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EDITORIAL

What is the purpose of launching the *World Journal of Medical Genetics*?

Hans van Bokhoven

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Abstract

Congratulations to the publisher, members of the editorial board of the journal, all the authors and readers for launching the *World Journal of Medical Genetics* (*WJMG*) as a new member of the World series journal family! Following the completion of the Human Genome Project, medical genetic research has seen spectacular progress over the last decade. The number of genes that have been linked to Mendelian human traits has grown exponentially and currently this process is peaking with the access to robust genome-wide sequencing power. The genomics revolution is also seen for elucidation of rare and common DNA variants that increase risk for common disorders. Given this fast progress, there is an increasing need for making the results of genetics and genomics studies rapidly and freely available to the larger community. Thus, the decision for inaugurating this new journal is a timely one. The *WJMG* is a peer-reviewed, open-access periodical centered in all aspects of medical genetics research, with multidisciplinary coverage: from human phenotype to genetic and genomic mutations and variations to the study of pathological mechanisms. If you want to share new results of your research with a link to medical genetics with your peers, you will find the *WJMG* a good media to publish your papers!

Key words: Medical genetics; Genomics; Biomedical sciences; Peer-reviewed; Open-access; Journal

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Figure 1 Editor-in-Chief of the *World Journal of Medical Genetics*. Hans van Bokhoven, Professor, PhD, Department of Human Genetics, Molecular Neurogenetics Unit, Nijmegen Centre for Molecular Life Sciences and Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

INTRODUCTION

I am Hans van Bokhoven, a full professor from the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands (Figure 1) and the Editor-in-Chief of

the *World Journal of Medical Genetics* (*World J Med Genet*, *WJMG*, online ISSN 2220-3184, DOI: 10.5496). It is my great honor to introduce the *WJMG* as a new forum for exchanging new results and sharing new hypotheses relevant to clinical genetics and to fundamental and diagnostic molecular genetics and genomics research. Congratulations to the publisher, members of editorial board of the journal, all the authors and readers for this memorable event!

I am very pleased to announce that the first issue of the *WJMG*, whose preparation was initiated on December 16, 2010, is officially published on December 27, 2011. The *WJMG* Editorial Board has now been established and consists of 103 distinguished experts from 28 countries. What is the purpose of launching the *WJMG* and what will the scope of the journal be? To start with the last question, the *WJMG* will cover new developments in all areas of medical genetics: research on the causes, the diagnosis and the management of hereditary disorders in man. Medical genetics has taken a prominent position in current medical practice and has branched into many medical specialties, such as neurology, endocrinology, oncology, psychiatry, ophthalmology, dermatology and many others.

Advances in elucidation of the etiology of the broad spectrum of disorders have been propelled by the scientific landmarks set by the Human Genome Project and various other genome projects[1,2]. In addition, technological improvements, such as microarray platforms and next generation sequencing machines, have made genome wide analyses feasible for individual laboratories. As a consequence, there are currently over 3300 disorders listed in OMIM (November 2011)[3] for which the molecular basis is known and new genes are added each day. However, there are at least an equally large number of human Mendelian disorders that are still to be resolved. In addition, genetic risk factors for common disorders are only beginning to be resolved. Thus, knowledge about the genetic contribution to human disease is still largely unexplored and the knowledge of multigenic diseases is also in progress. The high pace at which we can expect to find new genotype-phenotype connections warrants the introduction of the *WJMG* as a novel open access resource for communicating such findings to the medical genetics community. The *WJMG* will solicit contributions from all subdisciplines, which include clinical genetics, metabolic and biochemical genetics, cytogenetics, molecular genetics, DNA diagnostics, mitochondrial genetics and genetic counseling.

