



Commentary

## The Interpretation of Genetic Data - Considering the Effect of Changes to Gene Conformation -- If the Facts Don't Support the Theory, Change the Theory – How Does This Contribute to Understanding Diabetes?

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### Abstract

The theory that genetic change – the 'one gene one pathology' theory - is responsible for a particular medical condition is no longer sustainable. There is widespread recognition that the vast majority of medical conditions are multi-systemic, multi-pathological and polygenomic. This observation raises fundamental issues about the prevailing biomedical paradigm which is based upon the premise that a single biochemical marker can be an accurate determinant for a particular condition or that a single drug can be an effective treatment. The prevailing biomedical paradigm is complicated by a number of observations e.g. genetic mutations may be reversed by lifestyle changes, the brain regulates the autonomic nervous system and physiological systems, stress experienced through the senses influences brain function and the stable regulated function of the autonomic nervous system, biochemical changes are unable to explain the coherent function of networks of organs/physiological systems i.e. how these organ networks function in a coherent manner, or that many of the genes have no known or explained function.

In this short paper the author reviews the issues and makes a number of observations, in particular (i) that the brain functions as a neuroregulator which uses a biophysical mechanism to regulate the body's complex function, (ii) some genes are considered by geneticists to have no apparent function because they have not considered the possibility that these non-coding components of our DNA influence gene conformation and/or morphology (shape) and hence the subsequent expression of key proteins i.e. it is the physical and/or stereo-spatial shape of the genes and their resultant energetics which is most significant.

### Keywords

Non-coding DNA; Autonomic nervous system; Physiological systems; Neuroregulation; Genetic expression; Gene editing

### Commentary

Jenner's observation that milkmaids exposed to cowpox did not contract smallpox was immensely significant, not just for the medical significance of the observation, but for its scientific significance. This

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Received: October 10, 2017 Accepted: November 06, 2017 Published: November 14, 2017

was the first recorded incidence (actually it wasn't the first, but it is a good starting point) whereby the genetic change from one virus altered genetic predisposition to another virus i.e. that by changing genetic structure with the cowpox virus this protects against the smallpox virus. Accordingly, there is a need to better understand these phenomena and explain how the genetic change from one virus can confer immunity against another similar virus. Moreover if such a concept could apply to diseases which have genetic origins could this lead to a better understanding of how pathologies develop which influence the body's function?

Sanborn et al. [1] identified how changes to the 3D structure of the genome influence or are otherwise associated with the onset of complex genetic diseases. They illustrated that extremely minor single-nucleotide modifications of 'junk' DNA can influence the folding of significant portions of the genome e.g. the formation of genetic loops, which influence gene expression. Whalen, Truty and Pollard [2] reported how the complex 3D structure of chromatin can bring remote regions of DNA in close proximity. Kim et al. [3] reported how methylation influences, how chromosomes compact and how such mechanisms are organised influences gene expression. This initial evidence suggests that gene conformation is significant.

To continue, gene editing techniques [4] provide us with the opportunity to splice a particular adduct into our DNA i.e. to remove an unwanted genetic component and replace it with another. This would be the ideal mechanism to treat genetic diseases however the issue is complicated because there are very few cases where the one gene hypothesis applies e.g. Huntington's disease, sickle cell disease, and Duchenne muscular dystrophy. Nevertheless if we can successfully deploy such techniques it could be possible to alleviate all medical conditions which have fundamentally genetic origins. In principle this should be 100% successful, if the assumption that a particular single gene is responsible for a particular medical condition is accurate (for example ca 40% of patients with familial hypertrophic cardiomyopathy (HCM) have a mutation in the *MYBPC3* gene on chromosome 11 [5]), and if the technique can be specific to the task, however to date the success rate for such techniques remains relatively low [6,7]. Moreover it remains to be seen whether, following treatment, the patient makes a full recovery or whether their recovery is only a partial recovery i.e. that they remain in relatively poor health; and/or whether the effectiveness of gene editing techniques can be improved, particular so as an instrument to ameliorate the effect of genetically inherited point defects. For example 42 of the 58 embryos studied by Ma & co-workers did not carry the HCM mutation (in the *MYBPC3* gene) and the Crispr/Cas9 mechanism introduced undesirable genetic abnormalities.

