What nutrition does to our genes:

A modern paradigm for optimizing health and preventing non-communicable disease

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DNA

THE BLUEPRINT

METHYLATED DNA
HISTONES miRNA

WHAT HAS BEEN
PROGRAMMED

RNA, PROTEINS

WHAT APPEARS
TO HAPPEN

METABOLITES &
GENOME STABILITY

METABOLOMICS &
GENOMICS

IMPACT OF DIET ON THE GENOME AND METABOLISM

Kussmann et al Nature Outlook 2010

NUTRIGENOMICS

GENETICS

EPIGENETICS

TRANSCRIPTOMICS & PROTEOMICS

DIET
CHEMICAL GENOTOXINS

SOCIAL STATUS

PSYCHO STRESS

POOR LIFE-STYLE

MALNUTRITION

RADIATION
GENOME INSTABILITY
DNA DAMAGE BIOMARKERS

- RBC MN ASSAY
  “Howell-Jolly Bodies”

- LYMPHOCYTE CBMN ASSAY

- CHROMOSOME ABBS.

- COMET ASSAY

- TELOMERE LENGTH

- MITOCHONDRIAL DNA DELETION

- DNA OXIDATION

- DNA METHYLATION

- 8-Oxoguanine


### Chromosome Abnormalities in Severe Protein Calorie Malnutrition

**NATURE VOL. 232 JULY 23 1971**

Salvador Armendares
Fabio Salamanca
Silvestre Frenk

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<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (month)</th>
<th>Clinical type of malnutrition</th>
<th>Weight (g)</th>
<th>Height (cm)</th>
<th>Weight for height (%)</th>
<th>Weight for age (%)</th>
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<tbody>
<tr>
<td>I</td>
<td>M</td>
<td>60</td>
<td>Kwashiorkor</td>
<td>8.535</td>
<td>74</td>
<td>8%</td>
<td>54%</td>
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<tr>
<td>II</td>
<td>M</td>
<td>15</td>
<td>Kwashiorkor</td>
<td>5.990</td>
<td>66.5</td>
<td>19%</td>
<td>43%</td>
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<tr>
<td>III</td>
<td>F</td>
<td>15</td>
<td>Kwashiorkor</td>
<td>5.430</td>
<td>71</td>
<td>37%</td>
<td>48%</td>
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<tr>
<td>IV</td>
<td>F</td>
<td>14</td>
<td>Kwashiorkor</td>
<td>4.710</td>
<td>65.3</td>
<td>33%</td>
<td>54%</td>
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<tr>
<td>V</td>
<td>F</td>
<td>12</td>
<td>Kwashiorkor</td>
<td>6.050</td>
<td>69</td>
<td>23%</td>
<td>37%</td>
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<tr>
<td>VI</td>
<td>M</td>
<td>12</td>
<td>Marasmus</td>
<td>5.310</td>
<td>—</td>
<td>—</td>
<td>45%</td>
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<tr>
<td>VII</td>
<td>F</td>
<td>8</td>
<td>Marasmus</td>
<td>3.865</td>
<td>61.5</td>
<td>36%</td>
<td>54%</td>
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<tr>
<td>VIII</td>
<td>F</td>
<td>8</td>
<td>Marasmus</td>
<td>5.200</td>
<td>68</td>
<td>34%</td>
<td>37%</td>
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<tr>
<td>IX</td>
<td>F</td>
<td>3.5</td>
<td>Marasmus</td>
<td>3.160</td>
<td>61.5</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>X</td>
<td>M</td>
<td>1</td>
<td>Marasmus</td>
<td>2.430</td>
<td>—</td>
<td>—</td>
<td>40%</td>
</tr>
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</table>

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**CHROMOSOME ABERRATIONS**

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**5.5 fold difference in CAs**

[Graph showing chromosome aberrations for malnourished and well-nourished infants]

**MALNOURISHED INFANTS**

**WELL-NOURISHED INFANTS**
LYMPHOCYTE CYTOKINESIS-BLOCK MICRONUCLEUS ASSAY

Chromosomal DNA damage

- Genotoxins
- Nutrient deficiency
- Excess calories

- Strand breaks in DNA
- Chromosome malsegregation
- Telomere shortening/dysfunction

Cells with damaged & unstable genomes

Fenech M (2007)
DNA damage induction by Folic acid deficiency is of a similar magnitude as that induced by unsafe doses of ionising radiation.

IAEA annual safe exposure limit equivalent to 0.1-0.5 rad X-rays

Crott & Fenech 2002

Fenech & Morley, 1986

Increased lymphocyte micronucleus frequency in early pregnancy is associated prospectively with pre-eclampsia and/or intrauterine growth restriction (PEIUGR).
% variation in genome damage with increased intake relative to lowest tertile of intake

* P < 0.006

Vitamin E, Calcium, Folate, Retinol, Nicotinic acid, β-Carotene, Riboflavin, Pantothenic acid, Biotin

mid-tertile
highest tertile

Q. Which dietary pattern is optimal for genome integrity?

Q. Which dietary pattern will work for different genotypes or cultures?
TELOMERE (TTAGGG repeats) ARE ESSENTIAL FOR CHROMOSOME STABILITY

TELOMERE SHORTENING OR DYSFUNCTION INCREASES RISK FOR CANCER AND ACCELERATED SENESCENCE

**Diagram:**
- Chromosome
- Telomere
- Nucleus
- Cell
- Single-stranded Region
- Double-stranded Region
- DNA
- Telomeric DNA Repeats
- Base Pairs
- Subtelomeric regions
- TRF1
- TRF2
- TTAGGG
- AATCCC
- Telomerase
- G-strand overhang
- 150-200 nt
- 3' OH
- 10-15 kb human
- 25-40 kb mouse
Mutations in telomerase and telomere shelterin genes lead to a broad clinical phenotype of accelerated ageing.