SCOPE

The *WJMG* aims to rapidly report the most recent results in medical diagnostics, therapeutic techniques and equipment, clinical medical research, clinical and experimental techniques and methodology. Its purpose is to provide a platform to facilitate the integration of clinical and laboratory disciplines to highlight genotype-phenotype associations at a qualitative high level, which will help to improve diagnostic accuracy and medical care, and in the longer run, therapeutic intervention. The journal publishes original articles and reviews on the following topics: (1) Laboratory research, including but not limited to techniques in DNA/RNA sequencing, whole-genome linkage analyses and association studies, copy number variation profiling, epigenetic modifications in health and disease, elucidation of molecular and cellular pathways affected by gene mutations, determination of transcription factor binding sites, protein-protein interactions, preparation and transformation of induced pluripotent stem cells, animal models of human hereditary disorders and bioinformatics; and (2) Clinical genetics research on etiology, epidemiology, pathogenesis, morphology and function, signs and symptoms.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJMG* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of the *WJMG* include: (1) Editorial: to introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: to review the most representative achievements and comment on the current research status in the important fields and propose directions for the future research; (3) Topic Highlight: this column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: to update the development of old and new questions, highlight unsolved problems and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: to provide guidelines for clinical diagnosis and treatment; (6) Review: to systematically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status and make suggestions on future work; (7) Original Articles: to originally report the innovative and valuable findings in medical genetics; (8) Brief Articles: to briefly report the novel and innovative findings in medical genetics; (9) Case Report: to report a rare or typical case; (10) Letters to the Editor: to discuss and make reply to the contributions published in the *WJMG*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: to introduce

and comment on quality monographs of medical genetics; and (12) Guidelines: to introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in medical genetics.

So, if you want to share exciting novel results of your clinical, diagnostic or fundamental genetic research or your vision of new developments in the field of medical genetics research with your peers, the *WJMG* is a place you can feel at home. The staff and editorial board look forward to taking the *WJMG* to the top.

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EDITORIAL

Overlap of genetic influences in phenotypes classically categorized as psychiatric *vs* medical disorders

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Abstract

Psychiatric disorders have traditionally been segregated from medical disorders in terms of drugs, treatment, insurance coverage and training of clinicians. This segregation is consistent with the long-standing observation that there are inherent differences between psychiatric disorders (diseases relating to thoughts, feelings and behavior) and medical disorders (diseases relating to physical processes). However, these differences are growing less distinct as we improve our understanding of the roles of epistasis and pleiotropy in medical genetics. Both psychiatric and medical disorders are predisposed in part by genetic variation, and psychiatric disorders tend to be comorbid with medical disorders. One hypothesis on this interaction posits that certain combinations of genetic variants (epistasis) influence psychiatric disorders due to their impact on the brain, but the associated genes are also expressed in other tissues so the same groups of variants influence medical disorders (pleiotropy). The observation that psychiatric and medical disorders may interact is not novel. Equally, both epistasis and pleiotropy are fundamental concepts in medical genetics. However, we are just beginning to understand how genetic variation can influence both psychiatric and medical disorders. In our recent work, we have discovered gene networks significantly associated with psychiatric and substance use disorders. Invariably, these networks are also significantly associated with medical disorders. Recognizing how genetic variation can influence both psychiatric and medical disorders will help us to understand the etiology of the individual and comorbid disease phenotypes, predict and minimize side effects in drug and other treatments, and help to reduce stigma associated with psychiatric disorders.

Key words: Epistasis; Genetic pleiotropy; Comorbidity; Mental disorders; Medical disorders

Peer reviewer: Xiaoyi Gao, PhD, Assistant Professor, Department of Ophthalmology and Preventive Medicine, University of Southern California, 1450 San Pablo Street, Suite 4802, Los Angeles, CA 90033, United States

McEachin RC, Cavalcoli JD. Overlap of genetic influences in phenotypes classically categorized as psychiatric *vs* medical disorders. *World J Med Genet* 2011; 1(1): 4-10 Available from: URL: http://www.wjgnet.com/2220-3184/full/v1/i1/4.htm DOI: http://dx.doi.org/10.5496/wjmg.v1.i1.4

