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COMMENTARY

Cultural differences define diagnosis and genomic medicine practice: implications for undiagnosed diseases program in China

Xiaohong Duan (✉)[1], Thomas Markello[2], David Adams[2], Camilo Toro[2], Cynthia Tifft[2], William A. Gahl[2], Cornelius F. Boerkoel[2]

[1]*Department of Oral Biology, Clinic of Oral Rare Diseases and Genetic Diseases, School of Stomatology, the Fourth Military Medical University, Xi'an 710032, China;* [2]*NIH Undiagnosed Diseases Program, NIH Office of Rare Diseases Research and NHGRI, Bethesda, MD, USA*

Abstract **Despite the current acceleration and increasing leadership of Chinese genetics research, genetics and its clinical application have largely been imported to China from the Occident. Neither genetics nor the scientific reductionism underpinning its clinical application is integral to the traditional Chinese worldview. Given that disease concepts and their incumbent diagnoses are historically derived and culturally meaningful, we hypothesize that the cultural expectations of genetic diagnoses and medical genetics practice differ between the Occident and China. Specifically, we suggest that an undiagnosed diseases program in China will differ from the recently established Undiagnosed Diseases Program at the United States National Institutes of Health; a culturally sensitive concept will integrate traditional Chinese understanding of disease with the scientific reductionism of Occidental medicine.**

Keywords genetics; cultural differences; undiagnosed diseases program

Introduction

A fundamental need of human cultures is to understand the problems and processes that adversely affect health and wellbeing. Over the history of mankind, explanations have ranged from the mystical to the material, from the ethereal to the rationale, and from the uncontrollable to the manipulable. The particulars of the explanations are reflected by the diagnosis or name given to a disease; in other words, a diagnosis is a culturally or socially appropriate disease concept.

History of Occidental genetics

Through the Enlightenment, material and rational explanations assumed increasingly prominent roles in Occidental societies and now form the basis for pursuit of Occidental medical science. Medical scientific reductionism, which is the diminution of a complex event such as disease to its component parts, proposes that disease is the summation of the molecular and mechanistic properties of the components, whereas holism proposes that disease is not reducible to the sum of the properties of its individual molecular and mechanistic components [1]. In practice the reductionism of Occidental clinical medicine translates into a focus on the single factor most responsible, an emphasis on illness as a failure of homeostasis, a unidimensional risk modification for disease, and a treatment of individual problems additively [2].

Recently the molecular biology revolution, completion of a draft of the human genome, and the development of genomic technologies has led to a growing desire to achieve molecular genetic diagnoses, i.e., personalized or precision medicine. The entry of genetics into Occidental medicine is often traced to the detailed descriptions of inherited human traits in the 1600s, and the understanding of genetics and inheritance that developed during the seventeenth and eighteenth centuries then provided many of the concepts that would later form the basis of the modern medical genetics [3]. Of note, in 1753 Pierre Louis de Maupertius proposed equal contribution of

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Correspondence: xhduan@fmmu.edu.cn

both sexes to inheritance and the concept of a heritable mutation; in 1794 Erasmus Darwin proposed the progressive evolution of life; in 1859 Charles Darwin postulated evolution by natural selection; during 1865 to 1866 Gregor Mendel proposed particulate inheritance following clear mathematical ratios, and in 1883 August Weismann showed the continuity of the germ-plasm and disproved inheritance of acquired traits. By the early 1800s, Joseph Adams had classified several human disorders according to inheritance patterns with such clarity that he is often considered the founder of medical genetics [4]; however, a clear connection of these patterns to the principles of Mendelian genetics waited until the collaborative work of William Bateson and Archibald Garrod in the early 20th century [5,6]. The discipline of human genetics developed over the ensuing years and by the late 1950s medical genetics as a clinical pursuit came into its own [3].

The rapid adoption of genetic ideology in Occidental society reflects not only its tradition of scientific reductionism but also its sense of kinship. Occidental indigenous systems of kinship and of biomedical systems of representation are derived from a common stock of interpretations of the social and natural worlds [7]. The understanding of kinship and inheritance predated the work of Gregor Mendel and were likely foundational to Mendel's discoveries. Within Occidental kinship systems, the degrees of relatedness correspond to biological relatedness and do not distinguish between different lines of decent, i.e., kinship relations are accepted as bilateral and mirror Mendelian concepts of inheritance [8,9].

