Human Phenome Based on Traditional Chinese Medicine — A Solution to Congenital Syndromology

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Abstract: The occurrence of many congenital syndromes has long been an enigma. Clinically, the phenotype of any given genetic defect usually varies to some extent, whilst, pathogenetically, features within each syndrome are probably interconnected, albeit by largely unknown mechanisms. Through its unique theories such as the Jing-Mai (variously translated as the Channels, Vessels or Meridians), Zang-Fu (the Yin and Yang internal organs) and Wu-Xing (translated as the Five-Phase Correspondence or Five-Element theory), traditional Chinese medicine (TCM) seems to have comprehensively summarized the makeup of the human phenotypes. By combining the above TCM theories with modern medical knowledge, the intrinsic mechanisms between various aspects of the phenotypic makeup of the human individual, i.e. the Human Phenome, may be deduced. Analysis of congenital syndromes in light of the Human Phenome seems to suggest that various genetic defects may cause diseases in a similar fashion; i.e. primarily with structural abnormalities distributed along the four Jing-Mai connected with the Kidneys (midline defects) as well as “Marrow” aberrations (anomalies of hematology/immunology, endocrine, central nervous system and the bones). The derived Human Phenome may thereby enable a better understanding of such conditions and provide a model for the study of multigenic traits. On the other hand, blind spots of clinical observation and unknown aspects of human nature, e.g. circuits formed by the Jing-Mai, symmetries of the Jing-Mai and Zang-Fu, and correspondences between body physiques, spiritual factors and the external world may also be deduced. The TCM-based Human Phenome may thereby offer a fresh view for genotype-phenotype correlations, insights into gene-development mechanisms, as well as potential directions for the development of new treatments.

Keywords: Congenital Syndrome; Human Genome; Human Phenome; Phenotype; Traditional Chinese Medicine.
The Undefined Human Phenome

Imperfectly formed bodily structures probably play an important role in the pathogeneses of many diseases. Congenital syndromes constitute a special group of inborn disorders, with the latter also including many “isolated,” “late-onset” and “sub-clinical” congenital anomalies. Many congenital syndromes have been found to be attributable to particular genetic defects. Study of this will not only shed light on the mechanisms of congenital syndromes at both developmental and genetic levels, but may also provide crucial information for the understanding of the pathogeneses of many “isolated” and/or postnatal-onset disorders.

The occurrence of various congenital syndromes has long been an enigma. The term “syndrome” derives from a Greek word meaning “running together” and has been defined by the International Working Group as “a pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence or a polytopic field defect” (Spranger et al., 1982). However, in practice “polytopic developmental field defect” has been most commonly used for explaining a “syndrome.” Several thousand so-called multiple congenital anomaly/mental retardation syndromes (MCA/MRs) have so far been described and the list is still growing. Clinically, features of many MCA/MRs often overlap, which has caused considerable confusion.

Although many genetic defects have been associated with specific MCA/MRs, conventional medical knowledge often cannot explain the intrinsic mechanisms (in broad terms). As a result, the clustered features were usually presented in a rather unstructured manner. Clinically, failure to recognize the “full picture” of a syndrome has been a commonplace. It has become clear that much knowledge on phenotype delineation needs to be updated. For instance, conventional anatomy may not necessarily reflect the mechanisms of development, and the phenotype of any given genetic defect usually varies to some extent. On the other hand, it is likely that the majority, if not all, of the features within a “syndrome” are pathogenetically related. Introduction of a “Human Phenome” concept thereby seems necessary. Delineation of such a concept may significantly improve the understanding of human diseases and facilitate ongoing genomic research.

Truths about Traditional Chinese Medicine

The Jing-Luo System

The Jing-Luo system (variously translated as the Channels, Vessels or Meridians), as described by TCM, comprises Jing-Mai (a main trunk), Luo and Sun-Luo (primary and secondary collaterals) (Lu and Needham, 1980), and is thereby probably not thread-like. Fourteen major Jing-Mai have been described within the human body (The Academy of Traditional Chinese Medicine, 1975).