INTRODUCTION

Interaction between psychiatric and medical disorders has been observed for decades[1-3], although this interaction has not been well characterized with respect to the potential for common underlying genetic etiology. Disorders such as schizophrenia and diabetes are predisposed by multiple interacting genetic and environmental influences[4-6]. Identifying and understanding these interactions is critical to understanding the etiology of a range of common complex diseases[5,7-11], including psychiatric and medical

disorders that have very significant public health consequences[4,12-14]. In assessing genetic influences on complex disease, we use the term "epistasis" to mean "interaction between genes"[15,16]. This definition is broad, including any mechanism by which the effect of one gene or genetic variant influences the effect of another gene or genetic variant, resulting in the observed phenotype (changes in protein-protein binding, regulation of expression, post-transcriptional processing, translation, post-translational processing, activation/deactivation, translocation, response to environmental stimuli, *etc*.). Complex diseases also tend to be comorbid[17-20], consistent with pleiotropy having an influence on them. We use the term "pleiotropy" to mean that multiple phenotypes are influenced by a single genetic variant or set of variants[21,22]. Again, we use a simple and broad definition, including cases where any two or more phenotypes are influenced by a single variant or set of variants. Based on our recent work[18,19,23], our observation is that epistasis and pleiotropy are both important in understanding the genetic etiology of complex diseases. Note that environmental factors are important in the etiology of complex diseases but here we focus on genetic etiology. Also, while epistasis and pleiotropy apply to any phenotypes, the focus of our work is on comorbid diseases, where two or more complex disease phenotypes are seen in a single individual.

We first highlight progress and challenges in assessing genetic influences on psychiatric disorders as well as interactions between psychiatric and medical disorders. We then illustrate the roles of epistasis and pleiotropy in a complex psychiatric/medical comorbidity, based on a set of candidate genes that are statistically enriched (over-represented) in both schizophrenia and breast cancer literature. Finally, we offer observations on the significance of the overlap of genetic influences on psychiatric and medical disorders.

GENETIC VARIATION IN PSYCHIATRIC DISORDERS

Psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder, *etc*.) and medical disorders (diabetes, cancers, hypertension, *etc*.) are generally common complex diseases[24], predisposed by multiple interacting genetic and environmental influences. Substance use disorders (addiction to or dependence on cocaine, opium, alcohol, nicotine, *etc*.) are also complex diseases and they are often categorized as psychiatric disorders. Substance use disorders have characteristics of both psychiatric and medical disorders because they influence both behavior and physical condition, though they tend to have very clear environmental influences (i.e. the substances of abuse). Heritability estimates for psychiatric disorders range from 40% to 90%, depending on the disorder and population tested[24-26], strongly consistent with the hypothesis that genetic variation influences these disorders. However, efforts to find reproducible evidence of specific genetic influences have been frustrated due to locus heterogeneity, incomplete penetrance and interaction with environmental factors[24]. Efforts are currently under way to improve the success of these studies by the use of endophenotypes (sub-phenotypes), modeling the impact of environmental variation, identification of rare variants influencing the phenotype and the use of larger study populations or meta-analysis to improve power in hypothesis testing[27,28].

We have been pursuing a related approach for several years, leveraging epistasis and pleiotropy to improve the detection of sets of genetic variants associated with psychiatric disorders comorbid with substance use disorders[18,19,23]. We first noted that psychiatric and substance use disorders are often comorbid[29] and, in most populations tested, epidemiological evidence indicates that individuals diagnosed with psychiatric disorders are over-represented for substance use disorders and vice versa[29-37]. Data about genetic variants that influence psychiatric or substance use disorders is inherently noisy due to diverse populations and behaviorally based phenotype classifications. However, using the principles of epistasis and pleiotropy, we identify genetic variants at the intersection of a pair of comorbid diseases, effectively highlighting the association signal for the comorbidity and revealing biologically relevant gene sets which may be relevant to the molecular basis of the phenotype. Subsequently, we identify a network of genes that are candidates for influencing the comorbid phenotype. Interestingly, while we start out searching for candidate genes related to the psychiatric/substance use comorbidity, we invariably see medical disorders significantly over-represented in annotation for genes in these networks[18,19,23].

