Nutrigenetics and the scientific basis

Why the scepticism? A mixture of misinformation, misunderstanding, miscommunication and of course too much hype and extravagant, hard to believe, claims from *some* commercial operators.

What is it? Scientifically, nutrigenetics is the study of how genetic variation in individual genes affects an individual's response to particular nutrients and toxins in the diet.

What is it trying to do? Nutrigenetics aims to use genotype information from an individual to determine the properties of the proteins coded by certain genes and the effect this has on metabolism, transport and assimilation of nutrients in the diet and the effect on elimination of toxins. A genetic variation, e.g. a SNP, can affect the activity of an enzyme which can affect the metabolism of a nutrient such as folic acid. This is exactly analogous to pharmacogenetics where the variation in a gene affects the rate of drug metabolism.

We have standard guidelines on healthy eating which are based on many years of accumulated scientific evidence mainly from observational and intervention studies (NOT clinical trials). These guidelines have been developed to help maintain a healthy lifestyle for as long as possible. The aim of nutrigenetics is to be able to modify standard dietary guidelines according to the individual genotype and phenotype – again based on many years of accumulated scientific evidence mainly from observational and intervention studies. The level of evidence for nutrigenetics is similar to that used to develop and justify standard guidelines.

What does it mean for the consumer/patient? The use of genetic *information* both to guide dietary choices and to *inform* individuals about the importance of diet, food and metabolism. Nutrigenetics enables us to use genotype and phenotype to improve our understanding of how food works together with the body. The information aspect of the service is extremely important – the scientists use it and learn from it so why shouldn't the public? As long as the information is provided in a serious, responsible and correct manner then the result will be benefits for the patient/consumer.

Some credentials:

Eurogene - http://eurogene.biomed.ntua.gr/

The EU awarded an eTEN grant of €1.12million over 18 months to the Eurogene consortium (Scientific Director: Dr Keith Grimaldi) to setup and *implement* nutrigenetic services in the clinic. It is *not* a research grant but a market validation study for a product or service *already* existing that has market potential. The scope of the eTEN programme:

"Supporting the deployment of trans-European e-services in the public interest. The

programme aimed to accelerate the take-up of services[3] to sustain the European social model of an inclusive, cohesive society. "

In other words…to help existing services overcome barriers to market entry. To help get valuable services more penetrance in the market and encourage wider take-up.

The nutrigenetic service was judged by the INDEPENDENT expert review committee to be a valuable service which could have a positive impact on health in Europe. Some quotes from the reviewers:

- "the service is focused on the informed patient and the methods applied improving patients conformance to treatment"
- "The proposed service is very important and a high impact is anticipated"
- "..."The ability to support a healthy lifestyle through e-services proposed by the proposal contributes strongly to inclusiveness"

There are three pilot clinics:

- Germany: Department of Clinical Biochemistry and Pharmacology, University of Bonn
- Italy: Cardiovascular Diseases Centre, Isernia, Italy
- Spain: Barbastro Health Care Area, Spain

Micro2DNA – (http://micro2dna.intranet.gr)

An FP6 EU funded research and development project. Development of a portable genotyping system. Nutrigenetics was included as one of the test services to run on the machine (Dr Keith Grimaldi representing Sciona Ltd in the consortium) – SNP assays and specific software and algorithms for interpreting nutrigenetic advice as related to prevention of heart disease were developed in collaboration with the Universities of Oxford and Athens.

The Athens Weight Management Study - http://www.nutritionj.com/content/6/1/29

This study (senior author: Dr Keith Grimaldi) was published in *Nutrition Journal* in November 2007 and reached "Highly Accessed" status within 2 weeks of publication. It describes the benefits of a nutrigenetic diet vs. a standard low fat Mediterranean diet. In the nutrigenetic group there were greater improvements in glucose tolerance, LDL & HDL levels and homocysteine levels (all patients with raised homocysteine returned to normal). In addition long term weight loss (1 >year) was maintained in the nutrigenetic group but not in the standard group.

