

## Social psychiatry and the human genome: contextualising heritability\*

LEON EISENBERG

April 2003 marked the 50th anniversary of one of the great intellectual achievements of 20th century biological science: deciphering of the DNA code by Jim Watson and Francis Crick (Watson & Crick, 1953). It is also the month and year in which The National Human Genome Research Institute announced completing the human genome (Collins *et al*, 2003). Is this the time to hold a memorial mass to bury social psychiatry, an outmoded corpus of work, charming in its day but overtaken by the relentless pace of scientific advance?

Genetics as destiny has become a commonplace of public discourse. Garrison Keillor, an American humorist, has described an extended Norwegian kinship assembling for its traditional Thanksgiving dinner:

'After a half hour in the living room, all possible topics of conversation having been exhausted, we sat there eyeing each other in silence, hoping against hope that *genetics isn't everything!*'

Let me reassure you: *neither genetics nor genomics is everything!*

Working out the DNA code of the human genome is spectacular but, Watson and Crick to the contrary notwithstanding, it is not the 'secret of life' nor the blueprint for humankind. The dogma of one gene/one protein, a useful fable for its time, has been exploded; alternative splicing permits multiple proteins from a single gene. Thirty thousand plus genes code for 100 000 plus proteins; epigenetic post-translational modifications create the potential for a million different proteins that must interact to produce a viable human being. The assembly of these components reflects not merely the code but biological and social pulls and pushes at work during its fabrication. Men and women, in all our diversity, emerge from these intricate and unpredictable interactions.

The evolution of diabetes as a clinical disease dramatises the interplay between inheritance, mode of life, means of care and access to that care. Obesity is familial; diabetes is familial (Krolewski & Warram, 1994). Which genes on what chromosomes are determinative is still unknown, but there is a substantial genetic component to each. Each year, incidence rates for diabetes have been increasing in parallel with obesity and physical inactivity in the UK (Bagust *et al*, 2002), Australia (Dunstan *et al*, 2002) and the USA (Mokdad *et al*, 2003; Ogden *et al*, 2003). It is clear that the genes have not increased in frequency or mutated; the time interval is far too short. What has changed is the mode of life. Eating more and less wisely and exercising less often are not simply personal lifestyle choices. Obesity is fostered by commercial food packaging and by the 'cuisine' of fast food restaurants; indolence is promoted by television viewing (Hu *et al*, 2003) and by urban design (Macintyre *et al*, 1993): recreational facilities are in short supply and safety out of doors is not to be had in inner-city neighbourhoods, where obesity is endemic.

Indeed, the impact of the environment on the likelihood of developing diabetes may begin *in utero*. Adult offspring of mothers with Type 1 diabetes (as opposed to the offspring of fathers with Type 1) are more likely to show impaired glucose tolerance and defective insulin secretory response, probably attributable to *in utero* exposure (Sobngwi *et al*, 2003). Further support of this hypothesis is provided by Stride *et al* (2002) and Klupa *et al* (2002), who report that clinical symptoms in patients with maturity-onset diabetes of the young (a monogenic disorder) become evident at an earlier age if the mother was diabetic during pregnancy.

It is not only that diabetes is more common; diabetes has become a different disease. Medical progress has transformed non-insulin-dependent diabetes mellitus

from acute disease with death from coma and infection in young or middle adulthood to chronic disease with death postponed to senior years. The relevant genes have not changed, although their population distribution may well have, but insulin, antibiotics, renal dialysis and transplantation, antihypertensive drugs, vascular surgery and statins have prolonged survival at the cost of ocular, renal and cardiovascular complications. 'Epidemics' of diabetes continue to occur among Polynesians, native Americans and Aboriginal Australians as their lifestyles 'modernise' (Eisenberg, 1999). In the words of James Neel (1962):

'Genes and combinations of genes which were at one time an asset may in the face of environmental change become a liability.'

Nature and nurture stand in reciprocity, not opposition. Offspring inherit, along with their parents' genes, their parents, their peers and the places they inhabit. West & King (1987) have coined the term 'ontogenetic niche' to emphasise that organisms develop within an ecological and social setting that, like their genes, they share with their parents. It helps us to recognise that neighbourhood and neighbours matter, along with parents and siblings. The ontogenetic niche is a legacy that guides development, which is a crucial link between parents and offspring, an envelope of life changes. Replacing the rhetorical contrast 'nature versus nurture' with 'nature, niche and nurture' emphasises the conjunctions rather than the oppositions that shape the developmental trajectory.