INTERACTION OF PSYCHIATRIC AND MEDICAL DISORDERS

Consortia have been formed to improve the detection of genetic variation influencing medical disorders and these groups have seen some success[27,38,39], although the complexity of the genetic influences involved remain challenging[40-42]. Interestingly, interaction between psychiatric and medical disorders has been observed for many years[30,43-45] (e.g. colon cancer and breast cancer have been associated with schizophrenia[46], coronary disease has been associated with depression[47-49]), although the observed interactions do not necessarily point to genetic influences. For example, antipsychotics prescribed to schizophrenics (an environmental influence) may make them more vulnerable to hyperglycemia[50,51]. However, the observed interactions may well be due to some common element that predisposes both conditions[52] and common underlying genetic variation represents an important possible etiology. As a simple example, a variant in transcription factor TCF7L2 was recently found to increase risk for both diabetes and schizophrenia, although this single variant explains only a small amount of variation in either disease[53]. We hypothesize that explaining a greater portion of the genetic influence on a given

Table 1 Gene2MeSH results

Gene symbol	Entrez gene ID	MeSH descriptor	MeSH qualifier	PubMed citations	Citations expected	Fold change	χ^2	*P* value
AKT1	207	Schizophrenia	Genetics	26	8.97	2.9	31.4	2.97E-06
		Breast Neoplasms	Pathology	91	36.40	2.5	78.2	1.63E-14
COMT	1312	Schizophrenia	Genetics	176	6.96	25.3	4107.4	5.06E-186
		Breast Neoplasms	Genetics	68	28.33	2.4	55.3	8.43E-11
CYP2D6	1565	Schizophrenia	Drug therapy	45	4.89	9.2	330.0	1.28E-28
		Breast Neoplasms	Drug therapy	42	20.00	2.1	24.5	9.59E-06
ERBB4	2066	Schizophrenia	Genetics	6	0.59	10.1	90.4	1.63E-08
		Breast Neoplasms	Pathology	27	4.43	6.1	114.9	5.28E-14
NRG1	3084	Schizophrenia	Genetics	98	1.85	53.1	5011.8	2.84E-140
		Breast Neoplasms	Pathology	24	7.50	3.2	36.1	7.39E-07
SOD2	6648	Schizophrenia	Genetics	16	3.64	4.4	42.8	1.07E-06
		Breast Neoplasms	Genetics	50	14.71	3.4	85.1	9.33E-14

The intersection of Gene2MeSH output for MeSH "descriptor: Schizophrenia" and MeSH "descriptor: Breast neoplasms" yields 6 genes significantly over-represented in PubMed abstracts annotated for both descriptors. Fold changes are calculated within Gene2MeSH as citations observed/expected. χ^2 statistics and their corresponding *P*-values are also developed from these values. This gene set became input to the GeneGo modeling.

comorbidity can be accomplished by leveraging epistasis and pleiotropy in modeling the combined phenotype.

MODELING

We have previously reported modeling interactions among clusters of candidate genes for comorbid psychiatric and substance use disorders[18,19,23] to help us understand how the genetic influences impact the comorbidity and how the relevant substances interact with the genes involved. Summarizing the process, we firstly identify a set of candidate genes for the comorbidity *via*: genome wide expression or association studies, literature mining, Gene2MeSH[54] and/or the Genetic Association Database[55]; secondly, establish biological context for the set of genes by modeling their interactions *via*: Prioritizing Disease Genes by Analysis of Common Elements[56], Gene Relationships Among Implicated Loci[57] and/or GeneGo[58]; and thirdly, identify, report and interpret over-represented concepts in annotation for genes in these networks *via*: the Database for Annotation Visualization and Integrated Discovery[59], ConceptGen[60] and/or GeneGo[58].

As expected, the genes in the networks developed are significantly over-represented for annotation consistent with psychiatric and substance use disorders. However, we noted that each of these networks is also significantly over-represented by genes annotated for their roles in medical disorders. This observation in multiple studies leads us to hypothesize that, in a genetic sense, distinctions made between psychiatric and medical disorders are arbitrary.

Candidate gene selection

To illustrate how psychiatric and medical disorders share constellations of genetic influences, we followed the observed interaction between schizophrenia and breast cancer[46]. To minimize the chance of pursuing a spurious association, we searched PubMed for ["schizophrenia" (MeSH Terms) AND "breast neoplasms"(MeSH Terms)] and found 43 papers annotated for this comorbidity. We then began a candidate gene search using Gene2MeSH[54], which identifies genes that are significantly over-represented (*P*-value < 10^{-5}) in annotation for PubMed abstracts that are also annotated for given Medical Subject Headings (MeSH). Note that, while we recognize that a simple PubMed search may be subject to publication bias, Gene2MeSH overcomes this bias in calculating significance values. We searched for human genes over-represented for MeSH annotation "descriptor: Schizophrenia" (145 genes) and MeSH annotation "descriptor: Breast Neoplasms" (164 genes). We selected the 6 genes at the intersection of these sets for follow-up analysis (Table 1).