Improved weight management using genetic information to personalize a calorie controlled diet

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Background

Gene-environment studies demonstrate variability in nutrient requirements depending upon individual variations in genes affecting nutrient metabolism and transport. This study investigated whether the inclusion of genetic information to personalize a patient's diet (nutrigenetics) could improve long term weight management.

Methods

Patients with a history of failures at weight loss were offered a nutrigenetic test screening 24 variants in 19 genes involved in metabolism. 50 patients were in the nutrigenetic group and 43 patients attending the same clinic were selected for comparison using algorithms to match the characteristics: age, sex, frequency of clinical visits and BMI at initial clinic visit. The second group of 43 patients did not receive a nutrigenetic test. BMI reduction at 100 and > 300 days and blood fasting glucose were measured.

Results

After 300 days of follow-up individuals in the nutrigenetic group were more likely to have maintained some weight loss (73%) than those in the comparison group (32%), resulting in an age and gender adjusted OR of 5.74 (95% CI 1.74–22.52). Average BMI reduction in the nutrigenetic group was 1.93 kg/m^2(5.6% loss) vs. an average BMI gain of 0.51 kg/m^2(2.2% gain) ($p < 0.023$). Among patients with a starting blood fasting glucose of > 100 mg/dL, 57% (17/30) of the nutrigenetic group but only 25% (4/16) of the non-tested group had levels reduced to < 100 mg/dL after > 90 days of weight management therapy (OR for lowering glucose to < 100 mg/dL due to diet = 1.98 95%CI 1.01, 3.87, $p < 0.046$).

Conclusion

Addition of nutrigenetically tailored diets resulted in better compliance, longer-term BMI reduction and improvements in blood glucose levels.

NuGO: The European Nutrigenomics Organisation (www.nugo.org)

NuGO is a European-funded Network of Excellence, the full title of which is 'The European Nutrigenomics Organisation: linking genomics, nutrition and health research'.

NuGO is funded by the European Commission's Research Directorate General under the Food Quality and Safety Priority of the Sixth Framework Programme for Research and Technological Development. The project began in January 2004 and will be funded until December 2009, but NuGO is anticipated to continue in one form or another.

Twenty-three (23) NuGO Partners consisting of research organisations, universities and small-medium-sized businesses from ten European countries form the core of NuGO, and their common aims is to make future nutrigenomics research better and easier.

The annual NuGo week conference will be held this year in Tuscany, 31st August – 3rd September

Dr Keith Grimaldi is a member of several NuGo workgroups

Clearly the EU would not be funding these projects (both at research and applied level) if there was not strong science already supporting the fields of nutrigenetics and nutrigenomics.

Is there any scientific evidence for Nutrigenetics? Yes, a lot. Apart from our own studies (see above) there are literally thousands of peer reviewed studies that have been published over the last two decades that demonstrate gene-diet interactions. The level of scientific study is in general very high and is of similar quality to the scientific evidence used to justify standard dietary advice such as high fruit and vegetables, low saturated fats, low sugars etc. A bibliography of key references coving genes in the nutrigenetic panel can be found at the end of this document.

