprocal relationship, in which both act as a selecting environment for the other. An example of this lies in the heterozygote advantage of PKU, and its elevated frequencies of occurrence in Europe. Woolf et al<sup>15</sup> conclude that mothers of children with PKU have a significantly low miscarriage rate, and thus PKU perpetuates itself,

causing disease. Furthermore, Saugstad<sup>16</sup> declares that couples heterogeous for PKU have both a higher fertility and viability, granting them a biological fitness. Also, the increased levels of phenylalanine in heterozygotes “must have been advantageous under different climatic conditions and against the background of different diets and social circumstances”<sup>17</sup>. Working on this thread, an analysis of the cultural and biological interactive relationships in society can be formulated.

Culture affects biology through the discovery of the mechanisms underlying PKU. Through this understanding, a specialized diet was formed to treat the disease. This same diet comes to affect the biology of populations with PKU, because it excludes meats, fish, milk, cheese, bread, cake, nuts, and many other common food items<sup>18</sup>. This causes increased emotional stress, and biological side effects such as reduced blood levels of certain nutrients<sup>19</sup>. For example, Mosely et al. readdressed the issue of essential fatty acid levels in patients, finding statistically significant reductions of these in plasma levels<sup>20</sup>. Moreover, many of the patients afflicted with PKU stop this diet as soon as they finish puberty, when their nervous system finishes developing, leaving the metabolic effects in place<sup>21</sup>. If a woman gets pregnant with high levels of phenylalanine in her blood, there is a 75-90% chance of the child being born with mental defects<sup>22</sup>. Effective treatment has only been available for one generation; therefore, it is too recent to have a large impact on the frequency of the alleles<sup>23</sup>.

Biology’s influence on culture is represented by current studies being done in the biotechnology area. “As products move down the continuum from pharmaceutical...to healthful foods, scientists are working to determine the mechanisms behind the effective folk medicine”<sup>24</sup>: In an article delineating the current trends in scientific research, the authors cite the prevalence of PKU and the research of this disease as changing a trend in science to adapt to the cultural trend of more popular health food trends. For example, the discovery of the protein

Glycomacropeptide from whey (discovered for PKU treatment) represents the greater connotations of the protein-based philosophy of some special diets that are becoming cultural staples<sup>25</sup>. Also, a social solution had to be found for the biological problem of phenylketonuria. For example, PKU as a major cause of mental retardation in the 1950s and 1960s has all but disappeared in the US, because of large-scale screening efforts initiated by a Congress ruling in 1966<sup>26</sup>.

As time passes, population genetics will be an important tool in assessing the effect of the heterozygote advantage on the culture of different countries, as well as the manner in which scientific discoveries will determine the genetic fate of a patient (See Module II).

## **Module II: Genetics and Gene Therapy**

“PKU demonstrates that the conceptualization of life as transmission of information has helped reframe the concept of disease as qualitative “errors” in genetic instruction, rather than quantitative dysfunctions. As a result, the PKU model has been spectacularly successful in guiding treatment of this inherited metabolic error through a diet begun at birth”<sup>27</sup>.

In recent years, there has been a paradigm shift in society. Diseases are thought to be caused not only by the works of unknown forces, environmental factors, or the mere broad concept of inheritance – popular knowledge has it that many of the diseases can be found in exact loci on the human chromosomes. This has simplified and reduced the perception of genetic knowledge and of humans.

However, although the rationale for the knowledge of genetic research is health and delivery, empirical evidence demonstrates that biotechnology companies will develop gene tests and interventions with respect to drug therapies where there is a market<sup>28</sup>. With the dietary cure for the symptoms of phenylketonuria, there will be an increase in the frequency of the alleles. It is of interest to note the US is by far the largest market for pharmaceutical products, as well as the country with the highest growth<sup>29</sup>, and one of the few to screen and treat PKU effectively.

Therefore, the future of commercial biotechnology will be directed by biology to directly affect the health and culture of its patients through the analysis of the populations affected with different diseases, one of the ones with growing prevalence being phenylketonuria.

An autosomal recessive trait such as phenylketonuria is an oversimplification. Scriver and Waters (1999) go to the extent to declare that “even the category of monogenic traits is an artificial division”<sup>30</sup>. Biology has driven culture to embrace this genetic revolution, in both a wary and enthusiastic manner. It will also cause the rational reaction to biology: the use of gene therapy to overcome the mutations that cause phenylketonuria. However, at this moment, none of the efforts have been successful in addressing the biochemical genetic basis<sup>31</sup>. Somatic gene therapy remains in the distant future. Fang et al. infused a recombinant adenoviral vector containing human PAH cDNA into the PAH mouse model, which reduced the blood phenylalanine to normal. However, the effect was transient, and due to a strong immune response against the adenoviral vector, it remains unduplicable<sup>32</sup>. At this moment, this venue is being explored further, in an attempt to further the individualized care to the patient.