Biological contextualization

To place the 6 candidate genes identified in our Gene2MeSH search into context, we used GeneGo's MetaCore database of protein-protein and protein-small molecule interactions to build a gene network model of the candidate genes, plus their closest interactors, using the following parameter settings: (1) shortest paths algorithm; (2) merged network; (3) no canonical pathways; (4) 2 maximum steps in the path; (5) show disconnected seed nodes; (6) show shortest path edges only; (7) discard low trust interactions; (8) use functional interactions; (9) use binding interactions; and (10) do not use compound-target interactions.

Enriched concepts

The resulting network (Figure 1) is organized by cellular compartment and shows the close and multi-layered interactions among these 6 genes and their interactors. Note that Figure 1 has 31 icons representing 43 genes because some of the icons represent dimerized proteins that act as a single unit. Based on MetaCore data, GeneGo calculates that the larger network is significantly enriched for genes annotated for brain diseases, cancers and hormone sensitive disorders (Table 2). This annotation is consistent with the hypothesis of shared genetic

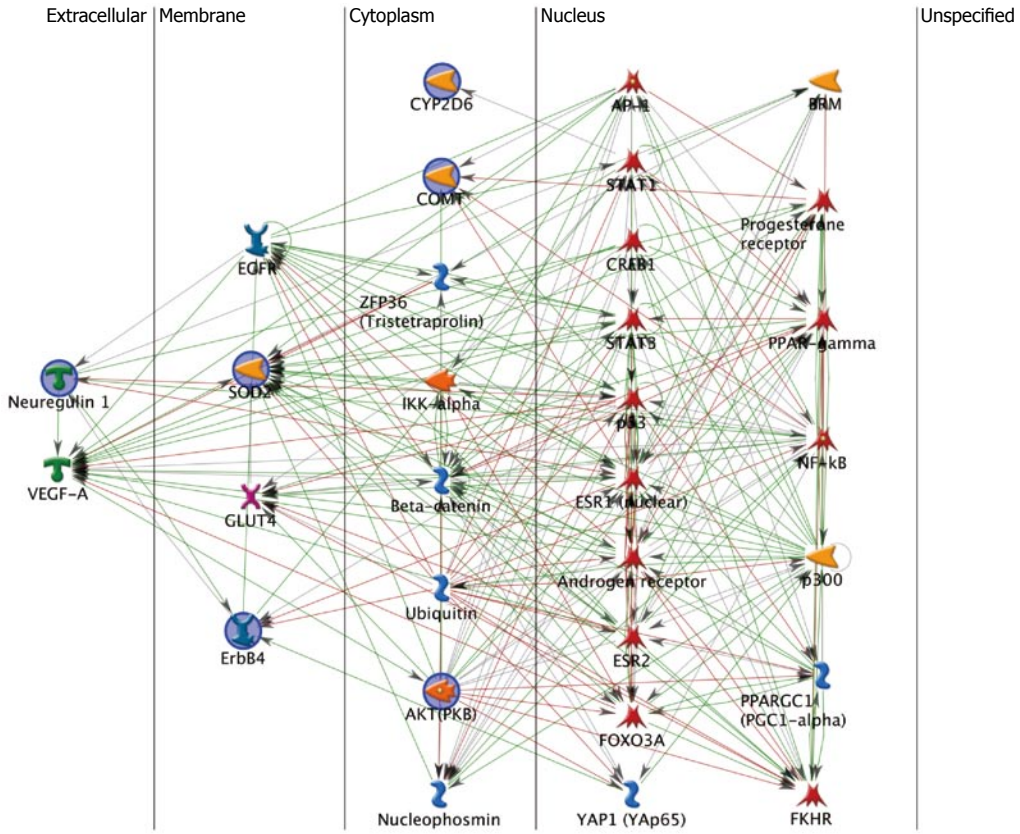

Figure 1 Systems biology model. GeneGo modeling shows how the 6 candidate genes identified by Gene2MeSH (circled in blue) interact with a tight-knit set of 37 additional genes, 13 of which regulate gene expression, and 5 of which are hormone responsive. The network also highlights the multiple positive and negative feedback cycles contained in the network. See www.genego.com for description of icons, colors and links in the figure.

