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OPINION ARTICLE

Systems Cytogenomics: Are We Ready Yet?

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Abstract: With the introduction of systems theory to genetics, numerous opportunities for genomic research have been identified. Consequences of DNA sequence variations are systematically evaluated using the network- or pathway-based analysis, a technological basis of systems biology or, more precisely, systems genomics. Despite comprehensive descriptions of advantages offered by systems genomic approaches, pathway-based analysis is uncommon in cytogenetic (cytogenomic) studies, *i.e.* genome analysis at the chromosomal level. Here, we would like to express our opinion that current cytogenomics benefits from the application of systems biology methodology. Accordingly, systems cytogenomics appears to be a biomedical area requiring more attention than it actually receives.

Keywords: Cytogenomics, chromosome, systems biology, pathway, genome, DNA sequence.

1. INTRODUCTION

Systems genomics is an important part of current bioscience, providing evidence-based theoretical and empirical discoveries [1, 2]. However, systems genomics approaches are rarely used in cytogenetic/cytogenomic research (*i.e.*, genome analysis at chromosomal and subchromosomal levels) regardless of the proven efficiency and applicability [3]. In the post-genomic era, data analysis by systems biology (bioinformatic) techniques has become a key contributor to the success of a study dedicated to genome biology/medicine [4, 5]. Pathway-based views on genome variability enhance significantly our understanding of the role played by genomic variations in health and disease [6, 7]. Indeed, network analysis of macromolecular interactions using data on sequence variations highlights molecular and cellular mechanisms for human diseases [8, 9]. At chromosomal and/or subchromosomal levels, systems biology approaches targeting genome variability seem to be more sophisticated because of the involvement of large genomic loci (chromosome abnormalities simultaneously affect numerous co-localized genes). Nonetheless, pathway-based techniques are effectively applicable to chromosomal imbalances and copy number variations (CNV), providing exciting results for basic and diagnostic research (reviewed recently in [10]). Additionally, systems genomics has been used as a platform for single-cell genomic (cytogenomic) analysis for studying intercellular genomic, transcriptomic and proteomic variability [11, 12]. Thus, systems genomic analysis may be considered as an important tool for cytogenetic (molecular cytogenetic) and cytogenomic research.

Genomic variations at chromosomal and subchromosomal levels are the commonest genetic cause of human mortality and morbidity [13, 14]. *In silico* methods have been systematically used for the development of techniques for detecting chromosomal imbalances [15-17]. However, studies investigating chromosomal and subchromosomal imbalances using systems biology techniques are exclusive [10]. Nonetheless, approaches to determine the phenotypic outcome of microscopic and submicroscopic genome variations are available (*i.e.*, CNV prioritization; pathway-based phenome analysis in patients with chromosomal abnormalities) [18]. Numerous gene prioritization methods are able to be adopted for analyzing large sets of co-localized genes affected by a chromosome imbalance [19, 20]. Furthermore, systems biology analysis of chromosomal behavior and variations has been successfully applied for studying genome organization in interphase nuclei, somatic genome evolution in cancer, phylogenetic genome evolution, and DNA damage response [21-24]. More excitedly, systems genomics approaches to diseases caused by chromosomal imbalances provide opportunities for treating these presumably incurable conditions [25]. Bioinformatic analyses have been systematically proposed as a valuable tool for diagnostic cytogenomic research [26, 27]. In total, understanding of disease mechanisms mediated by chromosome abnormalities and/or instability does require systems genomics (cytogenomics) methodology [28]. However, systems genomics analysis is uncommonly used in molecular cytogenetic and cytogenomic research, as mentioned previously. It is highly likely that this problem persists because of the lack of comprehensive workflows in systems cytogenomics. Consequently, we have endeavored to develop one.

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Using the results of cytogenomic/bioinformatic research obtained by our colleagues [29, 30] and us [10, 18, 25, 31-34], we have introduced systems cytogenomics workflow, which is schematically shown in Fig. (**1**). Briefly, cytogenetic analysis (single-cell visualization/microscopic whole-genome analysis at the chromosomal level albeit at low resolution) and cytogenomic analysis (whole-genome analysis of chromosomal imbalances and CNV at the molecular level) generate two data sets, which are useful for uncovering CNV, chromosomal abnormalities/instability/-variants. Systems biology analysis is then applied for the pathway-based classification in a gene-centric way. In the present workflow, the classification is an *in silico* modulation of potential consequences of the genomic variations at transcriptome, proteome, and metabolome levels for prioritizing CNV and candidate processes. Once classification is successfully performed, the knowledge regarding disease mechanisms, susceptibility to multifactorial diseases or phenotypic properties, alterations to the maintenance of genome stability (*i.e.*, molecular causes of chromosome instability if uncovered by cytogenetic analysis), *etc*. can be obtained. Certainly, there may be alternative systems cytogenomics workflows. Still, this one has been already found applicable in basic and diagnostic research [10, 12, 18, 25, 31, 32]. One may further suggest this workflow to include data sets obtained by next-generation sequencing, which complement systems knowledge on genomic variability at the DNA level and the functional consequences.