Example 1 – *MTHFR*

This gene codes for an enzyme that metabolises folic acid. There is a common polymorphism (SNP) at position 677 in the gene where an individual will either have a “C” or a “T”. Since we have two copies of the gene, one from each parent, the possible individual genotypes are “CC”, “CT” and “TT”. The change from a C to a T changes an amino acid in the enzyme: Alanine to Valine. The presence of the valine reduces the enzyme activity by over 50% and this version is common (up to 40% Italians will have at least one copy of 677T, the lower activity enzyme). Folic acid is important in DNA synthesis & DNA methlyation and in the latter pathway homocysteine is utilised (it is recycled into methionine). Homocysteine is an amino acid that is linked to raised risks of a number of diseases including stroke, cardiovascular disease and osteoporosis. It has been demonstrated in many repeated studies that individuals with the T version of the gene and low intake of folic acid plus other B vitamins are likely to have a raised homocysteine levels into the higher risk range. It has also been demonstrated repeatedly that simply increasing folic acid in the diet will reverse the trend and restore homocysteine levels to normal. The levels of folic acid required to restore the levels to normal have been shown to be between 400-800 µg which is well below the recommended upper limit (RDA for folic acid in USA is 400 µg and 200 µg in Europe). So in individuals with the T genotype the very simple nutritional advice is to increase levels of folic acid plus other B vitamins to a daily intake above the RDA, e.g 600-800 µg for folic acid (see refs 3, 20 and 58 for details).

An indication of the extent to which this gene diet relationship has been studied is shown by a www.pubmed.com search on 26th May, 2009, for [MTHFR + polymorphism] which returned 2,015 articles and a more specific search for [MTHFR + polymorphism + folic + acid] returned 603 scienticific publications.

The relevance of nutrigenetics is illustrated by the fact that most doctors when faced with a patient with raised homocysteine will prescribe folic acid and other B vitamins…the nutrigenetic approach is to determine the appropriate daily levels for individuals so that their homocysteine *never* actually exceeds the risk levels

Example 2 – SOD2 (mnSOD)

An antioxidant enzyme present in two common forms:
15% = Ala-Ala
50% = Ala-Val
35% = Val-Val

Secondo lo studio citato sotto NON c'è nessun link fra il polimorfismo e il rischio di prostate cancer...
According to the study cited below there is NO link between the polymorphism and risk of prostate cancer

BUT...

If the level of antioxidants is included in the analysis it reveals *a very strong* link: Individuals with the Ala-Ala version who have a LOW level of antioxidants have a 3x increased risk of prostate cancer PERO'

This study demonstrates two things:

1. The importance of diet and the possibility of giving personal advice to reduce the risk of a disease – i.e. people with Ala-Ala need to include more antioxidants in their diet (note that this study has been repeated and confirmed by others)

2. A reason for the controversy, or scepticism, sometimes expressed regarding nutrigenetics. There have been many studies in the past that looked ONLY at gene and disease, without taking into account the diet and the results have often been in conflict with each other. These results have been used to criticise the field, to say thay there is no certainty, but in reality such studies have no relevance for nutrigenetics. For MnSOD ALL the studies that have included gene-diet-disease have given similar results i.e. that possesion of the Ala version together with a low level of antioxidants increases the risk - the gene-disease link is ONLY discovered in people with low dietary antioxidants.

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Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk

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Background: The manganese superoxide dismutase (*MnSOD*) gene encodes an antioxidant enzyme (SOD2) that may protect cells from oxidative damage. The MnSOD allele with *Val* as amino acid 16 encodes a protein that has 30–40% lower activity compared with the*MnSOD Ala* variant, hence possibly increasing susceptibility to oxidative stress. On the other hand, some epidemiologic studies suggest that the *Ala* allele is associated with a higher risk of cancer, including prostate cancer. *Methods:* We conducted a nested case–control study in the Health Professionals Follow-up Study with 612 incident prostate cancer cases and 612 matched controls to investigate the role of the *MnSOD* gene *Ala16Val* polymorphism and its joint association with plasma carotenoid concentrations in relation to risk of total prostate cancer and aggressive prostate cancer (advanced stage or Gleason sum ≥7). *Results:* The allele frequencies in the controls were49.8% for *Ala* and 50.2% for *Val*. No association was found between the *MnSOD* genotype and risk of total and aggressive prostate cancer. Furthermore, no statistically significant interaction was observed between the *MnSOD* genotype and any of the plasma carotenoids in relation to risk of total and aggressive prostate cancer. In analyses in which we combined data from plasma and dietary carotenoids and created a quintile score to reflect long-term carotenoid status, a 3-fold [95% confidence interval: 1.37–7.02] increased risk of aggressive prostate cancer was observed among men with the *Ala/Ala* genotype in the presence of low long-term lycopene status (*P*-value, test for interaction = 0.02) as compared with men with the *Ala/Val+Val/Val* genotypes with low long-term lycopene status. *Conclusion:* In this cohort of mainly white men, the *MnSOD* gene *Ala16Val* polymorphism was not associated with total or aggressive prostate cancer risk.However, men with the *MnSOD Ala/Ala* genotype who had low long-term lycopene status had a higher risk of aggressive prostate cancercompared with individuals with the other genotypes. These results are consistent with findings from earlier studies that reported when antioxidant status is low, the *MnSOD Ala/Ala* genotype may be associated with an increased risk of aggressive prostate cancer.