Although initially misunderstood and used to justify eugenics and discrimination, genetics has gradually defined fundamental principles within Occidental thought [10,11]. Combined with the dominant Occidental view of kinship, these principles provide a context for understanding and diagnosing inherited diseases, and when integrated with scientific reductionism, they lead to the quest for a molecular and mechanistic diagnosis within one's genetic composition. By extension, this logic underlies the genomic focus of personalized or precision medicine concepts in the Occident.

Diagnosis and the NIH Undiagnosed Diseases Program (UDP)

As established in 2008, the purpose of the NIH UDP is to provide answers to patients with conditions that have eluded diagnosis and to advance medical knowledge about rare and common diseases [12]. As an embodiment of rationalism's application of scientific methodology to medicine, the NIH UDP is founded on the principles that illness is maladaptation to an ecological niche and that many genetic causes of maladaptation are likely to be identifiable by sequencing the exome or genome. In this context, common diseases arise by abrupt changes in the ecological niche that expose genetic variants underlying susceptibility and resistance to the ecological change, whereas rare diseases, which affect ~8% of the population, likely arise from strong genetic and epigenetic mutations causing maladaptation within a stable ecological niche [10]. It is the latter disorders refractory to diagnosis that are the focus of the NIH UDP.

The raison d'être of the NIH UDP has been the integration of thorough disease characterization with genomic technologies such as exome sequencing. The NIH UDP is therefore emblematic of the Occidental pursuit of diagnoses within the strictures of scientific reductionism, particularly genetics. In other words, the intrinsic cultural need for a rational molecular diagnosis justifies the existence of and expenditures for a program focused on diagnosis alone.

Implementation of the UDP genetic approach to diagnosis has identified several challenges. First, efficient use of genomic technologies for identification of novel disorders requires the participation of a family because the family is the origin of the genetic changes underlying the disease. Second, identification of novel, rare and unique mutations in an individual with an undiagnosed disease has required generation of a paradigm for proof of causation because the traditional methods of achieving association is not attainable, i.e., association via identification in multiple individuals with mutations in the same gene. Nonetheless, despite these obstacles, the UDP has been able to provide material and rational explanations, i.e., diagnoses, to 20%–30% of the individuals evaluated.

Relevance of Occidental diagnoses to other cultures

The question then is whether diagnoses such as those derived from the NIH UDP have social value in societies that did not come through the crucible of the Enlightenment and do not fully share Occidental concepts of kinship. This is of particular relevance since institutions in other countries have sought the advice of the NIH UDP for implementing similar programs even though their societies have not entirely adopted Occidental post-Enlightenment thought as their dominant worldview.

An example of such a country is China. Traditionally Chinese medicine has focused on explanations of symptoms in terms of regional climates and imbalances within individual constitutions. Additionally traditional Chinese society has had a different view of kinship than that predominant in the Occident. Therefore, since disease concepts are historically situated, socially defined and culturally meaningful, we hypothesize that the reductionist genetic diagnoses characteristic of the scientific reductionism of the Occident are less relevant in Chinese society. To address this, we focus our subsequent discussion on genetics and medical diagnosis in Chinese society.

History of medical genetics in China

The earliest genetic studies in China can be traced back to the 1920s when foreign-trained Chinese researchers returned to China and disseminated principles of genetics including the theories of T. H. Morgan. Genetic courses were developed in the early 1920s at National South-east University in China and used textbooks such as *Genetics in Relation to Agriculture* (EB Babcock and RE Clausen) and *Mechanism of Mendelian Heredity* (TH Morgan). Concurrently genetic studies of *Drosophila* (fruit flies), *Harmonia* (ladybug), *Oryza* (rice) and *Triticum* (wheat) progressed rapidly. The first Chinese medical genetics report, concerning the inheritance of tongue upfolding, appeared in 1948 [13].