Strong, non-random correspondences have been discovered between the described paths of Jing-Mai and features of many MCA/MRs, suggesting that the Jing-Luo system probably exists and has represented the connections between various parts of the human body during
embryonic development (Li-Ling, 2001). Comparing the Jing-Mai connections with developmental mechanisms of the heart has further suggested that such correspondences are probably comprehensive (Li-Ling, 2003). Importantly, the patterns of Jing-Mai connections seem to differ substantially from those of the nerves or blood vessels, suggesting that the Jing-Luo system is a separate system and is the missing links between the scattered features seen in many MCA/MRs. Comparing the paths of Jing-Mai with features of MCA/MRs, as exemplified in the analysis of the phenotypes of the 22q11 deletion (Li-Ling et al., submitted), seems to have provided the best, thought indirect, evidence for the former’s existence. It also becomes clear that, for a long time, the close relationship between the Jing-Luo system and the blood vessels and/or nerve plexus has rendered the results of various attempted measurements of Jing-Mai (Hu, 1999) invalid upon critical reviewing. Notably, Langevin and Yandow (2002) have recently discovered probable correspondences between the paths of the Jing-Luo system and connective tissue planes within the body, which seems supportive of the former’s role in development.

The Zang-Fu System

TCM has classified the internal organs of the human body into Zang and Fu (the Yin and Yang internal organs) and defined each of them not by precise morphology but rather by connections with fundamental substances and other parts of the body (see below). Comparing Zang-Fu theories with the features of many MCA/MRs has also suggested that, at least in part, the former has correctly summarized the comprehensive functions of visceral structures (Li-Ling, 2001).

An important concept in Zang-Fu theory is the JING. JING is thought to be “the substance essential for development, growth and maturation.” “Conception is made possible by the power of JING, growth to maturity is the blossoming of JING, and the decline into old age reflects the weakening of the JING” (Kaptchuk, 1983). The JING concept therefore has probably referred to the genetic material as well as its activities. “The Kidneys store the JING” (it may be helpful here to interpret the Kidneys as themselves at the embryonic stage). An injured JING, in the form of various genetic mutations, may thereby result in abnormal development that primarily distributes along the four Jing-Mai connected with the Kidneys, which significantly overlap with the body’s developmental midline (Li-Ling, 2001).

The Wu-Xing System

TCM has also developed a Wu-Xing system (translated as the Five-Phase Correspondence or Five-Element theory), which has summarized not only the correspondences between the five Zang and other parts of the body, e.g. Fu, tissues, orifices, etc., but also the body functions and spiritual factors, e.g. pathological actions, sounds, emotions, etc. (Kaptchuk, 1983; Ni, 1995) (Table 1).
The Jing-Luo, Zang-Fu and Wu-Xing theories, constituting the fundamental concepts of TCM, seem to have summarized, respectively, the physical, functional and spiritual aspects of human phenotypes. By combining such theories with modern medical knowledge, the intrinsic mechanisms between various aspects of the phenotypic makeup of the human individual, i.e. the Human Phenome, may be deduced (Fig. 1). As shown in Fig. 1, whilst adapting the Jing-Mai connections between Zang and Fu, the Human Phenome has provided an explanation for the TCM concept of “Marrow,” which has encompassed modern entities including hematolgy/immunology, endocrine, central nervous system and the bones. In this context, each component of the human phenotypic makeup is viewed through its Jing-Mai connections and/or functions defined by the Zang-Fu and Wu-Xing theories, differing substantially from conventionally defined “bodily systems” based on anatomy and/or physiology. As exemplified in the analysis of the phenotypes of 22q11 deletion, comparing with previously proposed mechanisms for MCA/MRs such as neurocristopathy, polytopic developmental field defects or vascular disruption sequences (Lammer and Opitz, 1986; van Mierop and Kutsche, 1986; Shprintzen et al., 1997), the TCM-based Human Phenome seems to have provided a much clearer view for the co-occurrence of seemingly unconnected features and even enabled prediction of previously unnoticed anomalies (Li-Ling et al., submitted).
Opitz (1985) had generalized the features of MCA/MRs as: (1) all primary malformations are causally non-specific; (2) in time, most will be shown to be causally heterogeneous, i.e. the causes are many, but the final common developmental pathways are few; (3) most primary malformations are anomalies of incomplete formation; and (4) they affect mostly midline morphogenetic processes. Interestingly, in the light of the Human Phenome, different mechanisms, genetic or non-genetic, seem capable of causing congenital syndromes in a similar fashion. For instance, MCA/MRs caused by chromosome aberrations, e.g. trisomy-21 (Down syndrome, MIM (Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/) 190865), inv dup22q11 (Cat-eye syndrome, MIM 115470), single gene mutations, e.g. JAG1 (Alagille syndrome, MIM 118450), DHCR7 (Smith-Lemli-Opitz syndrome, MIM 270400), and even unknown genetic mechanisms, e.g. Craniosynostosis with radial defects (MIM 218600), Short rib-polydactyly syndrome I/IV (MIM 263530/269860), seem to have all manifested primarily with midline defects and "Marrow" anomalies. Common features of MCA/MRs including pre- and/or postnatal growth retardation, failure to thrive, short stature, frontonasal malformations, ear and eye anomalies, genitourinary malformations, skeletal malformations, neurological/mental disorders, congenital heart defects (especially outflow tract defects), anorectal malformations,
hematological/immunological disorders, etc. seem mostly classifiable as anomalies distributed along the Jing-Mai connected with the Kidneys (midline defects) or aberrant functions of the Marrow. This seems to have not only agreed with, but also advanced Opitz’s theory.