The achievements in genomics and systems biology have become the essence of systems medicine. The latter has recently become an integrated part of biomedical research and molecular diagnostics. A series of studies have already demonstrated that systems genomics methodology increases the potential of health care and bioscience research [35-37]. Cytogenomics and molecular cytogenetics empowered by systems biology methodology represent a new chapter in the global genetic odyssey - systems cytogenomics. Studies performed using systems cytogenomics methodology are able to provide valuable data, the use of which is important for uncovering new disease mechanisms and creating therapeutic opportunities (personalized treatment) [10, 38]. The proposed workflow may certainly help in the development and applicability of this area of genome and chromosome research. Obviously, the described systems cytogenomics workflow may be expanded. In our opinion, the expansion of systems cytogenomics workflow would include sequencing data and the analysis by systems genomics methods [1, 2, 11]. In addition, one has is to be aware of current achievements in 3D genomics (spatial-dependent genome behavior in interphase nuclei) [39, 40], which could also be included in a systems cytogenomics workflow.

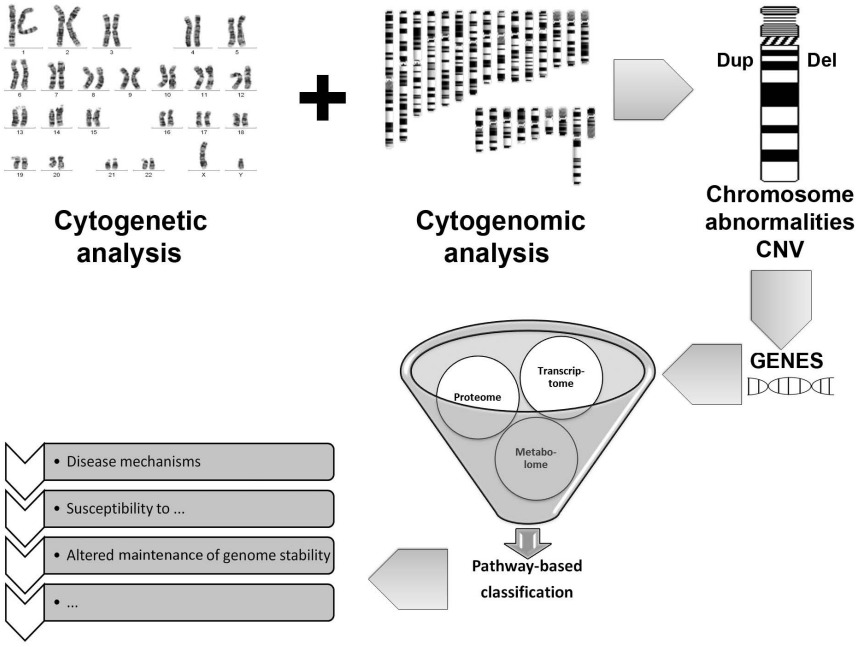

Fig. (1). Systems cytogenomics workflow. Cytogenetic and cytogenomic analyses generate data sets on CNV, subchromosomal and chromosomal variations/abnormalities, chromosome instability. Whole-genome cytogenetic analysis reveals chromosomal abnormalities and variants as well as chromosome instability by visualization (microscopy) at a resolution of 3-10 Mb. On the other hand, whole-genome cytogenomic analysis highlights CNV and the genes involved in the imbalanced rearrangements. Systems biology techniques (*i.e.* bioinformatic analysis of possible functional consequences of chromosomal imbalances/CNV at transcriptome, proteome (interactome), and metabolome levels) allow the pathway-based classification of genome variations. Consequently, the systems cytogenomics workflow offers unraveling disease mechanisms, uncovering susceptibility to multifactorial diseases (phenotypic properties) and to genome/chromosome instability (*i.e.* alterations to genome stability maintenance pathways). Certainly, the pathway-based classification of genome variations is not limited to these opportunities.

CONCLUSION

The present opinion article aimed at providing a brief overview of systems genomics in the light of cytogenomic and cytogenetic (chromosome) research. As one may see, these biomedical fields benefit from the use of systems biology methods. We do believe that our work will help to promote systems cytogenomics, and it will receive more attention than it actually does.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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