Despite the influence of Lysenko's thinking and the turbulent years of the mid-twentieth century, Chinese medical genetics and human population genetics continued to develop. Three years after the report of Down syndrome by Dr. Jérôme Lejeune in 1959 [14], Klinefetter syndrome was reported from China [15]. In 1963, a Chinese population genetic study reported sex-linked inheritance and a prevalence of 7.5% and 0.92% for color blindness among male and female adolescents respectively [16]. 1964 brought the first report of a biochemical disorder, glucose-6-phosphate dehydrogenase deficiency [17] and 1965 brought a detailed description of Chinese human chromosomes [18]. The chorionic villus sampling for prenatal diagnosis was reported from China in 1975 [19], six years prior to its advent in the Occident [20]. In 1975 several reports defined the prevalence and heritability of endemic cretinism (or congenital hypothyroidism) in Dabie Mountain region of Anhui province and the prevalence of 115 monogenic diseases, chromosomal disorders and rare diseases appeared [21].

Consequences of increased Chinese investment in genetics research

As the "Cultural Revolution" receded, Chinese medical genetics began to advance more quickly. By 1977, a long-term plan was agreed upon to make Chinese medical genetics research internationally recognized [22]. This laid the foundation for the Chinese Human Genome Project (CHGP), which allowed Chinese researchers to contribute about 1% of the total human genome sequence to the international Human Genome Project [23]. The Chinese genomics community is now contributing 200 full human genomes to the 1000-Genomes Project, and is increasingly influential internationally as reflected by the number of genetics and genomics publications from Chinese institutions (Fig. 1).

With this genetic and basic science research platform, China has an unprecedented opportunity to make a contribution to our understanding of both rare and common diseases. Recognizing this, Chinese geneticists and governmental authorities proposed a long-term plan for supporting genetic research into rare diseases in 2010 [24]. Addressing the need for diagnosis and care of affected Chinese individuals will both increase our understanding of the characteristics of known disorders and define disorders currently undescribed in the Occident [25].

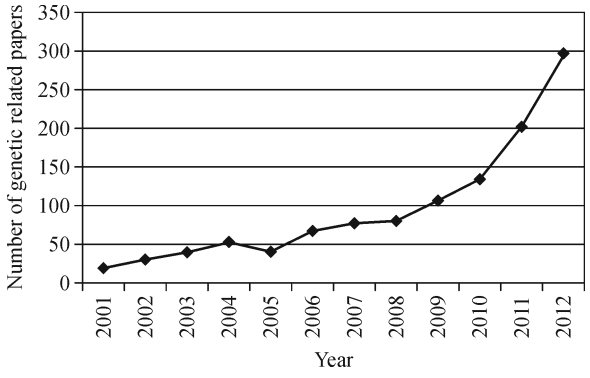

Fig. 1 Annual number of articles from Chinese institutions that were published in the ten journals with the highest 5-year impact factors in the discipline of genetics and heredity (2011 JCR data).

Approximately 93.3% of Chinese are Han and most of the remaining 6.7% are from the 55 official minorities, who reside predominantly in western regions [26]. The Han Chinese are genetically diverse and arise from the interbreeding of multiple peoples who have migrated across China [26,27]. Consistent with this, the prevalence of inherited disorders shows no evidence of genetic drift or founder effects, although the high frequency of β-thalassemia trait among southern Chinese is suggestive of selection for malarial resistance [28]. Therefore, aside from the population isolates [29], the Han Chinese are unlikely to segregate specific disorders compared to other outbred populations.

Future of medical genetics practice in China

The application of research in human genetics to Chinese medical practice requires the resolution of four issues: (1) overcoming the limitations imposed by the small size of current Chinese families, (2) developing ethical standards for the implementation of diagnostic and therapeutic breakthroughs, (3) integrating Occidental medical reductionism or scientific reductionism with the Chinese worldview and (4) incorporating biological concepts of inheritance into the cultural understanding of familial relationships [30].

Traditionally, China was considered a land of large families [31], a phenomenon that is now historical. The late 1970s witnessed the implementation of the influential one-child-per-family policy. Consequently, in 2004, 69.3% of families had

one child, 27.3% of families had two children, and 3.4% of families had three children [32]. This challenges traditional genetic studies that depend on multiplex families, although emerging technologies have facilitated disease gene discovery in smaller families, particularly if a cohort can be assembled [33].