**Human Phenome versus Human Genome**

With the sequencing of the Human Genome completed, the unprecedented Human Genome Project (HGP) has passed an important milestone. As Reeves (2000) put it, the HGP has started to look at the Human Genome more from its functions. In many ways, the Human Phenome is similar to the Human Genome. Whilst the latter comprises the full set of human chromosomes and mitochondrial DNA, the TCM-based Human Phenome, with its physical, functional and spiritual components, also seems to be complete. On the other hand, a tremendous amount of information is, and may remain, unknown about the Human Genome (for instance the so-called junk DNA), and similarly much is yet to be found out about the Human Phenome.

Although many methods have been developed for studying the functions of genes, to find out exactly what each gene does within our body still seems to be a daunting task. Gene expressed patterns, as revealed by hybridization (for which large numbers of tissue sections may be required since many genes are expressed ubiquitously and continuously), may not necessarily tell the function of most genes. On the other hand, phenotypes caused by gene mutations, as demonstrated in many studies, may not be the phenotype directly related to that particular gene. It has also to be born in mind that the phenotypes of many vital genes may never be seen since defects of such genes are not compatible with life at all. Even for those less important genes, neither the severest nor the mildest forms of their clinical outcome may be fully recognizable. Furthermore, manifestation of many genetic defects may also contain secondary disorders that can be both structural and functional.

Deciphering the function(s) of a gene often has to rely on studying of its phenotypes. However, clinically observed phenotypes may be influenced by many factors. These may include (1) “incomplete penetrance” of the gene; (2) stochastic events during embryonic development; (3) involvement of too many vital organs may result in non-viability; (4) different compensatory ability of each organ; (5) partial observation, e.g. denied autopsy, mental/psychiatric disorders that may only become apparent at older ages, etc.; and (6) different technical detectability of each organ. At the organ level, natural selection during fetal life may further distort a phenotype we see. Theoretically, since the phenotype of any given genetic defect is probably also influenced by the rest of the genes within the genome, the complete phenome for individual genes may never be known, though by statistics and comparison, one may at least find out which genes are more crucial than others.

**JING versus Genes — A Perfect Model for Multifactorial Traits**

Needless to say, the estimated 30,000–40,000 or so genes contained in the Human Genome are interconnected to form a complex with the enormous functions, known and unknown.
Schmickel (1986) had proposed a “contiguous gene syndrome” concept for correlating individual features of a syndrome to mutations of physically closely located genes. However, for many syndromes, single “candidate” genes have already been identified (Budarf and Emanuel, 1997). It becomes apparent that various genetic defects, at the levels of whole chromosomes, chromosomal segments or single genes, may result in “syndromes” in a similar manner. In other words, gain, loss or substitution of genetic material may cause similar disturbances to the expression of the whole genome.

The Human Phenome seems to have provided a summary for the overall correlation between defects of genes, i.e. injuries to the JING, and the onset of disease phenotypes. In terms of logic, the TCM-based Human Phenome seems to be a typical “gray box” lying between the over-generalizations of TCM and over-meticulosity of conventional genetics research. This may in fact well suit the complex interconnections between those many genes involved with particular disease processes. Take Hirschsprung disease (MIM 142623) for example. Although its causative genes have been mapped to 5p12-p13.1, 10q11.2 and 19p13.3, we may not be surprised that the same disorder has also been associated with many other genetic defects including trisomy-21 and 22q11 deletion. In other words, gain or loss of genetic material in the latter conditions can probably also influence the “main” genetic control (if any) of anorectal development. The same theory may be applicable to other “non-specific” or “minor” features seen in MCA/MRs.

For gross genetic disorders such as trisomy-21 and 22q11 deletion, it may not be possible to pinpoint the causative gene(s) underlying each of the involved features. On the other hand, by generalizing such genetic defects as injuries to the JING, ideas such as “The Kidneys store the JING” and “The Kidneys produce the Marrow” seem clearly applicable to “unusual” features such as leukemia seen in trisomy-21 and genitourinary malformations in 22q11 deletion. Notably, the above generalization neither denies the necessity for identifying the causative gene(s) (if any) for important traits such as Alzheimer disease, nor does it overlook all the characteristic features of each syndrome.

