Nutrigenomics: Food to match your genes

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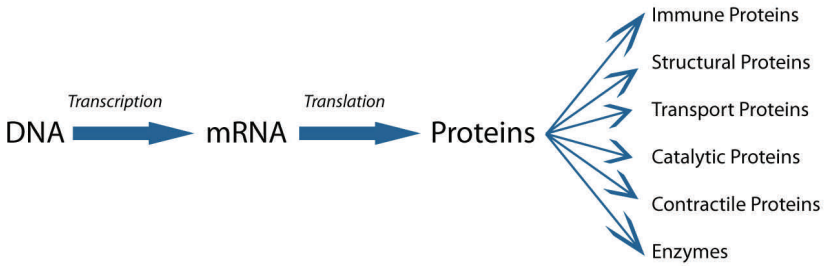
Scientists have known for a long time that our genes influence how our body responds to, and uses nutrients, the chemicals from the food we eat that we need to live and grow. For example, a large proportion of the world's adult population are unable to drink milk because their bodies have stopped producing an enzyme that breaks down (digests) a sugar in the milk called lactose. This happens because a gene is switched off, so the enzyme needed to digest the milk can't be produced. People who lack this enzyme start to feel uncomfortable 30 minutes to 2 hours after consuming milk and milk products.

Common symptoms of a lack of the lactose enzyme include:

- abdominal pain
- abdominal bloating
- gas (burping and wind)
- diarrhoea
- nausea

The easiest way for people to avoid these symptoms is to not eat dairy foods or to eat lactose free dairy foods.

As well as genes influencing how we respond to food, as seen in the lactose example above, nutrients can also affect how DNA is transcribed to mRNA and then to proteins i.e. gene expression. For example, a nutrient called folate , which is found in green vegetables, citrus, whole grain cereals and bread is essential for making DNA and RNA.



The sequencing of the human genome has opened up a new field of research on the interaction between genes and food called Nutrigenomics. Nutrigenomics research looks at how we can provide personalised nutrition advice based on each person's genetic make-up and how we can also create functional foods — foods that contain nutrients that benefit the health of the body. The examples of gene-food interactions that you will be looking at in this paper are Pellagra, Phenylketonuria and Folate.

Pellagra.

A deficiency or shortage of niacin, commonly known as Vitamin B_3, in your diet can result in pellagra; a disease causing diarrhoea, dermatitis (skin rash) and dementia (mental confusion and forgetfulness). In the past people got niacin from foods containing flour, but with modern processing techniques the niacin is now removed when the wheat is made into flour (see Box 1: Whole Grains). In the 1940s, to reduce the high numbers of children suffering from pellagra, niacin was added back in to the processed flour. The adding of a chemical like niacin to food is called fortification. This was one of the earliest examples of making a functional food.

Box 1: Whole Grains

Grains (wheat, oats, rice and barley) are used to make foods such as cereals, bread, flour and pasta. Each grain kernel is made up of bran, germ and endosperm (see diagram at right). Before the widespread use of machines to process grains, the whole grain was used to make these other foods. This meant as well as getting a source of energy, people also received the essential vitamins and minerals found in the bran and germ.

However, the process of refining grains for use in foods means that the bran and the germ are mechanically removed, leaving only the endosperm. As a result, a valuable source of vitamins and minerals is lost. This contributed to the rise of a number of deficiency diseases, such as pellagra, and led to the need to fortify food with synthetic (human-made) forms of the missing nutrients. Another example of fortification is folic acid, a chemical which is added to replace the folate that is also lost in the refining process.

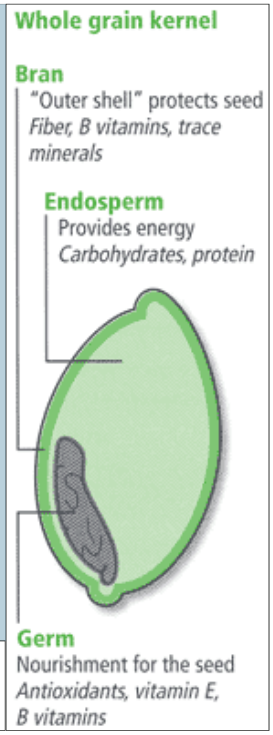


Diagram from: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2000/2000DGBrochureGrainTrain.pdf

Phenylketonuria

Phenylketonuria (PKU) is a good example of how genes determine the way our bodies react to nutrients in our food and where eating the right food can be used to treat a disorder caused by a mutation in the genes.