Gene editing techniques may overlook the complex nature of the body's function, in particular how each person is genetically different [8] which must therefore influence our ability to express particular proteins and hence our susceptibility and exposure to different pathogens – viruses, virus-like particles, bacteria, etc - thereby explaining why there is a reaction by a minority of children to particular vaccines. Indeed, could it be possible that such gene editing techniques may inadvertently worsen the health of those treated? This could be expected to be so, at least in some cases, if gene editing failed to take into account how the brain regulates the body's function.

Most medical conditions comprise a spectrum of pathological coordinates which arise from weight, age, stress (which is experienced through the senses), and exposure to viruses and environmental toxins. They can be genetic and/or phenotypic (see Note 1). An estimated 5-10% of medical conditions are currently considered to have a genetic basis [9-12] i.e. an estimated 90-95% of medical conditions are due to phenotype (the influence of lifestyle and the environment and upon which modern medicine is based); however it is increasingly recognised that most medical conditions are polygenomic, multi-pathological and multi-systemic i.e. (i) most medical conditions have a complex range of genetic correlates - the mono-genetic, monopathological model is inadequate; (ii) the conditions invariably comprise both genetic and phenotypic correlates - genotype and phenotype are coexistent [13]; (iii) the conditions are expressed as a complex range of pathological processes; (iv) the pathological processes can occur in a wide range of organs throughout the body - which function in different physiological systems.

### Note 1

In this article the term 'phenotype' is used to describe non-genetic, lifestyle-related pathologies.

That the brain regulates the autonomic nervous system and physiological systems [14-16] is immensely significant. This highlights the biodynamic nature of how the brain regulates the body's function, in particular the function of the visceral organs i.e. that pathological onset is the consequence of the failure of the brain to regulate the coherent function of the organ networks; and how biochemical change at the visceral level alters brain function. This explains how for example beta-blockers slow heart beat and result in weight gain [17] or how psychotropic drugs introduced through the digestive system i.e. at the visceral level, subsequently influence brain function [18].

Furthermore initial research has illustrated that emergent non-drug therapeutic modalities, based upon the understanding that the brain regulates the function of the autonomic nervous system and physiological systems, which act upon this neural mechanism may have a 75-95% level of effectiveness [19,20].

Venter JC led one of the teams which were considered to have decoded our DNA. Significantly he commented that despite having deciphered the chemical structure of DNA (actually this has never been fully completed, specific parts of our DNA have not yet been decoded [21]) this had not led to an in-depth understanding of how our DNA works. He described the genome as 'having identified the parts list and of needing the operating manual' [22] i.e. understanding of how the brain regulates the autonomic nervous system and physiological systems. This article suggests that Grakov's Strannik software technology may, at least to some extent, be 'the operating manual' sought by Venter [23]. The issue is increasingly exacerbated by numerous observations which question the validity of the 'parts list' hypothesis i.e. 'we have the parts list, now we can understand how the body functions' e.g.

Hutchison and Venter [24] synthesised a bacterial genome and found that ca 30-40% of identified genes - non-coding DNA - cannot be ascribed to any known function. Rizvi & Raza [25] report how telomere length is associated with aging and the onset of age-related diseases i.e. pathological onset shortens the length of telomeres [26], however other researchers have illustrated that improved diet and lifestyle can reduce the rate of attrition and perhaps lengthen the telomeres [27]. In addition, (i) genes in humans often

