Syntropy, genetic testing and personalized medicine

The concept of syntropic diseases was proposed at the beginning of the last century to emphasize the phenomenon of nonrandom co-occurrence of human disorders. Common genes underlying specific syntropic diseases were called syntropic genes. The application of this concept to contemporary genomic studies will facilitate the understanding of the molecular basis of complex diseases, provide future direction for discovering new targets for therapy and prognosis, and may even lead to the reassessment of disease classification for the practice of more precise personalized medicine. With the acceptance of the syntropic genes theory, new genetic tests, focused on markers pointing to a set of pathogenetically linked diseases rather than to a single nosology, can be developed.

KEYWORDS: cardiovascular disease continuum ■ classification of disease ■ comorbidity ■ diseasome ■ dystropy ■ immune-mediated disease ■ syntropic genes ■ syntropy

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Health authorities worldwide express an expanding interest in personalized healthcare. The idea of personalized medicine itself is at least 2000 years old. In J Evans' opinion, it was introduced by Galen who noticed [1]:

> "…but remember throughout that no external cause is efficient without a predisposition of the body itself. Otherwise, external causes which affect one would affect all…"

Certainly, clinical medicine always looked for, discovered and used certain somatometric, psychological or biochemical markers to assess an individualized diagnosis for a patient. However, during the contemporary stage of personalized medicine, there is a strong demand for access to scientifically substantiated personal genomic testing, especially with respect to common diseases (CD) in humans. This issue is being actively debated [1–8], with the dispute participants split into those who defend the 'control' or 'prohibition' of access, specifically to 'direct-to-consumer genetic testing' (avoiding medical authorities), and those who argue for 'intelligent and innovative models' and believe that public–private partnerships can resolve the issues [9].

The barriers to providing personal genomic services include: an insufficient understanding of gene–gene, gene–environmental interactions and the interactions between genetic information and epigenetic factors; the insufficient number of genetic markers that reliably differentiate disease risk; health service systems requiring reorganization, including physician and patient education; the automation of genetic information identification and implementation of economic estimates of personal genomic services [5]. It is our belief that there is another phenomenon that makes it difficult to measure the genetic risk of complex diseases, and this is polypathy or comorbidity.

Syntropy & syntropic genes

Until recently, a major tool for identifying the genetic components of susceptibility to CD were genetic association studies investigating healthy controls and cases affected by a single disease. Genome-wide association studies (GWAS) follow this tradition and test multiple (more than 500,000) markers for an association with a specific disease. However, global clinical epidemiological studies call attention to the fact that many patients suffer from several CD simultaneously. The term 'syntropy' was used for the first time by German clinicians Pfaundler and von Seht in 1921 to designate the diseases that tend to co-occur in patients and their close relatives more often than what is expected by chance [10]. They also put forward the terms 'dystropy' and 'neutropy' to denote mutually exclusive and randomly coincident diseases, respectively. Examples of syntropies and dystropies that have been discussed in the literature are summarized in TABLE 1 [11–16].

Cardiovascular disease continuum (CDC) is an example of an association of diseases that can be referred to as syntropy. CDC includes arterial hypertension (AH), coronary artery disease (CAD), dyslipidemia (DL), stroke, obesity,

Table 1. Examples of syntropic and dystropic diseases.	
Syntropy	**Dystropy**
Metabolic syndrome is a 'quartet' of syndromes: arterial hypertension, hypercholesterinemia, hyperglycemia and obesity	Sickle-cell anemia and tropical malaria *Plasmodium falciparum*
Pickwickian syndrome (obesity and narcolepsy)	Pulmonary tuberculosis and mitral stenosis
Saint's triad (cholelithiasis, diaphragmatic hernia and duodenal diverticulum)	Pulmonary tuberculosis and bronchial asthma
Atopy (bronchial asthma, allergic rhinitis and dermatitis)	Diabetes mellitus Type 1 and gastric ulcer
Autism, bipolar disorder and schizophrenia	Limpholeucosis and mieloleucosis
Data taken from [11–16].	

metabolic syndrome (MS) and Type 2 diabetes mellitus (T2D). Only 20–25% of patients with newly diagnosed CAD have only one concomitant disease (risk factor), while the remainder suffer from two or more diseases [17], and this conglomerate of diseases can be referred to as the CDC syntropy. It is also well known that 40% of T2D patients have three or more concomitant diseases [18].