Of course, there are limiting cases at either extreme. There are chromosomal malformations incompatible with foetal viability; there are environments lethal to every genome. But, in most clinical circumstances, the gene effects that we identify have been modified by the environments the organism has encountered; the environmental effects that we see are dependent on the genomes upon which they have acted.

Geneticists commonly employ a measure termed 'heritability' to identify the genetic contribution to a trait of interest. Its formalisms disregard variance arising from genotype–environment interactions, from assortative mating and from interactions between genes (i.e. different loci do not always act in additive fashion). Beyond matters of methodology, research on humans is constricted by the limited range of environments to which given populations have been exposed (in contrast to agricultural research where soil, temperature,

\*Modified from a paper presented at a conference in honour of Professor Julian Leff at the Institute of Psychiatry, London, 29 April 2003.

sunlight, irrigation, fertiliser and plant genotype can be modified systematically; Cavalli-Sforza & Bodmer, 1971). Estimates of heritability reflect no more than the findings on a specified population sampled in a given geographical range during a particular historical era. Rather than being a statistic applicable to all populations at all times, heritability estimates are context-bound and may be higher or lower (or perhaps even unmeasurable) in other populations, in other places, at other times. When phenocopies abound, heritability will be low or unmeasurable (Childs & Scriver, 1986). The epidemiology of rickets provides an instructive example.

Rickets was endemic in the USA in the 1920s. The discovery of vitamin D (McCollum *et al*, 1922) and the provision of D-enriched milk resulted in a dramatic decrease in the prevalence of rickets. Thus, Albright *et al* (1937) first reported D-resistant rickets in 1937, the genetic signals previously having been unrecognisable amid the environmental noise resulting from phenocopies. As improved living conditions in industrialised countries removed exogenous causes, the heritability of rickets increased – from undetectable levels towards a detectable one! Yet, exogenous rickets persists, albeit at a low rate, among such populations as Muslim women, who continue to cover almost all their skin surfaces with clothing after moving to countries in the Northern hemisphere where there is less ambient sunlight (Holick, 2001), and housebound elderly patients in Boston and Edmonton during winter months when atmospheric attenuation of ultraviolet radiation in the 290–315 nm band limits D-3 synthesis in the skin (Webb *et al*, 1988).

Very different phenotypes can arise from identical genomes, a phenomenon known as polyphenism; that is, the occurrence of several distinct phenotypes in a given species. Each phenotype develops facultatively depending upon cues from the internal and external environment. With changes in diet and season, dimorphic oak caterpillars express phenotypes so distinct that the two forms were originally classified as separate species. The difference between continuous phenotypic variation and discrete polyphenism is a complex underlying regulatory mechanism that controls a fork between divergent pathways.

The expression of a polyphenism begins when [extrinsic] signals are transduced into a developmental switch governed by the interplay of

hormone secretion, hormone titre, sensitivity threshold to the hormone, timing of the hormone-sensitive period, and specific cellular response to hormones' (Evans & Wheeler, 2001).

Female honeybee larvae differentiate into queens or workers with profound morphological differences despite identical genomes. Larvae that will become queens are reared in large vertically oriented brood cells. Queens are fed 'royal jelly' by nurse bees, but there is no unique 'royal' ingredient (Brouwers *et al*, 1987). What seems to matter are the large differences in the frequency, amount and composition of feedings for queens. Genetically governed programmes add their own effects downstream.

The developmental switch depends not on genomic differences between queens and workers but on the differential expression of entire suites of genes. Distinct developmental differences in titres of insect terpenoid juvenile hormone and ecdysone become manifest as the growth rate of queens continues to outpace that of workers (Hartfelder & Engels, 1998; Evans & Wheeler, 2000). The ultimate phenotypic outcomes are morphologically, reproductively and behaviourally distinct castes. Interplay between genome and socially organised behaviour is exquisitely adapted to the local environment. Plentiful nutrition (or too little of it) induces polyphenisms in bees and oak caterpillars, as do day length and humidity in aphids and butterflies, and population density and predator presence in other arthropods (Evans & Wheeler, 2001).