do not function in the same way in animals [28]. If so, what is the mechanism to explain this observation? How can this be explained by the current genetic paradigm? (ii) Over 40 genetic mutations are associated with the onset and progression of type 2 diabetes [29] and collectively influence the expression of insulin in response to levels of carbohydrates, fats or proteins although such genetic changes are often reversible if the patient improves their lifestyle and diet [30]. (iii) Different racial subtypes have differing spectrum of genes which function in a coherent manner to express pre-pro-insulin [31,32] i.e. the genetic expression of a protein is influenced by genetic point defects but also by epigenetic effects which influence gene structure by methylation and other processes. Accordingly, it is necessary to consider not just the chemical structure of the genes, which is significant, but also that the physical/spatial orientation of DNA and gene conformation [33] has a significant effect; therefore any factors which influence gene profile e.g. viruses [34,35] or virus-like vectors and/or particles [36-48] which incorporate their vRNA into our DNA and/or factors which adversely alter our DNA; must inevitably influence, to a greater or lesser extent, the energetics of the genes and thereby increase or decrease the ability to express particular proteins e.g. the insulin precursor and the prevailing levels of insulin [49] and/or stimulate the function of antibodies [50] which adversely influence beta-cell function. (iv) The genetic expression of proteins must be influenced, at least to some extent, by the prevailing reaction conditions, in particular by acidity [51] and temperature [52] - which are neurally regulated physiological systems; and perhaps also by other physiological systems. (v) Moreover such a hypothesis considers the influence of genotype in isolation. It ignores the potential influence of phenotype (the sympathetic stress response) upon which modern medicine is based; which leads to lower levels of essential minerals, vitamins and cofactors; lower levels of the immune response (there is an immune 'response' but not an immune 'system' (See note 2)) involving T-cells and other immunochemicals in response to a particular stress or stressor [53,54]; which could facilitate predisposition to infection and/or the onset and progression of a particular viral infection and hence influence the subsequent expression of pre-pro-insulin thereby leading to the development of type 1 diabetes. (v) Yang and coworkers [55] illustrated that different protein isoforms contribute to how the different proteins function in the cell. If so, what is the mechanism which contributes to, or regulates, which protein isoforms are expressed? (vi) Diabetes can occur in people who have healthy functioning pancreas' e.g. who have had a hysterectomy.

### Note 2

The immune response is provided by an apparently uncoordinated response provided by the spleen, bone marrow, thymus, lymphatic system, tonsils, etc. There is no evidence to date that these organs work in a coherently functioning physiological 'system' but instead that the immune response arises from the coherent function of all other neurally regulated physiological systems.

Lincez et al. [49] identified that reduced expression of the MDA5 gene IFIH1 prevents autoimmune diabetes. If so, this presents the following questions: (i) was the expression of the MDA5 gene IFIH1 increased in the past, perhaps in response to a gene-altering moiety? (ii) how does this gene contribute to autoimmune diabetes? (iii) why would the reduced expression of this gene influence the autoimmune response and production of antibodies responsible for suppressing the expression of pre-pro-insulin? (iv) how does the increased or decreased expression of this the MDA5 gene IFIH1 alter the dynamic

relationship between the many genes which contribute to the expression of pre-pro-insulin?

This short paper highlights published research which illustrates the changes of gene conformation is a significant factor influencing the genetic expression of proteins. It focusses upon diabetes and presents an explanation/hypothesis which appears to be consistent with most observed phenomenae, in particular that changes of gene conformation influence the genetic expression of proteins and/or precursors; that increased intercellular acidity influences the ability of proteins to react with their receptor proteins; that the brain regulates the coherent function of the autonomic nervous system and physiological systems; that stress (both psychological and psychophysiological) influences intercellular levels of essential minerals which influence protein expression and protein reactivity; that non-coding DNA acts to alter/optimize the expression of key proteins; that altered gene conformation influences the expression of immunochemicals, immune function, and predisposition to disease i.e. that conformational changes to the structure of DNA must be considered alongside chemical changes; that the order of exposure to different gene-altering vectors is cumulative and adversely influences genetic expression of proteins; and that altered gene conformation - incurred as a result of changes to gene structure - influences the expression of proteins, spectrum of antibodies, and hence, at least in the pancreatic beta-cells, the ability to produce and/or store insulin.