What is PKU?

People who have PKU (Phenylketonuria) have a genetic mutation that means their bodies are not capable of using an amino acid called phenylalanine. Phenylalanine is an essential amino acid, which means we have to get it from the food we eat as our bodies are unable to make it. Major food sources of phenylalanine include dairy products, meat, fish, poultry and some nuts and pulses. In people with PKU, phenylalanine from food gets converted to a chemical called phenylpyruvic acid, instead of being used to make other important substances needed by their bodies. Phenylpyruvic acid cannot be used by the body, so it builds up resulting in damage to the brain and other organs (Fig 1).

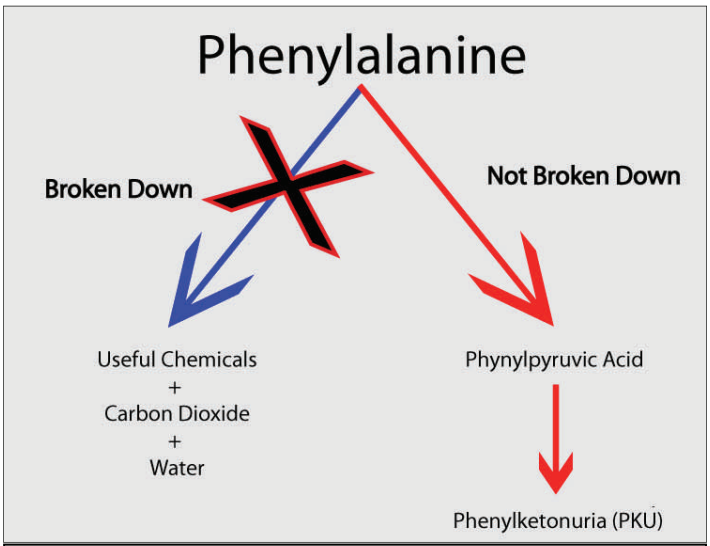


Fig 1: Phenylalanine metabolic pathway.

How is PKU detected?

Soon after you were born a few drops of blood were taken from your heel (Fig 2). This happens to all babies born in New Zealand. The blood is screened to see if a baby might be at risk from rare but life-threatening metabolic disorders, which prevent the chemical reactions essential for life from occurring.

One of the disorders that is screened for is PKU (Phenylketonuria). Children with PKU are at risk of severe brain problems such as mental retardation and seizures. It can also affect their thinking skills and can cause emotional problems. Doctors have been screening babies in New Zealand for PKU since the 1960s.

