Published in final edited form as:

JAMA Neurol. 2013 June ; 70(6): 684–685. doi:10.1001/jamaneurol.2013.2854.

From the Genetic Code to Neuromics

Roger N. Rosenberg, MD

Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas.

IN 1968, MARSHALL NIRENBERG WON THE NOBEL Prize in Medicine for deciphering the genetic code. At the time, I was a postdoctoral fellow in his laboratory, the Laboratory of Biochemical Genetics at the National Heart and Lung Institute of the National Institutes of Health. We were working on the molecular differentiation of neuroblastoma cells and neuroblasts from dissociated mouse brain in cell culture. Enzyme activities for neurotransmitter synthesis and degradation were characterized with the degree of morphologic cellular differentiation. These experiments and others of a similar nature represented the beginning of the era of neurobiochemical genetics. Discussions in the laboratory at that time focused on the application of the genetic code and development of methods for deciphering mutations causal of neurological disease. Discussions with Nirenberg included ideas and concepts of potential brain codes for memory and learning. It was a scientifically intense, creative, and productive time for all of us in the laboratory, projecting how the nascent fields of neurogenetics and neurogenomics (neuromics) would unfold and eventually enter the clinic.

Forty-five years later, genetics, neuromics, and epigenetics have without question revolutionized our understanding of brain functions and the molecular pathogenesis of brain development, brain aging, and neurological disease. Among other significant genetic maps, “A neurologic gene map” chapter in the fourth edition of our genetics book describes scores of genetic neurological diseases, with their chromosomal locations, causal genes, mode of inheritance, and specific mutations.¹ Rapid sequencing of patient DNA is now possible to demonstrate the causal mutation in hours or days and institute therapy, where possible, quickly and accurately, and with more regularity and impressive clinical benefit. The genetic code has entered the neurological clinic, bringing clarity and precision of diagnosis and leading to therapy and disease prevention.

Another neuroscientific revolution is now just getting under way. It portends greater positive results of genetic regulation and control of neuroembryogenesis, brain development, learning, memory, brain aging, and expression of neurological diseases. Neuromics and epigenetics represent the disciplines that are directed at the interplay of the entire genome, all 3 billion nucleotides in the human haplotype, to induce neuroblast, glioblast, and microglial proliferation and differentiation to create the human brain. Furthermore,

Correspondence: Dr Rosenberg, Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9036 (roger.rosenberg@utsouthwestern.edu).

Conflict of Interest Disclosures: Dr Rosenberg’s work is funded by clinical trial research grants with Pfizer, Janssen, Baxter, and Eli Lilly Inc. He has a US patent for amyloid beta gene vaccines.

environmental stimuli constantly modulate neuronal/glial activities through changes in epigenetic expression. Progress has been incredibly rapid and this issue of *JAMA Neurology* provides original investigations and reviews that document these new advances.

The human genome was first sequenced in 2001.^{2–4} It was a remarkable achievement, and it provided the dictionary of human linear DNA sequences now waiting to be read and understood. How these static data are interpreted and used to produce a living cell, a neuroblast from another differentiated cell, and with it specific differentiated neuronal functions, is the next step. It is the next chapter in the book of codes initiated by Nirenberg in the 1960s.

In 2012, the Encyclopedia of DNA Elements (ENCODE) was published.⁵ The aim of the ENCODE was to describe all functional elements encoded in the human genome. After 9 years of investigation, 30 papers, and 1640 data sets, 147 different cell types representing 80% of the human genome's components have now been assigned at least 1 biochemical function. Yet another chapter has been added to the book of codes initiated by Nirenberg.

The epigenetic code of cellular differentiation is coming into focus including patterns of histone protein acetylation and methylation, micro RNA expression, RNA editing, and binding of sequence-specific DNA elements within introns and intergenic regions of the genome. The epigenetic molecular mechanisms of regulation of gene expression by endogenous and environmental stimuli are now being defined and expressed. The ENCODE represents a foundational data set for explaining and understanding the human genome, the genomic facts for how a neuron differentiates from a totipotent undifferentiated stem cell, and how specific genetic mutations can cause disease with a precise phenotype.

In this issue, Tsuji⁶ discusses the availability of high-throughput genome sequencing technologies in providing understanding not only of hereditary but also sporadic neurological diseases. Pittman and Hardy⁷ emphasize the remarkable advances owing to array genotyping and next-generation sequencing. Qureshi and Mehler⁸ review the emerging new data showing that epigenetic mechanisms influence brain evolution, development, gene expression, neural stem cell maintenance and differentiation, and learning and memory. The data they present are compelling, demonstrating that epigenetic mechanisms regulate structure and activity of the genome in response to intracellular and environmental cues. Akbarian et al⁹ provide an overview on age-related changes in the brain's chromatin structures and highlight potential epigenetic drug targets for cognitive decline and age-related neurodegenerative disease. De Jager and Bennett¹⁰ suggest we are at an inflection point at which gene discovery efforts are transitioning toward the functional characterization of implicated genetic variation crucial for understanding events that lead to a syndromic diagnosis for neurodegenerative diseases.