Will it create the perfect diet? No. This is *not claimed*. Using the current evidence that is available in the peer reviewed scientific literature nutrigenetics can be used to create a diet that is better than the standard “one size fits all” guidelines. We still have a LOT to learn, maybe we will never reach that perfect diet, but we do have some knowledge that we can use now, we are taking those essential first steps.

So what is the point, will it really help? The aim of all dietary advice is to establish good eating habits *permanently* because good health in later life depends a great deal on how earlier life is lived. Small changes, even apparently insignificant changes, can make a big difference over 10-20 years. For example the calorie excess per day required to gain 15 Kg from age 20 to age 40 is only 10 calories, that’s just half a spoonful of sugar extra per day!

So how do explain the dramatic results of the Athens study? The nutrigenetic diet helped people to manage their weight loss with much more success compared to those on the standard diet, even after over 1 year. There are at least 2 probable reasons:

a) The nutrigenetic diet was nutritionally better – especially because when a person is trying to lose weight he/she eats less and therefore has to make sure that the correct amount of essential nutrients are consumed in fewer calories.

b) Motivation. By using genetics to explain how food is metabolised and why different people have different dietary requirements helps the individual to better understand the reasons for eating fruit, vegetables, less saturated fats, etc, than if the information is presented in a generic way, as it has been for the past decades without much success. Presented in a personalised context leads to higher long term compliance.

Most probably the answer is a combination and it is quite likely that at present the motivation element is greater than the dietary value element – but that is not important. Nutrigenetics is used to give *information* to people about themselves as well as to guide dietary choices. The information element is extremely important which is why we spend a lot of time trying to communicate it effectively both to practitioner and client.

What about clinical trials? Clinical trial evidence is not generally achievable for any type of dietary advice that aims towards long term good health. Double-blind, short duration, randomised clinical trials will work for single molecule pharmaceuticals but not for the complexity of food.

What nutrigenetics is NOT: Nutrigenetics is not a diagnostic nor a predictor of disease. It makes no attempt to determine relative risks and odds ratios of complex diseases such as type 2 diabetes, cardiovascular disease, etc. The focus of attention of nutrigenetics is generally not the final disease but the many intermediate "risk factors" such as homocysteine, LDL cholesterol, hypertension etc. cardiovascular disease for example has many possible causes (hypertension, high cholesterol, inflammation, etc) and each gene-diet interaction focuses on just one area. For example the knowledge of the *MTHFR* genotype is not used to predict the risk of heart disease or stroke but to define the daily requirement for folic acid, vitamins B6 and B12. It has been demonstrated many many times that individuals with the 677TT version of the enzyme WILL have raised homocysteine if there is not adequate folic acid in the diet. Therefore the nutrigenetic test advice will be to consume an adequate amount of folic acid (600-800 µg / day) – and this WILL keep homocysteine levels lower. Most doctors who find a patient has high homocysteine levels will treat it with folic acid, B6 and B12, the aim of the nutrigenetic test is to ensure adequate amounts of these vitamins are in the diet BEFORE the levels become raised.

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