Bronchial asthma (BA), atopic dermatitis/eczema (AD) and allergic rhinitis (hayfever) are examples of immune-mediated diseases which display syntropic features and often appear together in one patient and his/her family members. BA is suffered by approximately 60% of children with severe AD, and for many this disease association continues into adulthood [19]. A similar combination of diseases is also observed for Type I diabetes (T1D), autoimmune thyroiditis (Grave's disease and Hashimoto's disease) and celiac disease [20]. Additional examples of syntropy have been described for immune-mediated diseases [21].

An initial hypothesis regarding the causes of syntropy emphasized environmental factors as key players. Currently, apart from environmental influences, genetic factors are considered to be important to the development of syntropy: the diseases found in combination are thought to have a common inheritance or, as described by Stern, 'common soil' [12]. Common genes underlying specific syntropic diseases are called syntropic genes, in contrast to dystropic genes, which determine the mutual exclusion of certain (dystropic) diseases (**Box 1**) [15,22].

A similar idea, accompanied by an impressive statistical analysis, was discussed in a recent publication by Goh *et al.* [23]. Based on the associations between 1248 diseases and 1777 genes, a global network of gene–disease interactions was presented and the term 'diseasome' was proposed to describe the network. Functional modules, blocks of genes associated with several diseases that appear either together or separately can be identified within this network. The concept of a network of interacting genes and diseases was also put forth and tested by Rzhetsky *et al.* [14]. They analyzed 1.5 million patient records and 161 diseases, and proposed an approach which allowed the estimation of the extent of genetic overlap between these diseases. Rzhetsky and colleagues concluded that multifactorial disease phenotypes are highly genetically correlated and assumed that this finding would have immediate practical implications for the design of gene-mapping studies of complex phenotypes, including those which appear to be independent. Earlier, Williams *et al.*, in a sample of 2204 individuals that included 525 monozygous twins and 577 dizygous twins, calculated genetic correlations between AH, migraine, Raynaud's syndrome and CAD, and hypothesized that a shared genetic factor predisposing to vasospasm underlies all these diseases [24]. Finally, Torkamani *et al.* demonstrated a high degree of overlap between SNPs significant in GWAS of CAD, AH, T2D and bipolar disorders, as well as for several immune-mediated diseases [25]. In particular, it was shown that among the 1000 SNPs that were most significantly associated with the diseases, 57 are shared by CAD and T2D, 81 are shared by AH and T2D, and 63 are shared by AH and CAD. These genetic correlations between diseases were highly significant. Also, strong correlations were discovered between autoimmune diseases, such as rheumatoid arthritis and T1D. Interestingly, a significant genetic correlation was found between

Box 1. The definition of syntropy and syntropic genes.
▪ Syntropy is a natural generic phenomenon of a nonrandom combination of two or more pathological conditions (nosologies or syndromes) in an individual and his/her nearest relatives, and has evolutionary and genetic bases
▪ Syntropy is a part (an extract) of the human phenome, comprised of a landscape of interacting traits and diseases resonating continual molecular–genetic causality
▪ Syntropic genes are a set of functionally interacting genes located throughout the human genome, coregulated and involved in the metabolic pathways common to a given syntropy

BP, CAD and T2D, as well as between AH and Crohn's disease – seemingly unrelated disorders. This study highlights the presence of unexpected links between these diseases, but it also has implications for the medical–genetic counselling for risk assessment of combinations of diseases, or syntropies, rather than for single diseases.

Syntropic genes of two disease conglomerates

In our studies, we considered two groups of syntropic disorders, CDC [15] and allergic diseases (ADis) [16]. We used the information regarding the genetic associations from the Human Genome Epidemiology (HuGE) Navigator database [26] to identify genes associated with the separate diseases of CDC and ADis, and then only chose those genes which were associated with all disorders in a syntropy. In the database, all the genes are ranked according to a score that is calculated as a ratio of a number of positive findings (e.g., classic associations, GWAS, genetic testing, meta-analysis and genetic models) to all studies cited in PubMed. We only considered genes with the score of 0.01 or more to increase the strength of the result. This approach allowed us to identify 21 syntropic genes for CDC and 10 genes for ADis (TABLE 2).

Certainly, these genes do not encompass all the hereditary components of susceptibility to the studied syntropy. The number of genes

Table 2. Syntropic genes of cardiovascular disease continuum[†] and allergic diseases[‡].