Even the process of neo-natal screening, driven by the symptoms’ degree of affliction (mental retardation) and the possibility for easily avoidance of these (new diet), brings with it new cultural connotations. Biology has driven culture not only in compliance with the diet, but also in the more controversial issue of genetic privacy in the general population. At this moment, “much of the screening is mandatory or routine, parents typically have to opt out of the screening rather than having to give informed consent for the screening to be accomplished”<sup>33</sup>. The Congress’ 1966 approval of the genetic screening was due to biological factors such as the increasing prevalence of PKU and the clear treatment to avoid its symptoms<sup>34</sup>. However, this screening has expanded to include testing of genetic conditions which are untreatable or non-

pathological. These programs are evidence that the United States is interested in identifying these conditions, at least in part to influence parents' future reproductive decision making<sup>35</sup>.

The relationship between biology and culture can be analysed through the role of genetics and the public policy that ensued due to discoveries in this area.

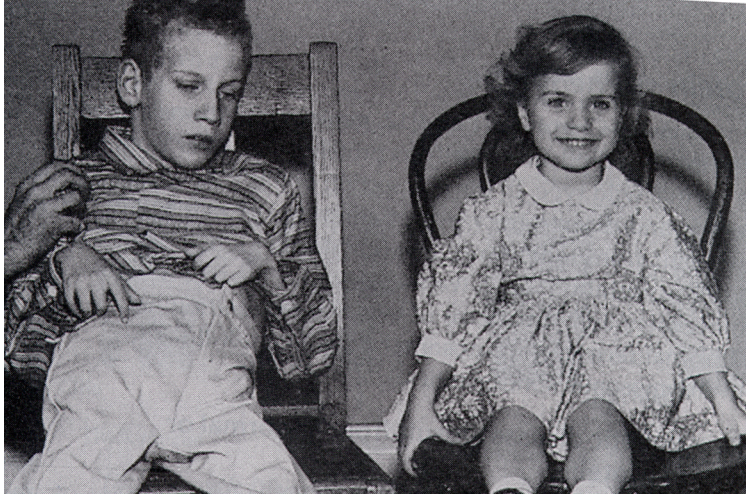
## **Conclusion**

Strong correlations have been presented between biology and culture, using PKU as a hallmark disease; however, correlation does not necessarily infer causation. More research needs to be done, especially considering the relationship of culture and biology regarding the heterozygote advantage. In this area, more evidence to support PKU as a disease and its correlational impact was found, than the impact of culture on biology (or vice versa) regarding the advantage itself of heterozygosity. (To this date, the clearest evidence between culture and biology has been presented through the studies of malaria and sickle cell anemia in African populations.) Although persuasive examples were presented, the evidence did not point clearly to a causal relationship between both factors.

The more important relationship is that of genotype and the environment with phenotype, where the variation of the genotype and environment are directly related (and contribute) to the phenotype of the organism.

## Appendix I

*Two siblings afflicted with PKU. The older child, an eleven year old boy, was untreated, whereas his younger sister received dietary treatment.*



## Appendix II

**Table I:** Common mutation spectrum in Northern European Population

Frequency	Nucleotide change/rearrangements	Phenotype
<i>Missense mutations</i>		
18%	Arg23 $\square$ Gln	Benign Hyperphenylalaninemia
20%	Arg408 $\square$ Trp	Classic PKU
14%	Arg158 $\square$ Gln	Mild PKU
<i>Nonsense mutation</i>		
38%	IVS12DS, G-A, +1	Classic PKU