### Syndromes of Telomere Shortening

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>hTR</td>
<td>Sporadic IPF 1–3%</td>
</tr>
</tbody>
</table>
| hTERT     | Familial IPF<sup>a</sup> 8–15%  
Sporadic and familial aplastic anemia ~3–5%  
Autosomal dominant DC<sup>b</sup> |
| DKC1      | X-linked DC  
Hoyeraal-Hreiderasson |
| TINF2     | Sporadic DC  
Autosomal dominant DC  
Hoyeraal-Hreiderasson |
| NOP10     | Autosomal Recessive DC |
| NHP2      | Autosomal Recessive DC |

<sup>a</sup> IPF refers to idiopathic pulmonary fibrosis.

<sup>b</sup> DC refers to dyskeratosis congenita.
HIGH PLASMA ZINC & REDUCED FOLATE CARRIER G80A POLYMORPHISM ARE ASSOCIATED WITH SHORTER TELOMERE LENGTH IN AUSTRALIAN CHILDREN FROM HIGHER SOCIO-ECONOMIC STATUS FAMILIES

Regression coefficients for prediction of telomere length

<table>
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<tr>
<th>Term</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Boys</td>
<td>0</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>Girls</td>
<td>1.72</td>
<td>-15.13 to 18.56</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>-1.11 to -1.03</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>-5.59</td>
<td>-26.75 to 15.57</td>
<td>0.60</td>
</tr>
<tr>
<td>9</td>
<td>-1.91</td>
<td>-23.44 to 19.61</td>
<td>0.86</td>
</tr>
<tr>
<td>Month of blood collection</td>
<td>-1.75</td>
<td>-5.08 to 1.59</td>
<td>0.30</td>
</tr>
<tr>
<td>Plasma zinc (µmol/L)</td>
<td>-6.07</td>
<td>-1.11 to -1.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Highest parental education</td>
<td>0</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>Some high school</td>
<td>-11.93</td>
<td>-60.16 to 36.30</td>
<td>0.63</td>
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<tr>
<td>Completed high school</td>
<td>-37.12</td>
<td>-79.29 to 5.06</td>
<td>0.08</td>
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<tr>
<td>Trade certificate</td>
<td>-35.93</td>
<td>-74.46 to 2.60</td>
<td>0.07</td>
</tr>
<tr>
<td>University/college</td>
<td>0</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>RFC 80GG</td>
<td>0</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>RFC 80GA</td>
<td>-13.76</td>
<td>-32.04 to 4.51</td>
<td>0.14</td>
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<tr>
<td>RFC 80AA</td>
<td>-25.70</td>
<td>-50.67 to -0.74</td>
<td>0.04</td>
</tr>
</tbody>
</table>

RFC, reduced folate carrier

• N=437 children
• Age = 3-9 years
• Higher socio-economic status
• Location = Perth, Australia

16th John M Kinney Nestlé-Nutrition Award
LOW DIETARY ANTIOXIDANT AND WHITE BREAD INTAKE IS ASSOCIATED WITH SHORTER TELOMERES IN CHILDREN AND ADOLESCENTS IN SPAIN

N= 287 children, adolescents
Age = 6-18 years
Location: Spain

R=0.16
P=0.007

Garcia-Calzon et al
LONGER

MEDITERRANEAN DIET

PRUDENT KOREAN DIET

HIGHER DIETARY ANTIOXIDANTS, VITC, VIT E, FIBRE

HIGHER SERUM VIT C, VIT D, VIT E, CAROTENOIDS, Ca/Mg RATIO

HIGHER INTRA CELLULAR Zn

Ω3-FATTY ACID SUPP INTAKE

CALORIC RESTRICTION, HOLISTIC DIET/LIFESTYLE

MULTIVITAMIN USE

CURRENT

“limited” KNOWLEDGE

SHORTER

HIGHER DIETARY INTAKE OF:

RED & PROCESSED MEAT, WHITE BREAD, SWEETENED SODA DRINKS, SODIUM SHORT-MED CHAIN SAT FATS, N6 PUFA, LINOLEIC ACID

HIGHER PLASMA Ca, Mg, Zn HOMOCYSTEINE

LOWEST/HIGHEST QUINTILES SERUM FOLATE

OBESITY, PSYCHOLOGICAL & OXIDATIVE STRESS

MULTIVITAMIN USE

Dhillon, Bull and Fenech 2015
Molecular Basis of Nutrition and Ageing (in press)
DNA damage increases with age ....or.... poor choices of nutrition, life-style, physical and socio-psychological environments?

MISSION
• Promote the science of nutrigenomics and nutrigenetics in the Asia-Pacific region.
• Facilitate communication and collaboration amongst researchers, clinicians and nutrition industry.
• Organisation of the biennial Asia-Pacific Nutrigenomics & Nutrigenetics conference.

VISION
• A thriving/collaborative nutrigenomics and nutrigenetics research community in Asia-Pacific region
• Consumers have a better understanding of the science of nutrigenomics and nutrigenetics.
• Health professionals are properly educated and accredited to utilise nutrigenomics & nutrigenetics
• Nutrition Industry is better informed to provide safe and effective products.