Gene symbol	Gene product	Chromosomal location
Cardiovascular disease continuum		
ABCA1	ATP-binding cassette, subfamily A, member 1	9q22-q21
ACE	Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	17q23
ADRB2	Adrenergic β-2-receptor, surface	5q32-q34
AGT	Angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	1q42-q43
AGTR1	Angiotensin II receptor, type 1	3q21-q25
APOA1	Apolipoprotein AI	11q23
APOE	Apolipoprotein E	19q13.2
CETP	Cholesteryl ester transfer protein, plasma	16q21
GNB3	Guanine nucleotide binding protein, β polypeptide 3	12p13
IL6	Interleukin 6 (interferon, β2)	7p21
LIPC	Lipase, hepatic	15q21-q23
LPL	Lipoprotein lipase	8p22
MTHFR	5,10-methylenetetrahydrofolate reductase (NADPH)	1p36.3
NOS3	Nitric oxide synthase 3 (endothelial cell)	7q36
SELE	Selectin E	1q23-q25
TNF	TNF superfamily, member 2	6p21.3
PPARG	Peroxisome proliferator-activated receptor γ	3p25
ADIPOQ	Adiponectin, C1Q and collagen domain containing	3q27
ESR1	Estrogen receptor 1	6q25.1
LTA	Lymphotoxin α (TNF superfamily, member 1)	6p21.3
SERPINE1	Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	7q21.3-q22
Allergic diseases		
HLA-DQA1	Major histocompatibility complex, class II, DQ α1	6p21.3
HLA-DQB1	Major histocompatibility complex, class II, DQ β1	6p21.3
HLA-DRB1	Major histocompatibility complex, class II, DR β1	6p21.3
IL10	Interleukin 10	1q31-q32
IL13	Interleukin 13	5q31
IL4	Interleukin 4	5q31.1
IL4RA	Interleukin 4 receptor	16p12.1-p11.2
LTC4S	Leukotriene C4 synthase	5q35
MS4A2	Membrane-spanning 4-domains, subfamily A, member 2 (Fc fragment of IgE, high affinity I, receptor for; β polypeptide)	11q13
TGFB1	Transforming growth factor β1	19q13.2

[†]*Arterial hypertension, coronary artery disease, dyslipidemia, metabolic syndrome and noninsulin-dependent diabetes mellitus.*
[‡]*Bronchial asthma, atopic dermatitis, allergic rhinitis, pollynosis, drug allergy, food allergy, urticaria/Quinke's edema and IgE levels.*

underlying any particular disease included in the CDC or ADis syntropies is much higher. However, for the total CDC and ADis syntropies, according to the HuGE Navigator data and ranking criteria, the control of the development and structure of the whole CDC and ADis syntropies can be attributed to only these 21 and 10 genes, respectively, and these genes can be called the syntropic genes of CDC and ADis. For CDC, the functional realm of the syntropic genes is mainly comprised of lipid metabolism, renin–angiotensin–aldosterone system regulation, sympathoadrenal system function, inflammation development and endothelial function. For ADis, the common functions appear to be the initiation and regulation of immune response (primarily the humoral response) and inflammation.

Using the information on shared (common) and nonshared (disease-specific) genes, we conducted a hierarchical cluster analysis of the CDC and ADis syntropic diseases to consider whether the diseases had any gene-based relationships. Two tight clusters are seen for CDC; one is comprised of AH, CAD, stroke and DL, while the other is composed of MS, obesity and T2D (Figure 1). Two large clusters were also revealed for ADis; the first includes Ig-E levels, BA and AD, while the second cluster is divided into two clades with seasonal ADs, such as allergic rhinitis and pollinosis in one clade, and urticaria/Quincke's edema, food allergy and drug allergy comprising the second clade. More detailed information and discussion of this analysis are presented in the original publications [15,16,27].

It is clear that the shared/nonshared gene-based clustering supports the existing view on the etiology and pathogenesis of cardiovascular diseases and allergic disorders, and coincides with the system of diagnosis accepted in clinical practice. This approach can potentially be applied to any other syntropic disease groups. It would be interesting to analyze the genetic clustering of all human diseases for the purpose of building a natural genetic-based system of their classification.

We argue that a general problem with estimates of the genetic risks for CD is that the phenomenon of comorbidity (syntropy) and mutual exclusion (dystropy) of the disease is ignored. It is likely that syntropy appears more often than dystropy, but this premise may be erroneous simply because the coincidence of diseases is considered more frequently. Syntropy is probably not just a simple sum of diseases and traits, but a natural pathological entity that must be taken into account in treatment, prophylaxis and prognosis, including genetic counseling. The use of a syntropy rather than separate diseases as the subject of genetic studies seems to be rewarding and can lead to a deeper insight into the understanding of the diseasome organization and mechanisms of its development.