Table 2 Over-represented disease annotation for systems biology model

Disease	Percent of network genes annotated (%)	*P* value
Ovarian neoplasms	76.74	5.80E-29
Ovarian diseases	76.74	3.24E-27
Adnexal diseases	76.74	3.89E-27
Mesothelioma	48.84	2.04E-26
Neoplasms, mesothelial	48.84	2.50E-26
Gonadal disorders	76.74	4.23E-26
Genital neoplasms, female	79.07	8.70E-26
Hyperoxia	30.23	2.10E-23
Genital diseases, female	83.72	4.75E-22
Astrocytoma	72.09	4.82E-22
Neoplasms, connective and soft tissue	62.79	1.64E-21
Glioblastoma	69.77	3.67E-21

The 43 genes in the GeneGo model developed from the 6 candidate genes show significant over-representation for cancers, especially hormone sensitive cancers, and brain diseases, including brain cancers. *P* values characterizing the significance of enrichment are calculated within the GeneGo software based on a hypergeometric distribution.

vulnerability to schizophrenia and breast cancer, and emphasizes that these disorders are genetically related to the broader phenotypes. The "hubs" for the network shown in Figure 1, the genes with the most interactions, are Androgen receptor (33 interactions) and Estrogen receptor 1 (32 interactions), consistent with hormone response. Other notable hubs include p53, strongly associated with cancers[61] (30 interactions), and Estrogen receptor 2, a homolog to Estrogen receptor 1 (22 interactions). Of the 43 genes in this network, 22 are transcription factors, consistent with an important role for regulation of gene expression.

"Adnexal Diseases" and "Hyperoxia" are over-represented phenotypes (Table 2) that we have not been able to place into the context of brain disorders or cancers. Equally, "positive regulation of nitrogen compound metabolic process" is the most significantly over-represented Gene Ontology biological process in the annotation for these genes (*P*-value: 3.49×10^{-37}) and, again, we have not been able to place this process into context. These may represent spurious associations. However, based on our previous experience, we hesitate to dismiss the evidence for these associations. They could represent novel puzzle pieces that will be appreciated only when other pieces are discovered and put into context. This was the case when we first noticed that medical disorders were significantly enriched in annotation for networks based on psychiatric/substance use comorbidities.

IMPLICATIONS

Genetic variation's influence on complex disease is agnostic to categorization of psychiatric *vs* medical disorders. We present a view on comorbidity research that opens

the door to analysis of new combinations of related phenotypes, which could also shed light on single-disorder phenotypes. We propose that, based on epidemiological evidence, we can search for genetic influences on comorbidities that might otherwise seem unrelated[62-65]. Over-represented concepts found in annotation for genes in these networks serve as positive controls in model building and provide insight into the biological context of the genetic influences. These insights may also provide novel background on fundamental processes that would not be evident without the network model. These insights can then be applied to improve our understanding of the comorbidity and each of the single-disorder phenotypes. The methods we describe are not biased by disease terminology and are only biased based on the literature and gene set categorizations and annotations. By using multiple data sources we hope to minimize that bias but recognize that it still exists.

Therapy and drug side effects

At least 16 genes in the network in Figure 1 are annotated in GeneGo's MetaDrug database as being known targets for currently available therapeutic drugs. Arguably, any of these drugs has potential for therapeutic use in schizophrenia or breast cancer, as well as the related phenotypes seen in Table 2. The multiple positive and negative feedback loops evident in Figure 1 are also indicative of the complex nature of epistasis in this comorbidity. Development of drugs for therapeutic use can benefit from this work by incorporating the understanding that these genes have complex interactions that must be considered when targeting any one of them or any combination of them. In the larger sense, this network is not unique in modeling comorbid psychiatric and medical disorders; rather this is the pattern that we have seen in previous work and it is consistent with side effects seen in a range of treatment protocols[66-71]. By improving our understanding of the multiple interacting genetic and environmental influences on any disease phenotype, we should be able to better predict therapeutic interactions and side effects, and reduce their negative effects on the patient[72].