The Human Phenome seems to also enable a better understanding for multi-factorial diseases. Deleterious environmental factors may all be generalized as disturbance to the JING. Treating DiGeorge anomaly as abnormal development along the Kidney Jing-Mai within the chest and neck (Li-Ling, 2001), one may become less puzzled with the fact that, in addition to 22q11 deletion, maternal diabetes and many other chromosomal abnormalities, e.g. 10p deletion, may cause the same anomaly (Gosseye et al., 1982; Digilio et al., 1995; van Esch et al., 1999).

Man as a Holy Integration

The Circulation of Qi

The 14 Jing-Mai within the human body consecutively connect to form two circuits (Li-Ling, 2001). Such connections seem to imply some kind of circulation, or periodic activity along the Jing-Mai. TCM theories regard the Jing-Mai as the paths for Qi and Blood
This may be interpreted as: (1) the Jing-Mai has a close relationship with the blood vessels, and (2) there are probably rhythmic cellular activities along the Jing-Mai.

**Wonderful Symmetries**

Highlighted by the balance between Yin and Yang, symmetries may be found everywhere in TCM. Typical symmetries of the Jing-Mai include internal versus external, proximal versus distal, upper and lower, etc. Symmetries of the Zang-Fu and Wu-Xing include the couplings of Zang (in addition to the Pericardium) and Fu, and those between body physiques, functions and spiritual factors (Table 1). Such couplings are intriguing because, developmentally, they may have correctly summarized the interconnections between the formation of individual organs and deserve in-depth research.

**Body, Mind and the Universe**

The Wu-Xing theory of TCM seems to have extended the correspondences between human physiques and physiology to broader terms such as the mind and the Universe. Such summaries, though unproven, may provide important clues for a wide range of research spanning biochemistry, physiology, pharmacology, nutrition and psychiatry.

**Implications of the Human Phenome**

To bridge DNA and human diseases, in addition to our emphasis on “functional genomics,” we probably need to improve our clinical views — how much of a gap after all is there between different bodily systems? The biggest gap, if any, seems to lie between various clinical specialties where repetition of “three blind men and the elephant” has been commonplace. Clearly, without the Human Phenome, clinicians could only dwell on “bird watching” and counting on luck, and are prone to presenting confusing and even misleading pictures, which might have greatly increased the difficulties of deciphering the functions of genes.

From the view of the Human Phenome, many existing names seem to refer to a similar phenotype. The significance of “finding a most suitable label” becomes questionable — clinical features of patients almost always differ, and any label of “genetic disease” is stigmatic anyway. With the delineation of the Human Phenome, the essence of “functional genomics” seems to have become more specific — to identify the main genetic controls (if any) for important traits. In this sense, “syndrome labeling” may be improved, since not all MCA/MRs have been labeled with their most common features or etiologies (Cohen, 1997).

Strictly speaking, the TCM theories have yet to be thoroughly proven. Many questions remain to be answered. Here an interesting question is: for an integrated system, when a substantial part of it has been shown to be correct, how likely will the remaining turn out to be also true? For the unknown part of the Human Phenome, Jing-Mai connections, aforementioned symmetries, and Wu-Xing theories will probably provide the best clues for
exploration. For individual organs, the Jing-Mai connections may be used as guidance for studying their developmental pathologies.

Treatment-wise, the TCM-based Human Phenome may also provide clues for clinicians. Importantly, the inseparable relationships between various parts of the body, e.g., interior and exterior, central and peripheral, physical and spiritual, etc., demand a more holistic approach to disease. Notably, TCM utilizes mainly the five Zang as the gateways for adjusting the balances within the body. An interesting question will be whether, by reflecting the organization of human phenotypic makeup, the Human Phenome has already correctly summarized the activities of the Human Genome? If so, traditional Chinese herbal medicines may have already been a correct way for modulating the activities of the Human Genome. Surely, acupuncture probably has certain influences upon internal organs (Hu, 1999). While the effect of therapeutic initiatives at the single-gene level, i.e., gene therapy, seems unsure (Nature Medicine Editorial, January 2000), treatment based on the rationales of TCM, e.g., acupuncture and/or Chinese medicinal herbs, may prove to be effective. Such treatment has already existed in China for several thousand years.

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References