Syntropy, human phenome & personalized medicine

The human genome project disclosed the myriad of gene variations associated with human health and disease. Yet, before completion of the whole-genome sequencing project, the 'Human
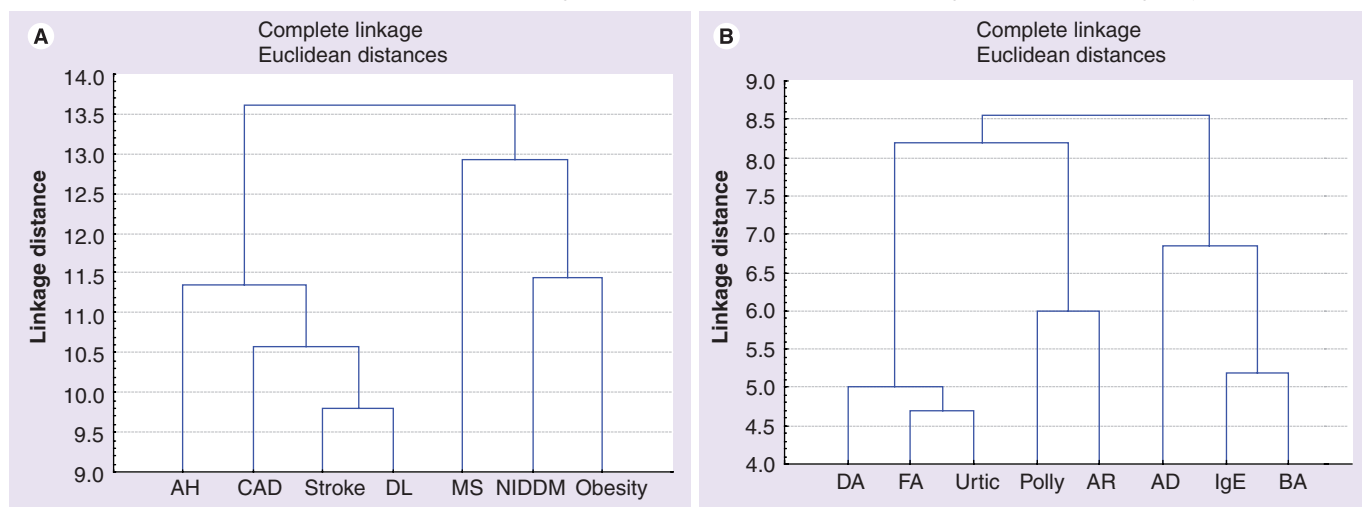

Figure 1. Clusters of cardiovascular disease continuum diseases and allergic diseases according to genes shared by them.
(A) Cardiovascular disease continuum diseases and **(B)** allergic diseases.
AD: Atopic dermatitis; ADis: Allergic diseases; AH: Arterial hypertension; AR: Allergic rhinitis; BA: Bronchial asthma; CAD: Coronary artery disease; DA: Drug allergy; DL: Dyslipidemia; IgE: Immunoglobulin-E level; MS: Metabolic syndrome; NIDDM: Noninsulin-dependent diabetes mellitus; Polly: Pollynosis; Urtic: Urticaria/Quinke's edema.

Phenome' project was being discussed [28,29]. Defining 'phenome' by analogy with the term 'genome' as the whole phenotypic representation of a species, it was highlighted at the same time that 'an important practical difference between genome and phenome is that, while the genome is bound (approximately 3 billion base pairs), the phenome is not (its bind depends on how far we go)' [30]. Considering the situation of a bounded genome and an unbounded phenome, according to Sing *et al.* [31], researchers are 'faced with reconciling a high-dimensional causal-state space of molecular networks that connect DNA variation and the well-established role of exposures to high-risk environmental agents with the emergent, discrete, clinical outcomes that are relevant to medicine and public health'. In this respect, a specific syntropy is a component of the phenome; a block of traits (normal or abnormal) for which a more meaningful search for genotypic blocks (syntropic genes) is possible. Interacting syntropic genes can reveal stable synergetic effects, raising the likelihood of using these genetic ensembles in clinical practice. Individual genomotypes can be significant for personalized medicine.

It is well recognized that any single gene polymorphism explains just 1–8% of total disease risk for common traits in a population; however, the additive effects of several polymorphisms, such the variants, can be 20–70% of total genetic risk [32]. Striking examples of synergism in gene–gene interactions are accumulating and they should be noted by clinicians. For instance, a study of 1120 German children, aged 9–11 years, showed that the combined effect of polymorphisms of the *IL4, IL13, STAT6* and *IL4RA* genes raises the risk of the increased IgE up to 10.8-times and the risk of bronchial asthma is increased up to 16.8 times as compared with the effects of individual polymorphisms [33]. It has also been calculated that a genetic test that includes 12 gene polymorphisms discovered in GWASs performed during the last 2–3 years would identify those men of 40 years or older who have twice the lifetime risk of CAD (from 49%–79%) of men with elevated levels of low-density lipoprotein cholesterol [5].