Is polyphenism relevant to human development? Charles Scriver (2002) applies the term to clinical situations in which phenotypes differ strikingly despite genetic identity. Consider two 5-year-old children, each with two mutant genes for phenylalanine hydroxylase (PAH). The patient whose genotype has gone unrecognised manifests microcephaly, severe mental deficiency, seizures and psychotic behaviour. The child identified by metabolic screening in the newborn nursery and kept on a low phenylalanine diet from the first week of life is within normal range. Both carry two copies of mutant autosomal recessive genes, but their phenotypes are extraordinarily different. Comparable 'polyphenisms' can be seen when congenital hypothyroidism, galactosaemia or homocystinuria are detected by neonatal screening programmes and are managed appropriately. Despite genotypic identity, phenotypic outcome in

untreated and treated cases is as night is to day.

The relationship between genotype and phenotype is complex, even in Mendelian disorders such as phenylketonuria. More than 400 different mutations have been identified in the PAH gene (deletions, insertions, splicing defects, missense and nonsense mutations). Most phenylketonurics are compound heterozygotes, having inherited different mutations from each parent. The principal determinant of the phenotype in what is unequivocally a genetic disorder is the social environment: namely, access to metabolic control through diet, the age at which it is achieved and the degree of control attained (National Institutes of Health, 2000).

How is social experience transmuted into development? There is a two-way traffic between genes and behaviour. In rats, maternal licking, grooming and nursing behaviour (LGN) shapes endocrine and behavioural stress responses in offspring (Francis *et al*, 1999). Adult offspring of high-LGN dams are less fearful and show diminished hypothalamic–pituitary–adrenal responses to stress. The female pups of high-LGN dams become high-LGN dams themselves, suggesting genes at work. However, when female pups born to low-LGN dams are cross-fostered to high-LGN dams, they too become high-LGN dams. Maternal behaviour has been transmitted across generations by non-genomic means – if you will, by 'culture'. How does that happen? Maternal care regulates gene expression in brain regions controlling stress responses. Pups exposed to high-LGN display increased hippocampal glucocorticoid receptor mRNA expression, higher central benzodiazepine receptor levels in the amygdala and lower corticotrophin-releasing factor mRNA in the paraventricular nucleus of the hypothalamus. Social experience alters gene expression for the long term.

Thus, I am a celebrant: social psychiatry is not only alive and well, but it has a bright future precisely because of genomics. As haplotype analysis disaggregates relatively homogeneous biological entities from the chaotic clinical syndromes in DSM-IV (American Psychiatric Association, 1994) and ICD-9 (World Health Organization, 1978), the task of social psychiatry will be simpler. Just as environmental 'noise' reduction in clinical rickets through vitamin D enrichment made it easier to detect the genetic 'signal', reducing

the genetic 'noise' in what is now called 'schizophrenia' will make it easier to detect the psychosocial protective and provocative factors decisive for schizophrenic syndrome X, but not for schizophrenic syndrome Y.

Genes set the boundaries of the possible; environments parse out the actual.

## DECLARATION OF INTEREST

None.