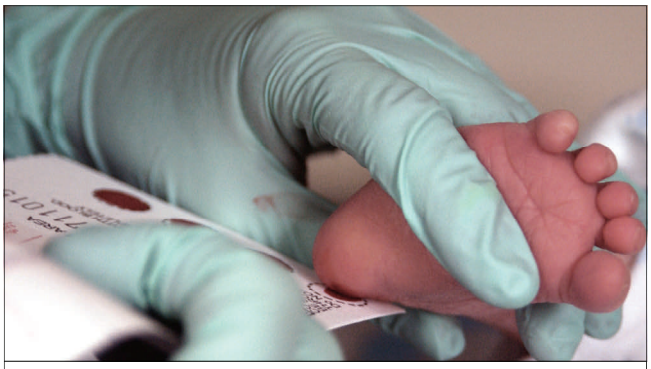


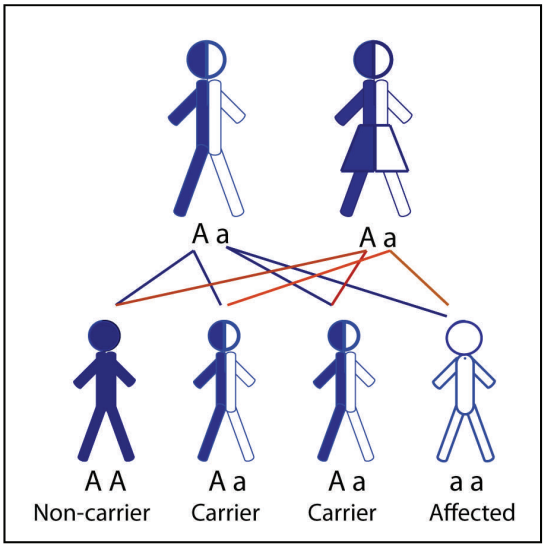
Fig 2: The blood of a baby being collected for screening. From http://www.af.mil/shared/media/photodb/photos/071212-F-6244S-292.jpg

How is PKU treated?

Babies that have a positive response for PKU (Phenylketonuria) cannot have food containing high levels of phenylalanine. They are either put onto a special diet of low phenylalanine food or if the mother is breast feeding, she needs to avoid foods that are high in phenylalanine. This is to prevent levels of phenylalanine in the blood from getting too high and damaging the brain. This special diet continues into adulthood.

The genetics behind PKU.

A gene on the DNA codes for an enzyme that breaks down phenylalanine into other chemicals that the body can use. A recessive mutation on this gene causes PKU. This means an affected person has to have two mutated alleles to have PKU i.e. one from each parent. A person with one mutated allele is called a 'carrier' for PKU. Carriers are not affected by PKU but their children might be.



Folate

Folate is one of the B group vitamins (like niacin) and is essential for the synthesis (making) of the nucleic acids RNA and DNA. It is also involved in DNA replication and repair. Folate acts as a co-factor for many enzymes, allowing them to catalyse reactions.

Australia and New Zealand have common food standards and as part of this the two countries agreed to make it compulsory from 2009 for bakers to add folic acid to bread. Folic acid is a synthetic form of folate used in food fortification and vitamin supplements. But in August 2009 the New Zealand government decided **not** to introduce the law that would make folic acid fortification compulsory. This decision was made after considering the opinions of groups both for and against fortification. Australia did make folic acid fortification compulsory.

Folate and Pregnancy

Scientists and doctors have known for some time that low folate levels in pregnant women can lead to neural-tube defects (NTD) in babies. The two main NTD are spina bifida and anencephaly. In spina bifida, the fetal spinal column doesn't close completely during the first month of pregnancy (Fig 3). This often leads to nerve damage, which can result in some paralysis of the legs. In babies with anencephaly, much of the brain does not develop. These babies are either born dead (stillborn) or die shortly after birth.

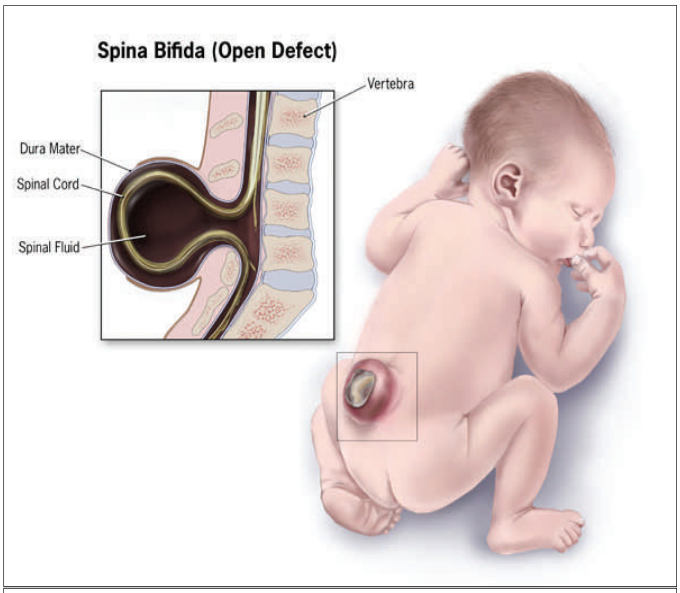


Fig 3: Drawing of a baby with Spina Bifida. From: http://www.cdc.gov/ncbddd/birthdefects/SpinaBifida-graphic.htm

Neural tube defects (NTD) are one of the most common birth defects. In New Zealand each year around 25 children are stillborn or born alive with a NTD. Similar numbers of pregnancies are terminated each year because the embryo has a NTD. Babies that do survive (10–15 per year) face a lifetime of medical intervention and significant physical disability[1].