Replication of association

A challenging facet of complex disease research is the frequent failure to replicate significant findings in follow-on analyses[24]. The hypothesis that epistasis and pleiotropy are important in complex comorbidities is consistent with these observations where, for example, in one study the direction of association for a given comorbidity is positive[46] and in other study the direction is negative[73]. The alternate direction of correlation should actually be viewed as additional evidence of a relationship between common gene variants and these diseases. A model consistent with this phenomenon posits that a given set of genetic variants could be positively associated with both a psychiatric disorder and a medical disorder, while the same gene set with a slight change in variation, perhaps in a different population, could reverse the direction of effect for one of the disorders. Equally, minor changes in other interacting genes or environmental effects could yield population specific, gender specific or environment specific effects that hamper replication efforts.

Stigma

A significant challenge for psychiatric patients is the stigma associated with diagnosis and treatment for their disorders, interfering with essentially every facet of their lives[12]. Part of this stigma comes from the preconception that there is something inherently different about psychiatric disorders when compared with medical disorders. This stigma is also the result of our lack of understanding of the etiology of psychiatric disorders and, in many cases, our inability to effectively treat these disorders. The growing recognition that psychiatric disorders are influenced by the same complex interacting genetic and environmental influences that predispose medical disorders, which are better accepted by society, may help to ease the stigma associated with psychiatric disorders. Overcoming this stigma may then lead individuals back to productive lifestyles and healthier relationships[12].

CONCLUSION

Psychiatric and medical disorders have traditionally been segregated, in part due to our understanding that psychiatric disorders are fundamentally different from medical disorders. In some ways this is true, although our improved understanding of both epistasis and pleiotropy in genetic predisposition to complex diseases makes the distinctions less clear. The methods we have been developing provide a way to identify common genetic influences on psychiatric and medical disorders that might otherwise seem distinct. These methods use existing annotation of genes and pathways, and the vast amount of biological and medical research literature currently available, to identify genes involved in comorbidities. The hope is that by identifying potential common genetic variants in comorbid diseases, we can improve medicine by better understanding basic molecular processes and gene or pathway interactions; leverage common therapeutic agents already developed for different diseases or disorders; and raise awareness of the potential for genetic etiology that is common across medical and psychiatric disorders.

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OBSERVATION

Research progress in the cell origin of basal cell carcinoma

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Abstract

Identification of the cell origin of human neoplasms remains a challenging but important task in cancer research. The outcomes in this area of study may allow us to design novel strategies for early cancer detection and targeted cancer therapeutics. Skin is a great organ to study cancer stem cells because stem cells in skin have been well investigated and approaches of genetic manipulation in specific cell compartments are available to mimic clinical skin cancer in a mouse model. Recently, by using different genetic engineered mouse models, several groups have tried to discover which cell type in skin was responsible for the initiation of basal cell carcinoma, the most common type of skin cancer. These studies raised more questions but also showed more ways for future investigation.

Key words: Basal cell carcinoma; Sonic hedgehog signaling; Mouse model; Stem cell

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CELL ORIGIN OF BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is one of the most common human cancers, so named based on its histological similarity to basal keratinocytes[1]. Almost all BCCs exhibit activation of the Hh signaling pathway, which is a critical regulator of cell proliferation, tissue differentiation and tissue polarity[2]. In normal skin, Hh signaling is temporally and spatially controlled to regulate hair follicle (HF) growth and morphogenesis[3], but dys-regulated in BCC due to loss-of-function mutations in PTCH1 or gain-of-function mutations in SMO[2]. Basal keratinocytes of skin are composed of different types of cells, including stem cells residing within the interfollicular epidermis (IFE) and HF[4,5]. It is still not clear which cell type is responsible for BCC formation. Recently, several groups reported new data to demonstrate the cell origin of BCC by activating Hh signaling in different cell populations in mouse skin.