Renewed investments in genetic research in China and the application of genetic findings to medical practice have prompted societal debate about the ethical application of genetic technologies. As in other societies, the role of genetic testing is influenced by the modern Chinese view of the family and of diagnosis. The former is an admixture of traditional beliefs and legacies of various state policies, and the latter is an admixture of Occidental and traditional Chinese medicine.

Delineating a molecular diagnosis for a disease is critical for many North American and European families to achieve psychological closure; this need likely arises from the tacit acceptance of scientific reductionism in these societies [34]. In the absence of such a diagnosis, patients and families frequently report decreased psychological and economic well-being [35]. Based upon its history, Chinese culture might not be as constrained by the scientific reductionism of Occidental thought. Rather, the materialist concepts of regional climate and individual constitutions as well as yin and yang imbalances have a significant role in diagnosis for traditional Chinese medicine [36]. Additionally, since such diagnoses are based on symptoms, no ill individual is necessarily undiagnosed or without potential interventions.

Traditionally Chinese kinship has been strongly patrilineal and characterized by a hierarchical relationship among biological relatives [37]. Compared to the dominant Occidental concept of kinship, Chinese kinship defines complex and stratified relationships; it maintains a separate designation for almost every individual's kin based on generation, lineage, relative age, and gender. These kinship terms have survived well into current usage.

These observations suggest that the role of medical genetics in China is likely to be different from that in Occidental countries. First, patients may well seek solution in traditional Chinese medicine prior to or in place of pursuing a genetic diagnosis. Second, for those individuals retaining a strong sense of their cultural past, the genetic code may well be seen as the source not only of inherited visible traits but also of the invisible aspects of unique spiritual strengths, and indicative of this latter concept is the recent application of genomic technologies to define nine constitutions recognized in traditional Chinese medicine [36]. Third, because the Chinese system of kinship does not have a similar correspondence with the biological or Mendelian genetics concepts of equal bilateral heritable contributions and equality of siblings, the principles of medical genetics and personalized or precision medicine will likely be subsumed into Chinese culture differently than they have been in the Occident.

The role for an undiagnosed diseases program in Chinese medical practice

Since subjecting the unknown to human understanding is a universal drive, the need for a diagnosis is also part of the Chinese mind. However, the Chinese worldview uniquely defines what constitutes a satisfactory diagnosis [36]. The fundamental difference between Chinese and Occidental definitions of an acceptable diagnosis raises questions regarding the need for and the structure of an UDP within China. If a need exists, a culturally sensitive program must integrate traditional Chinese understanding of disease and kinship with the genomic interpretations of Occidental medicine.

Determination of the need for and structure of a Chinese UDP requires an inventory of (1) the reasons why Chinese currently seek medical genetics care, (2) an assessment of the components providing a satisfactory diagnosis for Chinese individuals, and (3) a delineation of those Chinese patients who perceive themselves without a diagnosis as well as a characterization of their rationale for this perception. As in any population, this inventory will need to account for religious, educational and socioeconomic differences. The resulting findings will allow determination of a need for a genomic medicine-based UDP in China and direction for culturally sensitive implementation of such a program if it is needed.

Regardless of the role for genomic medicine in Chinese society, the challenge for China and all countries is how best to address the health needs of its citizens. The size of the Chinese population would suggest that there are many individuals who might benefit from an undiagnosed diseases program based on principles of genetics. The challenges to implementing such a program in China will likely include impediments to applicant recruitment such as health insurance and the absence of consensus criteria for defining a disorder as undiagnosed. The latter will be addressed as China develops an organized medical genetic system to set standards, to assist with the diagnosis of known but rare genetic diseases and to provide genetic testing. Address of both impediments will likely require facilitation through governmental policy and funding. Despite these potential problems and the cultural differences between China and the Occident, we hypothesize that the integration of genetics and genomic techniques into Chinese medicine will facilitate the characterization of new diseases among the Chinese population and improve medical care.

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Compliance with ethics guidelines

Xiaohong Duan, Thomas Markello, David Adams, Camilo Toro, Cynthia Tifft, William A. Gahl, and Cornelius F. Boerkoel declare no conflicts of interest. This article does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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