The risk of neural tube defects (NTD) in the embryo can be significantly reduced by increasing the intake of folate by women before and during the first 28 days after fertilisation. Some studies suggest up to a 70% reduction in NTD can be achieved with folic acid supplementation[1]. As a result since the 1990s, governments have recommended that women planning to get pregnant should take folic acid supplements for the month before fertilisation and during the first three months of pregnancy.

Folate is also important in the prevention of congenital heart disease in babies, and stroke and coronary heart disease in later life. Congenital heart disease occurs when there is a problem with the heart's structure and function due to abnormal heart development before birth. It is responsible for more deaths in the first year of life than any other birth defects. Treating babies with congenital heart disease is difficult and very expensive to do[4].

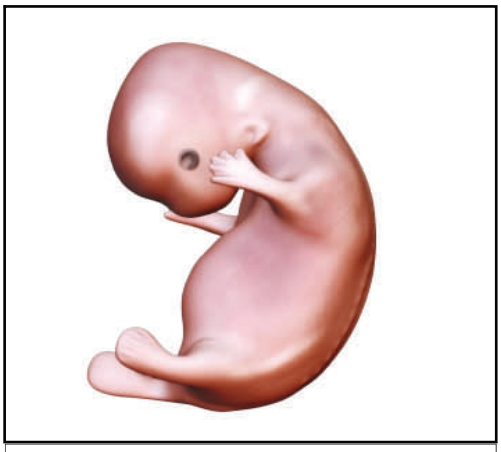


Fig 4: Drawing of a 9 week embryo. The spinal cord is just visible.

Why are neural tube defects still found in fetuses and babies?

Despite public health campaigns many women are unaware of the need to take folic acid supplements to reduce the occurrence of neural tube defects, especially prior to fertilisation. A Christchurch study found that only 17% of women take folic acid supplements during the time from before fertilisation to early pregnancy [(2)].

In New Zealand it appears that up to 50% of pregnancies are unplanned making folic acid supplementation ineffective[(1)]. This is because many women who get pregnant won't have been taking folic acid supplements and won't know that they need to start until after they get a positive pregnancy test, which is usually 6-8 weeks after their last menstrual period. Spinal cord formation is complete by the 8th week of pregnancy so the benefits of folic acid supplementation are too late (See Fig 4).

What can be done about this?

While there has been a drop in the number of babies born with neural tube defects (NTD), much of this is due to improvements in screening during pregnancy that can diagnose whether the fetus has a neural tube defect (See Box 2). Many women who receive diagnosis of a baby with a neural tube defect choose to terminate the pregnancy. The actual incidence of neural tube defects in both born and unborn babies, however, still remains high. This has a major impact on society due to the costs of terminating these pregnancies, the cost of caring for children with NTD and the emotional costs for parents of having to make a decision about whether to terminate the pregnancy or to look after a child born with major disabilities[(3)].

For many countries the answer to this issue has been the compulsory fortification of food with folate. 47 countries now have mandatory folate fortification including USA, Canada, and Australia[(4)]. As a result of this action the risk of neural tube defects in these countries has been reduced by 30-50%[(5)]. No European countries have mandatory fortification and in New Zealand the mandatory fortification of bread with folate will not occur until May 2012.

Box 2: Screening for Abnormalities During Pregnancy

In New Zealand, women can access pre-natal (before birth) screening and diagnostic tests for a number of conditions including Neural Tube Defects and Down Syndrome.

Screening is not the same as diagnosis.

A screening test indicates the *level of risk* that is present for a condition such as a neural tube defect. A positive result from screening suggests that there is an increased chance of a particular condition being present and a negative result means there is a decreased risk. People with positive screening results may decide to take the next step of pre-natal diagnostic testing which **will** tell them whether the condition is present or not in the fetus.
Pre-natal screening is not compulsory.