#### Acknowledgements

The author acknowledges the work of many researchers who, through their work, have made this article possible; also the research of Dr Igor Gennadyevich Grakov, developer of Strannik technology; and support from Dr Syed Hasan Parvez, former head of the CNRS Neuroendocrine Unit, Paris.

#### Conflict of Interest

The author is CEO of Mimex Montague Healthcare, a company which is devoted to the future commercialisation of Strannik technology.

#### References

1. Sanborn AL, Rao SS, Huang SC, Durand NC, Huntley MH, et al. (2015) Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes. *Natl Acad Sci USA* 112: E6456–E6465.
2. Whalen S, Truty RM, Pollard KS (2016) Enhancer–promoter interactions are encoded by complex genomic signatures on looping chromatin. *Nature Genetics* 48: 488-496.
3. Yoo J, Kim H, Aksimentiev A, Ha T (2016) Direct evidence for sequence-dependent attraction between double-stranded DNA controlled by methylation. *Nat Commun* 7: 11045.
4. Ledford H (2016) CRISPR: gene editing is just the beginning. The real power of the biological tool lies in exploring how genomes work. *Nature* 531: 156-159.
5. Ma H, Marti-Gutierrez N, Sang-Wook P, Wu J, LeeY, et al. (2017) Correction of a pathogenic gene mutation in human embryos. *Nature* 548: 413-419.
6. Cavazzana-Calvo M, Thrasher A, Mavilio F (2004) The future of gene therapy. *Nature* 427: 779-781.
7. Blaese RM, Culver KW, Miller AD, Carter CS, Fleisher T, et al. (1995) T Lymphocyte-Directed Gene Therapy for ADA- SCID: Initial Trial Results After 4 Years. *Science* 270: 475-480.
8. Johnston JJ, Lewis KL, Ng D, Singh LN, Wynter J, et al. (2015) Individualized Iterative Phenotyping from Genome-Wide Analysis of Loss-of-Function Mutations. *Am J Hum Genet* 96:913-925.
9. Pilacinski S, Zozulinska-Ziolkiewicz DA (2014) Influence of lifestyle on the course of type 1 diabetes mellitus. *Arch Med Sci* 10: 124-134.
10. Umpierrez GE, Pasquel FJ (2014) Primary prevention of type 2 diabetes by lifestyle intervention in primary care setting. *Rev Clin Esp* 214: 79-82.