A number of studies had demonstrated that the introduction of genetic markers into phenotype-based risk models can allow better classification of individuals into risk groups and sometimes improves prediction of future diseases [34–36]. Currently, existing genetic tests are focused on risk assessments for single diseases. Naturally existing disease conglomerates present two additional challenges: some alleles may be protective for one

disease but confer susceptibility to another [37], and diseases can potentiate each other's development. For example, hypertension can double the risk of noninsulin-dependent diabetes mellitus (NIDDM), heart attack and other pathological phenotypes in the cardiovascular continuum. In theory, revealing syntropic genes underlying multiple diseases may result in tests with better potential to predict common morbidity.

It is worth noting that the genetic testing of CD is at an early stage of penetrating into our individual genomes' *terra incognita* [38]. However, we need to go forward with personalized medicine while considering the unresolved theoretical questions and being mindful of the ethical issues, but advance forward and accumulate experience. In an ideal situation, it would have been desirable that genetic testing of CD predicted an outcome (e.g., treatment effect or disease risk) with 100% precision and robustness. However, in real life, and this always will be the case for CD, doctors make decisions using limited information, and provability of supporting knowledge is defined more accurately during the course of its use. Certainly, genetic tests will be used along with phenotypic markers for disease prognosis and treatment determination. In **Box 2**, several statements are presented which, in our opinion, should be taken into account at the current stage of personalized medicine development. Ultimately, the aim of genetic testing of widespread diseases is very precious; it aims to provide better health and life quality to as many people as possible.

Future perspective

Clinical medicine will be aware of the importance of the phenomenon of combined diseases (syntropy) in patients, providing individual protocols and schemes of treatment. Genetic profiling will also be focused on comorbidity

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Box 2. Some paradigms of genetic testing for multifactorial disease predisposition.

- While moral and 'absolute' knowledge represent an 'ideal world', clinical practice is the 'real world'
- Genetic testing provides a way to improve upon something which will never be identified perfectly and never be a simple area of application and a simple subject of study
- A reconstruction of mutual expectations of doctors, researchers and patients is a prerequisite for the successful advancement of genetic testing
- Clinical practice has to depend on evidence-based medicine, but the latter is a process of ongoing improvement in the provision of high-quality healthcare
- Genetic testing, not instead of, but together with phenotypic markers, can be utilized for personalized prognosis, which is always probabilistic

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rather than on a single disease. Other approaches to genetic-risk assessment for these forms of pathology will be required.

In traditional medicine, the 'nosology' concept is basic. However, shared susceptibility (or resistance) genes for different diseases (nosologies) provides proof of a 'pathological panorama' of diseases in contemporary human populations. This genetic approach to human diseases will lead to a reassessment of disease classification allowing the practice of personalized medicine to be more precise.

Executive summary

Syntropy & syntropic genes

- There are many different barriers to providing personal genomic services and the phenomenon of polypathy or comorbidity is one of these barriers.
- The major source of genetic information regarding the inherited component of susceptibility to common diseases came from genetic association studies considering single diseases.
- Epidemiological studies call attention to the fact that a considerable number of patients suffer from several diseases simultaneously.
- Cardiovascular disease continuum and immune-mediated diseases are examples of the disease associations that can be referred as a syntropy.
- Studying disease conglomerates allows for discovering unexpected links between diseases, and provides new possibilities for risk assessment: not a single disease but rather a combination of diseases – a syntropy.

Syntropy, human phenome & personalized medicine

- The phenome is defined by analogy with the term 'genome' as the whole phenotypic representation of a species. However, there is an important practical difference between the genome and phenome: while the genome is bound (approximately 3 billion base pairs), the phenome is not.
- Specific syntropy is the component of the phenome for which more meaningful searches for genotypic blocks (syntropic genes) is possible.
- Interacting syntropic genes can reveal stable synergetic effects, raising the likelihood of using genetic ensembles in clinical practice.
- Currently, existing genetic tests are focused on risk assessments for single diseases. Naturally existing disease conglomerates represent an additional challenge.
- The genetic approach to human disease systematics will lead to the reassessment of disease classification and improvement in the precision of the practice of personalized medicine.

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