## REFERENCES

- Albright, F., Butler, A. M. & Bloomberg, E. (1937)** Rickets resistant to vitamin D therapy. *American Journal of Diseases of Children*, **54**, 529–347.
- American Psychiatric Association (1994)** *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). Washington, DC: APA.
- Bagust, A., Hopkinson, P., Maslove, L., et al (2002)** The projected health care burden of Type II diabetes in the U.K. from 2000–2060. *Diabetic Medicine*, **19**(suppl. 4), 1–5.
- Brouwers, E. V. M., Ebert, R. & Beetsma, J. (1987)** Behavioural and physiological aspects of nurse bees in relation to the composition of larval food during caste differentiation in the honeybee. *Journal of Apicultural Research*, **26**, 11–23.
- Cavalli-Sforza, L. L. & Bodmer, W. F. (1971)** *The Genetics of Human Populations*. San Francisco: W. H. Freeman.
- Childs, B. & Scriver, C. R. (1986)** Age at onset and causes of disease. *Perspectives in Biology and Medicine*, **29**, 437–460.
- Collins, F. S., Morgan, M. & Patrinos, A. (2003)** The Human Genome Project: lessons from large-scale biology. *Science*, **300**, 286–290.
- Dunstan, D., Zimmet, P., Welborn, T., et al (2002)** The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes and Obesity Lifestyle Study. *Diabetic Care*, **25**, 829–834.
- Eisenberg, L. (1999)** Does social medicine still matter in an era of molecular medicine? *Journal of Urban Health*, **76**, 164–175.
- Evans, J. D. & Wheeler, D. E. (2000)** Expression profiles during honey bee caste determination. *Genome Biology*, **2**(1); <http://genomebiology.com/1000/2/1/research/0001>.
- & — (2001)** Gene expression and the evolution of polyphenisms. *BioEssays*, **23**, 62–68.
- Francis, R., DiOrio, J., Li, U. D., et al (1999)** Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*, **268**, 1155–1158.
- Hartfelder, K. & Engels, W. (1998)** Social insect polymorphism: hormonal regulation of plasticity in development and reproduction in the honeybee. *Current Topics in Developmental Biology*, **40**, 45–77.
- Holick, M. F. (2001)** Sunlight dilemma: risk of skin cancer or bone disease and muscle weakness. *Lancet*, **357**, 4–5.
- Hu, F. B., Li, T. Y., Colditz, G. A., et al (2003)** Television watching and other sedentary behavior in relation to risk of obesity and Type 2 diabetes mellitus in women. *Journal of the American Medical Association*, **289**, 1789–1791.
- Klupa, T., Warram, J. H., Antonellis, A., et al (2002)** Determinants of the development of diabetes (maturity-onset diabetes of the young) in carriers of HNF-1 $\alpha$  mutations (evidence for parent-of-origin effect). *Diabetes Care*, **25**, 2292–2301.
- Krolewski, A. S. & Warram, J. H. (1994)** Epidemiology of late complications of diabetes. In *Joslin's Diabetes Mellitus* (13th edn) (eds C. R. Kahn & G. C. Weir), pp. 605–619. Philadelphia: Lea & Febiger.
- Macintyre, S., Maciver, S. & Sooman, A. (1993)** Area, class and health: should we be focusing on places or people? *Journal of Social Policy*, **22**, 213–234.
- McCollum, E. V., Simmons, N., Becker, J. E., et al (1922)** Studies on experimental rickets, XXI: an experimental demonstration of existence of a vitamin which promotes calcium deposition. *Journal of Biological Chemistry*, **53**, 293–321.
- Mokdad, A., Ford, E., Bowman, E., et al (2003)** Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *Journal of the American Medical Association*, **289**, 76–79.
- National Institutes of Health (2000)** Phenylketonuria (PKU): screening and management. *NIH Consensus Statement 2000 October 16–18*, **17**(3), 1–133.
- Neel, J. V. (1962)** Diabetes mellitus: a thrifty genotype rendered detrimental by "progress"? *American Journal of Human Genetics*, **14**, 353–362.
- Ogden, C. L., Flegal, K. M., Carroll, M. D., et al (2003)** Prevalence and trend in overweight among US children and adolescents 1999–2000. *Journal of the American Medical Association*, **288**, 1728–1732.
- Scriver, C. (2002)** Why mutation analysis does not always predict clinical consequences. *Journal of Pediatrics*, **140**, 502–506.
- Sobngwi, E., Budou, P., Mauvis-Jarvis, F., et al (2003)** Effect of a diabetic environment *in utero* on predisposition to Type II diabetes. *Lancet*, **361**, 1861–1865.
- Stride, A., Shepherd, M., Frayling, T. M., et al (2002)** Intrauterine hyperglycemia is associated with an earlier diagnosis of diabetes in HNF-1 $\alpha$  gene mutation carriers. *Diabetes Care*, **25**, 2287–2291.
- Watson, J. D. & Crick, F. H. C. (1953)** Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature*, **171**, 737–738.
- Webb, A. R., Kline, L. & Holick, M. F. (1988)** Influence of season and latitude on the cutaneous synthesis of Vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote Vitamin D3 synthesis in human skin. *Journal of Clinical Endocrinology and Metabolism*, **67**, 373–378.
- West, M. J. & King, A. P. (1987)** Settling nature and nurture into an ontogenetic niche. *Developmental Psychobiology*, **20**, 549–562.
- World Health Organization (1978)** *Ninth Revision of the International Classification of Diseases and Related Health Problems* (ICD-9). Geneva: WHO.

LEON EISENBERG, MD, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115-6019, USA.  
E-mail: Leon.Eisenberg@HMS.Harvard.edu

(First received 10 July 2003, accepted 30 July 2003)