11. Liebhauser M, Ofner M, Mittermayer FR (2014) Successful Management of Type 2 Diabetes with Lifestyle Intervention: A Case Report. *International Journal for Vitamin and Nutrition Research* 84: 0133-0139.
12. Ewing GW, Ewing EN (2008) Neuro Regulation of the Physiological Systems by the Autonomic Nervous System – their relationship to Insulin Resistance and Metabolic Syndrome. *Biogenic Amines* 22: 208-239.
13. Ewing GW, Parvez SH (2010) The Multi-systemic Nature of Diabetes Mellitus: genotype or phenotype? *N Am J Med Sci* 2: 444-456.
14. Ewing GW, Parvez SH (2011) Mathematical Modeling the Systemic Regulation of Blood Glucose: 'a top-down' Systems Biology Approach. *Neuro Endocrine Letters* 32: 371-379.
15. Ewing GW (2015) The Framework of a Mathematical Model of the Autonomic Nervous System and Physiological Systems: Using the Neuroregulation of Blood Glucose as an Example. *J Comput Sci Syst Biol* 8: 59-73.
16. Ewing GW (2015) A comparison of the aims and objectives of the human brain project with Grakov's mathematical model of the autonomic nervous system (Strannik Technology). *Enliven: Neurol Neurotech* 1: 1-6.
17. Pischon T, Sharma AM (2001) Use of beta-blockers in obesity hypertension: potential role of weight gain. *Obes Rev* 2: 275-280.
18. Schulz P (2000) Psychotropic medication, psychiatric disorders, and higher brain functions. *Dialogues Clin Neuroscience* 2: 177-182.
19. Grakov IG, Ewing GW, Mohanlall R, Adams JK (2017) A summary or meta-analysis of data regarding the use of Strannik Virtual Scanning as a screening modality for healthcare. *Asian Journal of Pharmacy, Nursing and Medical Science* 5: 55-71.
20. Vysochin Yu (2001) Methodology and Technology of Invigoration of Different Population Orders (Consolidated 5 year Research Plan of Physical Training, Sports and Tourism State). Committee of the Russian Federation.
21. Shampo MA, Kyle RA (2011) J Craig Venter – The Human Genome Project. *Mayo Clin Proc* 86: e26-e27.
22. Blow N (2015) Decoding the Unsequenceable. *BioTechniques* 58: 52-58.
23. Ewing GW, Ewing EN (2014) Strannik Virtual Scanner Operating Manual. Mimex Montague Healthcare Limited.
24. Hutchison CA, Chuang RY, Noskov VN, Assad-Garcia N, Deerinck TJ, et al. (2016) Design and synthesis of a minimal bacterial genome. *Science* 351: aad6253.
25. Rizvi S, Raza ST, Mahdi F (2007) Telomere length variations in aging and age-related diseases. *Curr Aging Sci* 7: 161-167.
26. Shammass MA (2011) Telomeres, lifestyle, cancer, and aging. *Curr Opin Clin Nutr Metab Care* 14 : 28-34.
27. Ramunas J, Yakubov E, Brady JJ, Corbel SY, Holbrook C, et al. (2015) Transient delivery of modified mRNA encoding TERT rapidly extends telomeres in human cells. *FASEB Journal* 29: 1930-1939.
28. Cimon M, Getlin J, Maugh II TH (1998) Cancer Drugs Face Long Road From Mice to Men. *Los Angeles Times*, A.
29. McCarthy MI (2010) Genomics, type 2 diabetes, and obesity. *N Engl J Med* 363: 2339-2350.
30. Corella D, Carrasco P, Sorlí JV, Estruch R, Rico-Sanz J, et al. (2013) Mediterranean Diet Reduces the Adverse Effect of the TCF7L2-rs7903146 Polymorphism on Cardiovascular Risk Factors and Stroke Incidence. *Diabetes Care* 36: 3803-3811.
31. Qi Q, Wang X, Strizich G, Wang T (2015) Genetic Determinants of Type 2 Diabetes in Asians. *Int J Diabetol Vasc Dis Res* S1: 1-9.
32. Bodhini D, Radha V, Ghosh S, Majumder PP, Mohan V (2011) Lack of association of PTPN1 gene polymorphisms with type 2 diabetes in south Indians. *J Genet* 90: 323-326.
33. Matsuda Y, Takeuchi K, Obase K, Ito SI (2015) Spatial distribution and genetic structure of *Cenococcum geophilum* in coastal pine forests in Japan. *FEMS microbiology ecology* 91: fiv108.
34. Oikarinen S, Tauriainen S, Hober D, Lucas B, Vazeou A, et al. (2014) Virus antibody survey in different european populations indicates risk association between Coxsackievirus B1 and type 1 diabetes. *Diabetes* 63: 655-662.

