

## EDITORIAL



## Hamartoma Syndromes, Exome Sequencing, and a Protean Puzzle

John M. Opitz, M.D., and Lynn B. Jorde, Ph.D.

Gross malformations have been well known for centuries, even millennia. However, it was not until 1904 that Albrecht coined the concept of hamartoma. In 1934, the concept entered the field of developmental pathology generally in reference to tissue malformations. Hamartomata are localized overgrowths of a single tissue or combination of tissues, indigenous to the affected body part or organ, usually growing at the same rate as the normal components and causing little pain or functional impairment. They are a key finding in the Proteus syndrome, the cause of which has now been identified by Lindhurst et al.<sup>1</sup> in this issue of the *Journal*.

The Proteus syndrome appears to have been first described in American medicine by Temtamy and Rogers<sup>2</sup> in a 7-year-old boy with macrodactyly, hemihypertrophy of the right side of the body, depigmented skin patches over the trunk, and connective-tissue nevi over the dorsa of both hands, left foot, backs of elbows, and axillae. Wiedemann et al.<sup>3</sup> described four boys with a set of symptoms that the investigators called the “proteus” syndrome, consisting of progressive partial gigantism of hands or feet, pigmented nevi, hemihypertrophy, pulmonary cysts, sudden appearance of venous angiomas, and macrocephaly with hyperostosis. Severe Proteus syndrome, diagnosed as such, is a rare entity, and outright cancers in such patients are uncommon but deserve potential consideration in every patient.

An ingenious hypothesis that certain lethal mutations could survive only in a mosaic state<sup>4</sup> was confirmed previously in patients with McCune–Albright monostotic fibrous dysplasia and now has been confirmed again in the Proteus syndrome. Lindhurst et al. have elucidated the causal na-

ture of the many different hamartomata in the Proteus syndrome on the basis of the presence of a somatic activating mutation in oncogene *AKT1* and AKT phosphorylation levels in cell lines established from the lesions of their patients. Their findings will now make it possible to test the hypothesis that *AKT1* mutations cause many single or multiple hamartoma conditions and that Joseph C. Merrick (1860–1890), the “Elephant Man,” indeed had the Proteus syndrome.

The singular success of Lindhurst et al. in identifying the cause of the Proteus syndrome adds to the rapidly growing list of discoveries that have been made possible by large-scale DNA sequencing.<sup>5</sup> The authors focused on the exome, which represents the 1% of the genome that is composed of exons and therefore encodes proteins. DNA sequencing of this magnitude, which was prohibitively expensive just a few years ago, has become quite affordable after recent cost reductions of several orders of magnitude. Mutations that cause very rare genetic diseases, some of which have been intractable to traditional genetic approaches, such as linkage or association analysis, can now be pinpointed with the use of surprisingly small samples (often just a few index cases in one or two families).<sup>6</sup> Through exome sequencing, Lindhurst et al. generated billions of base pairs of sequence data. A major challenge is to manage and analyze these vast quantities of data so that genetic signals can be teased out efficiently and accurately. Several algorithms have been published within the past year to aid in identifying the small set of potentially causal variants in a genome of 3 billion base pairs.<sup>7</sup> As sequencing and analytic techniques continue to improve, it is likely that the

genetic causes of virtually all mendelian, or single-gene, disorders will be identified.

An important question is whether these new techniques can also uncover genes that contribute to common conditions, such as heart disease, common cancers, and diabetes. Genomewide association studies, in which relatively common DNA variants are compared in samples obtained from case and control subjects, have revealed hundreds of variants associated with common diseases, but these variants still account for a minor proportion of the total genetic causation of most common complex conditions.<sup>8</sup> Combinations of rare DNA variants, which can be effectively ascertained only by direct sequencing, may account for some of this “missing heritability.”<sup>9</sup> Because many causal variants may lie outside the exome,<sup>10</sup> sequencing of the entire genome may be required. Fortunately, even the cost of whole-genome sequencing is declining rapidly.

As our capacity to obtain and analyze DNA sequences continues to increase, solutions to riddles such as the Proteus syndrome may become commonplace. This promises a wellspring of new and exciting discoveries about the basic causes of human disease, and it will aid in accurate diagnoses and effective treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Departments of Pediatrics (Medical Genetics), Pathology, and Obstetrics and Gynecology (J.M.O.) and the Department of Human Genetics (J.M.O., L.B.J.), University of Utah, Salt Lake City.

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