The theme issue includes seminal and exciting observations on glucocerebrosidase mutations in dementia with Lewy bodies,¹¹ *C9ORF72* hexanucleotide repeat expansions in clinical Alzheimer disease,¹² *C9ORF72* hexanucleotide repeat expansion and Guam amyotrophic lateral sclerosis–parkinsonism–dementia complex,¹³ hereditary ataxias and spastic paraplegias in Portugal,¹⁴ adult-onset acid maltase deficiency,¹⁵ progranulin

mutations as a risk factor in Alzheimer disease,¹⁶ improvement of brain magnetic resonance imaging after stem cell transplantation in metachromatic leukodystrophy,¹⁷ and how exome sequencing reveals a novel *OPA3* mutation.¹⁸ The issue concludes with a discussion of DNA amyloid- β 42 vaccination as a possible alternative immunotherapy for Alzheimer disease.¹⁹

The phrase “the best is yet to come” is used frequently for expressing optimism and hope. In the case of neuromics, epigenetics of brain functions, accurate mutational diagnosis for an increasing number of neurological diseases, and drug development directed at specific molecular targets, the best has arrived, is arriving logarithmically within recent years, and gives strong evidence that the pace for effective therapy for all categories of neurological disease will occur commensurate with knowledge of the genetic code, the genome sequence, and the epigenetic program of gene regulation. This theme issue reflects great optimism based on facts, not hope.

Jim Watson said he never saw Francis Crick in a modest mood.²⁰ Now it should be said that all who read this issue should not be in a modest mood. What has transpired in neurogenetics/neuromics since the publication²¹ of the genetic code in 1965 is nothing short of miraculous!

REFERENCES

1. Rosenberg RN, Harding A, Delgado-Escueta AV, Iannaccone ST. A neurologic gene map In: Rosenberg RN, DiMauro S, Paulson HL, Ptáček L, Nestler EJ, eds. *The Molecular and Genetic Basis of Neurologic and Psychiatric Disease*. 4th Ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2008:855–867.
2. Lander ES, Linton LM, Birren B, et al.; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome [published correction appears in *Nature*. 2001;411(6838):720]. *Nature*. 2001;409(6822): 860–921. [PubMed: 11237011]
3. International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. *Nature*. 2004;431(7011):931–945. [PubMed: 15496913]
4. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science*. 2001;291(5507):1304–1351. [PubMed: 11181995]
5. Maher B. ENCODE: the human encyclopaedia. *Nature*. 2012;489(7414):46–48. [PubMed: 22962707]
6. Tsuji S. The neurogenomics view of neurological diseases [published online April 9, 2013]. *JAMA Neurol* 2013;70(6):689–694. [PubMed: 23571861]
7. Pittman A, Hardy J. Genetic analysis in neurology: the next 10 years [published online April 9, 2013]. *JAMA Neurol* 2013;70(6):696–702. [PubMed: 23571731]
8. Qureshi IA, Mehler MF. Understanding neurological disease mechanisms in the era of epigenetics [published online April 9, 2013]. *JAMA Neurol* 2013;70 (6):703–710. [PubMed: 23571666]
9. Akbarian S, Beeri MS, Haroutunian V. Epigenetic determinants of healthy and diseased brain aging and cognition [published online April 9, 2013]. *JAMA Neurol* 2013;70(6):711–718. [PubMed: 23571692]
10. De Jager PL, Bennett DA. An inflection point in gene discovery efforts for neurodegenerative diseases: from syndromic diagnoses toward endophenotypes and the epigenome [published online April 9, 2013]. *JAMA Neurol* 2013;70(6): 719–726. [PubMed: 23571780]
11. Nalls MA, Duran R, Lopez G, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies [published online April 15, 2013]. *JAMA Neurol* 2013;70(6):727–735. [PubMed: 23588557]

12. Harms M, Benitez BA, Cairns N, et al. C9ORF72 hexanucleotide repeat expansions in clinical Alzheimer disease [published online April 15, 2013]. *JAMA Neurol* 2013;70(6):736–741. [PubMed: 23588422]
13. Dombroski BA, Galasko DR, Mata IF, et al. *C9orf72* hexanucleotide repeat expansion and Guam amyotrophic lateral sclerosis–parkinsonism–dementia complex [published online April 15, 2013]. *JAMA Neurol* 2013;70(6):742–745. [PubMed: 23588498]
14. Coutinho P, Ruano L, Loureiro JL, et al. Hereditary ataxia and spastic paraplegia in Portugal: a population-based prevalence study [published online April 22, 2013]. *JAMA Neurol* 2013;70(6):746–755. [PubMed: 23609960]
15. Pascual JM, Roe CR. Systemic metabolic abnormalities in adult-onset acid maltase deficiency: beyond muscle glycogen accumulation [published online April 22, 2013]. *JAMA Neurol* 2013;70(6):756–763. [PubMed: 23609947]
16. Perry DC, Lehmann M, Yokoyama JS, et al. Progranulin mutations as a risk factor for Alzheimer disease [published online April 22, 2013]. *JAMA Neurol* 2013; 70(6):774–778. [PubMed: 23609919]
17. van Egmond ME, Pouwels PJW, Boelens J-J, et al. Improvement of white matter changes on neuroimaging modalities after stem cell transplant in metachromatic leukodystrophy [published online April 22, 2013]. *JAMA Neurol* 2013; 70(6):779–782. [PubMed: 23608771]
18. Arif B, Kumar KR, Seibler P, et al. A novel *OPA3* mutation revealed by exome sequencing: an example of reverse phenotyping [published April 29, 2013]. *JAMA Neurol* 2013;70(6):783–787. [PubMed: 23700088]
19. Rosenberg RN, Lambracht-Washington D. DNA A β 42 vaccination as possible alternative immunotherapy for Alzheimer disease [published online April 29, 2013]. *JAMA Neurol* 2013;70(6):772–773. [PubMed: 23700123]
20. Watson JD. *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*. New York, NY: Atheneum; 1968.
21. Nirenberg M, Leder P, Bernfield M, et al. RNA codewords and protein synthesis, VII: on the general nature of the RNA code. *Proc Natl Acad Sci U S A* 1965; 53(5):1161–1168. [PubMed: 5330357]