Women may decide to participate in pre-natal screening for a number of reasons including:

- wanting to know as much as possible about the pregnancy
- wanting to know whether or not the fetus is affected by a condition that is common in the whanau / family
- wanting the option of termination of an affected pregnancy
- wanting to know if the pregnancy is affected by a condition so that she and her partner can prepare in advance for a baby with an abnormality.

Conditions that can be tested for in New Zealand by pre-natal testing include:

- Physical abnormalities including neural tube defects (spina bifida), cardiac, renal and digestive abnormalities
- Aneuploidy Down (Trisomy 21), Edwards (Trisomy 18) and Patau (Trisomy 13) syndromes
- Aneuploidy affecting the sex chromosomes—Turner (XO), Klinefelter (XXY), Jacob (XYY) syndromes.

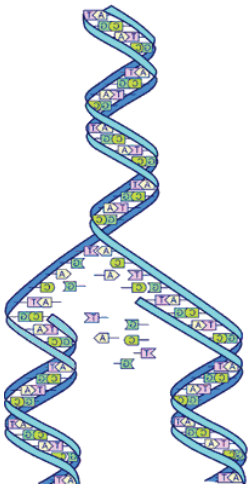
Is folate good for everyone?

This is the crucial question and is one of the main reasons why mandatory fortification is not universal. Research is increasingly showing that folate has dual effects in the body. This means it can be both beneficial and potentially harmful for the body (Table 1).

Disease	Incidence or prevalence in United Kingdom (population: 60 million)	Effect of increasing folate status
Neural tube defects	800 pregnancies/year	Protective; may reduce NTDs by up to 162/year
Colorectal polyps	22% prevalence in 55–64 year-olds	Dual effects: protects against but can encourage growth of the abnormal cells
Colorectal cancer	34, 400/year	Dual effects
Breast cancer	43, 000/year	Dual effects
Prostate cancer	32, 800/year	Dual effects
Stroke	97 000/year	Protective

Table 1. Some diseases that may be influenced by dietary folate status [6]

The dual role of folate in cancer



Folate is critical for cell division and growth. As stated earlier, it is an essential factor in the making of nucleic acids and is also important in DNA repair. Low levels of folate can result in low levels of thymine (T), one of the bases that make up DNA. When insufficient thymine is present then uracil (U) is inserted into the DNA strand instead. This causes an increase in breaks in the DNA strand, a known trigger for cancer[(6)(7)]. This suggests that **high** folate levels are likely to **protect** against the **formation** of cancer.

In cancer cells DNA replication and cell division occur at a very fast rate. Research has shown that if folate is **removed** from the cells or prevented from acting, this inhibits or slows down the abnormal growth of cells (tumours)[(6)(7)]. This research suggests that if cancer is already present, then folate is **beneficial** for cancer only if it is present at **low** levels, which is contradictory to the results described above.

Based on this many researchers now describe folate as having a dual effect on cancer: increasing folate levels will prevent the start of tumour formation, but if precancerous cells are already present then high levels of folate can speed up the development of these cells into cancer. This dual effect has been seen in colorectal, breast and prostate cancers[(7)]. For most people though, increasing folate intake in the diet will provide a level of protection from cancer.

Folate and Vitamin B_{12}

Research shows there is an interaction between folate and Vitamin B_{12}. In a study of elderly people, those with a Vitamin B_{12} deficiency who took folic acid supplements showed an increased risk of cognitive impairment, meaning their ability to think clearly was harmed[(7)(8)]. So high folate levels are a risk in people who have low levels of Vitamin B_{12}. On the other hand, another study showed that people who took folic acid supplements for three years showed improved performance on cognitive tests. In this study people with low Vitamin B_{12} levels were not included[(7)]. Two further studies on folate intake in the United States and Italy, also in the elderly, found that low folate intake or status is a risk factor for dementia (mental confusion and forgetfulness). These studies, however, did not measure the levels of Vitamin B_{12} [(7)]. This suggests levels of Vitamin B_{12} can alter the impact of folate on cognition.

The combination of low levels of Vitamin B_{12} and high folate levels in pregnant women has also been linked to an increase in obesity and the incidence of Type 2 diabetes in their children [(7)].