35. Laitinen OH, Honkanen H, Pakkanen O, Oikarinen S, Hankaniemi MM, et al. Coxsackievirus B1(CVB1) is associated with induction of Beta-Cell autoimmunity that portends type 1 diabetes. *Diabetes* 63: 446-455.
36. Classen JB (1996) Diabetes epidemic follows hepatitis B immunization program. *NZ Med J* 109: 195.
37. Tuomilehto J, Karvonen M, Pitkaniemi J, Virtala E, Kohtamäki K, et al. (1999) Record-high incidence of Type I (insulin-dependent) diabetes mellitus in Finnish children. The Finnish childhood type I diabetes registry group. *Diabetologia* 42: 655-660.
38. Tuomilehto J, Rewers M, Reunanen A, Lounamaa P, Lounamaa R, et al. (1991) Increasing trend in type 1 (insulin-dependent) diabetes mellitus in childhood in Finland. Analysis of age, calendar time and birth cohort effects during 1965 to 1984. *Diabetologia* 34: 282-287.
39. Kelly HA, Russel MT, Jones TW, Byrne GC (1994) Dramatic increase in incidence of insulin dependent diabetes mellitus in western Australia. *Med J Aust* 161: 426-429.
40. Rewers M, LaPorte RE, Walczak M, Dmochowski K, Bogaczynska E (1987) Apparent epidemic of insulin-dependent diabetes mellitus in Midwestern Poland. *Diabetes* 36: 106-113.
41. Classen JB, Classen DC (2003) Clustering of cases of type 1 diabetes mellitus occurring 2-4 years after vaccination is consistent with clustering after infections and progression to type I diabetes mellitus in autoantibody positive individuals. *J Pediatr Endocrinol Metab* 16:495-508.
42. Pawlowski B, Gries FA (1991) Mumps vaccination and type-1 diabetes. *Deutsche Medizinische Wochenschrift* 116: 635.
43. Adler JB, Mazzotta SA, Barkin JS (1991) Pancreatitis caused by measles, mumps, and rubella vaccine. *Pancreas* 6: 489-490.
44. Dotta F, Sebastiani G (2014) Enteroviral infections and development of type 1 diabetes: The Brothers Karamazov within the CVBs. *Diabetes* 63: 384-386.
45. Boettler T, von Herrath M (2011) Protection against or triggering of type 1 diabetes? Different roles for viral infections. *Expert Rev Clin Immunol* 7: 45-53.
46. Huisman W (2000) Vaccine-induced enhancement of viral infections. *Vaccine* 27: 505-512.
47. Cohen AD, Shoenfeld Y (1996) Vaccine-induced autoimmunity. *J Autoimmunity* 9: 699-703.
48. Pozzilli P, Visalli N, Coppolino G, Classen DC, Classen JB (2000) Hepatitis B vaccine associated with an increased risk of type 1 diabetes in Italy. American Diabetes Association Meeting, San Antonio, Texas.
49. Lincez PJ, Shanina I, Horwitz MS (2015) Reduced expression of the MDA5 gene IFIH1 prevents autoimmune diabetes. *Diabetes* 64: 2184-2193.
50. Sanderson NSR, Zimmermann M, Eilinger L, Gubser C, Schaeren-Wiemers N, et al. (2017) Cocapture of cognate and bystander antigens can activate autoreactive B cells. *PNAS* 114: 734-739.
51. Ewing GW (2012) pH is a Neurally Regulated Physiological System. Increased Acidity Alters Protein Conformation and Cell Morphology and is a Significant Factor in the Onset of Diabetes and Other Common Pathologies. *The Open Systems Biology Journal* 5: 1-12.
52. Stolwijk JAJ, Hardy JD (2001) Control of Body Temperature. *Handbook of Physiology, Reactions to Environmental Agents*. John Wiley & Sons, Inc.
53. Eizirik DL, Sammeth M, Bouckenoghe T, Bottu G, Sisino G, et al. (2012) The human pancreatic islet transcriptome: expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. *PLoS Genet* 8: e1002552.
54. Lehuen A, Diana J, Zaccone P, Cooke A (2010) Immune cell crosstalk in type 1 diabetes. *Nature Reviews Immunology* 10: 501-513.
55. Yang X, Coulombe-Huntingdon J, Kang S, Sheynkman GM, Hao T, et al. (2016) Widespread Expansion of Protein Interaction Capabilities by Alternative Splicing. *Cell* 164: 805-817.

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