## Endnotes

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- <sup>1</sup> Purves et al. Life: The Science of Biology. Sinauer Associates, Inc.; Sunderland, MA; 2001. Pp. 331.
- <sup>2</sup> Bickel et al. "Influence of phenylalanine intake on phenylketonuria". *Lancet* II: 812 – 823. Pp. 812.
- <sup>3</sup> Zschocke, Johannes. "Focus on the Molecular Genetics of Phenylketonuria". *Human Mutations* 21: 331 – 332 (2003). Pp. 331.
- <sup>4</sup> Purves et al., supra no. 1, p 331.
- <sup>5</sup> "Phenylketonuria", <http://www.pennhealth.com/ency/article001166.htm>. Date visited June 6, 2003.
- <sup>6</sup> Arnold, Georgianne, L. "E-Medicine – Phenylketonuria". <http://www.emedicine.com/PED/topic1787>. Date visited: June 6, 2003.
- <sup>7</sup> "Phenylketonuria", [http://jhhs.client.web-health.com/web-health/topics/GeneralHealth/generalhealthsub/gneralhealth/genetic\\_disorders/pku.html](http://jhhs.client.web-health.com/web-health/topics/GeneralHealth/generalhealthsub/gneralhealth/genetic_disorders/pku.html)
- <sup>8</sup> Arnold, supra no. 6.
- <sup>9</sup> "Phenylketonuria", supra no 7.
- <sup>10</sup> Purves et al., supra no 1, p. 332.
- <sup>11</sup> Roberts, Will. "Phenylketonuria: Mutations and Inheritance". <http://www.willroberts.com/pku/mutinh.html>. Date visited: June 6, 2003.
- <sup>12</sup> "Phenylketonuria", OMIM database.
- <sup>13</sup> Guttler et al. "Correlation between polymorphic DNA haplotypes at phenylalanine hydroxylase locus and clinical phenotypes of phenylketonuria". *Journal of Pediatrics* 110: 68-71 (1987).
- <sup>14</sup> Marvit et al. "GT to AT transition at a splice donor site causes skipping of preceding exon in phenylketonuria." *Nucleic Acids Research* 15 (1987). Pp. 5613-5628.
- <sup>15</sup> Woolf et al. "Phenylketonuria as a balanced polymorphism: the nature of the heterozygote advantage". *Annual of Human Genetics* 38:4 (1975). Pp. 461 – 469.
- <sup>16</sup> Saugstad, LF. "Heterozygote for the phenylketonuria allele". *Journal of Medical Genetics* 14:1 (1977). Pp. 20 – 24.
- <sup>17</sup> Krawczak, Michael and Zschocke, Johannes. "A Role for Overdominant Selection in Phenylketonuria? Evidence from Molecular Data". *Human Mutation* 21 (2003). Pp. 394 – 397.
- <sup>18</sup> Levy, Harvey. "Phenylketonuria: Old disease, new approach to treatment". *Proceeds from the National Academy of Sciences*, Vol 96 (1999). Pp. 1811 – 1813.
- <sup>19</sup> Levy, supra no 18. Pp 1811.
- <sup>20</sup> Cederbaum, Stephen. "Phenylketonuria: an update". *Current Opinions in Pediatrics* 14 (2002). Pp 702 – 706.
- <sup>21</sup> Marantz Henig, Joseph. The People's Health: A Memoir of Public Health and Its Evolution at Harvard. Joseph Henry Press; Washington D.C; 1997. Pp. 13.
- <sup>22</sup> Levy, HL and Ghavami, M. "Maternal Phenylketonuria: A metabolic teratogen". *Teratology* 53:3 (1996). Pp. 176 – 184.
- <sup>23</sup> Levy, supra no 18. Pp 1811.
- <sup>24</sup> Pszczola et al. "Research Trends in Healthful Foods". *Food Technology* 54:10 (2000). Pp. 45 – 52.
- <sup>25</sup> Ibid.
- <sup>26</sup> Marantz, supra no. 20. Pp. 12.
- <sup>27</sup> Annas, George and Elias, Sherman. Gene Mapping. Oxford University Press; New York; 1992. Pp. 121.
- <sup>28</sup> Yudell, Michael and DeSalle, Robert. The Genomic Revolution: Unveiling the Unity of Life. Joseph Henry Press, Washington DC; 2002. Pp. 187.
- <sup>29</sup> Ibid.
- <sup>30</sup> Scriver, Charles and Paula, Waters. "Monogenic traits are not simple: lessons from phenylketonuria". *TIG* 15:7 (1999). Pp. 267 – 272.
- <sup>31</sup> Levy, supra no. 18, pp. 1812.
- <sup>32</sup> Ibid.
- <sup>33</sup> Murray et al. The Human Genome Project and the Future of Health Care. Indiana University Press; Bloomington; 1996. Pp. 89.
- <sup>34</sup> Marantz, supra no. 20. Pp. 13
- <sup>35</sup> Murray et al. supra no. 33, Pp. 89.