How does folate work to prevent neural tube defects?

Scientists are still unsure exactly how folate acts to prevent neural tube defects (NTD). Other factors such as variation in genes, fertility drugs, Vitamin B_{12} deficiency, drugs, alcohol and maternal obesity have all been associated with neural tube defects (NTD).

What does this all mean?

It was thought that increasing folate levels through folic acid supplements, would be of overall benefit to the population by reducing the incidence of neural tube defects. Unfortunately because of the need to start taking supplements prior to fertilisation many women do not get sufficient folate to prevent neural tube defects in their babies. Consequently the law proposing compulsory folate fortification in bread was intended to ensure women of reproductive age get sufficient folate. This assumes that increasing folate levels through fortification of food, will do no harm to the whole population who are also exposed to the increased folate levels. Current scientific research is starting to suggest that it may not be as simple as this[7].

Until recently the main tool scientists had to carry out research into the effect of nutrient deficiencies or excess were population studies. Population studies follow a large number of people over a period of time to study their response to a particular health issue. This shows what happens in populations but not how individuals react to changing nutrient levels.

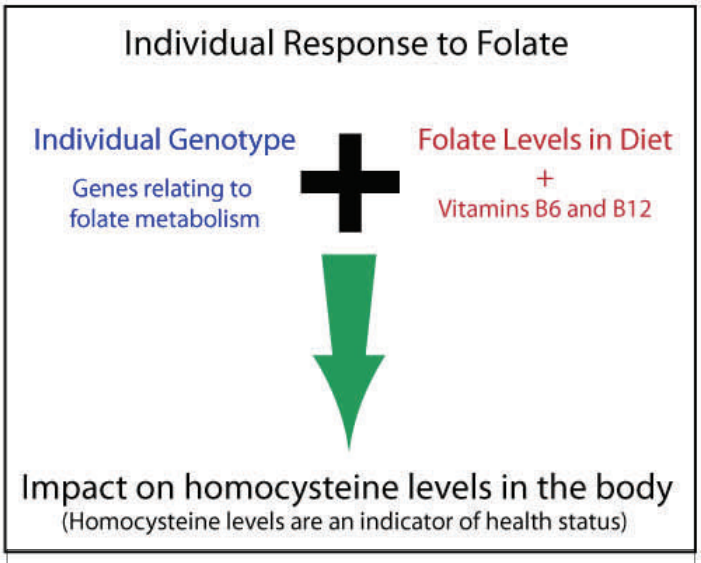


Fig 5: the interaction between genes and folate levels on health status.

Developments in genome analysis mean scientists are now able to identify at an individual level how people react to nutrients based on their genes. For example, how each person's body responds to folate and how much they need, depends on their genotype for key genes that control how folate is used by the body[10]. This means that a how healthy someone is influenced by both their individual genotype and the amount of folate and Vitamins B_6 and B_{12} that they have in their diet (Fig 5).

The fact that people vary in their response to folate due to genetic factors means that simply measuring their folate intake will not give a good indicator of whether the folate will benefit or potentially harm them. Instead scientists use the levels of a substance called homocysteine as an indicator of how healthy someone is. High levels of homocysteine are associated with increased risk of cardiovascular disease and damage to DNA and cells.

Eventually we will have the ability to personalise nutrition advice based on each person's individual genetic make-up. But in the meantime this is the question that society needs to decide on:

> When folic acid fortification is introduced, several hundred thousand people are exposed to an increased intake of folic acid for each neural tube defect pregnancy that is prevented.
> Does the benefit of folic acid fortification to a small number of babies, outweigh the possible risks of exposing everyone in the population to increased levels of folic acid?[6]

Further reading:

PKU

For more on the genetics behind PKU see LENScience wiki: http://lens.auckland.ac.nz
PKU Online community: http://www.pku.com/home.php

Folate

(Search for folate and folic acid in these websites)
New Zealand Medical Journal: http://www.nzma.org.nz/journal/index.shtml
New Zealand Food Safety authority: http://www.nzfsa.govt.nz/index.htm
Access Excellence: http://www.accessexcellence.org/
New Scientist: http://www.newscientist.com

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