Youssef *et al*[6] used different promoter-driven inducible cre expression, including keratin 14, Shh and keratin 15, to activate Hh pathway by induced expression of active SMO mutant, SmoM2. They found that murine BCCs almost exclusively derive from cells in IFE but not HFs. These results are not expected, based on the previous theory that BCC is HF-derived tumor. It is known that Hh signaling is physiologically required for HF growth *via* stimulation of proliferation of HF progenitors, and these cells might be naturally preferential to mediate Hh pathway-driven tumorigenesis. Soon after,

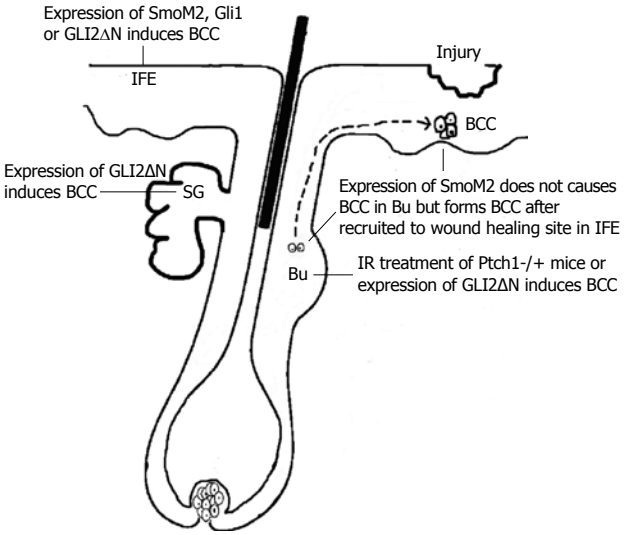

Figure 1 Different models used for cell origin investigation of basal cell carcinoma. IFE: Interfollicular epidermis; SG: Sebaceous gland; Bu; Bulge.

Wang *et al*[7] reported that development of BCCs in ion-irradiated Ptch1$^{+/-}$ mice were mainly from HF bulge cells. Through lineage tracing study, they found that the great majority of BCCs arose from K15-positive bulge cells. So, these two groups reached opposite conclusions about the putative cell of origin of BCC. One explanation for this discrepancy is that, in the two mouse models, forced expression of mutant Smo and loss of Ptch1 may be different in biological effects. In addition to the inhibition of Hh signaling, Ptch1 can bind cyclin B1 directly to prevent nuclear translocation of cyclin B1, and thus inhibit cell cycle progression[8]. Indeed, Wang *et al*[7] compared the location of cyclin B1 in tumors arising in the two models, and found more cyclin B1 accumulation in BCC of IR-treated Ptch1$^{+/-}$ mice than that of SmoM2 mice, indicating that nuclear cyclin B1 might facilitate BCC arising from follicle in their model.

No matter how Hh signaling is activated, Gli2 is the primary transcriptional effector for the Hh signaling pathway[9]. Grachtchouk *et al*[10] engineered mice expressing GLI2 activator (GLI2ΔN) selectively in different cell compartments of epidermis using a novel mouse model, in which Cre-lox and tet-regulated system are combined together to control not only tissue and temporal expression, but also the expression level of GLI2ΔN. Using this new system, they found that a BCC-like skin tumor could arise from different cell types in epidermis, such as Lgr5+ secondary hair germ in the resting HF, outer root sheath in growing HF, IFE and sebaceous gland, but cells in follicle bulge were resistant to GLI2ΔN-induced hyperplasia, probably because of increased apoptosis[10]. After they reduced GLI2ΔN expression level in basal cells by administrating a lower dose of doxycycline, mice developed a BCC-like abnormality, similar to lesions seen in mice expressing mutant Smo, which was thought to be a weaker Hh pathway activator in skin[11]. All these data together can provide another explanation for why Youssef *et al*[6] only saw IEF origin of BCC in K14:SmoM2 mouse and SmoM2 mutant failed to produce tumors from follicle stem cells in keratin 15-Cre mice.

The resistance of bulge cells to Hh pathway-induced transformation is probably due to the restriction of bulge microenvironment. It was reported that expression of negative regulators of the Hh pathway, such as Gli3 and Sufu, was up-regulated in follicle bulge stem cell niche[12] where a quiescent microenvironment was maintained[13]. However, during wound healing, as shown by the other two groups[14,15], bulge stem cells with high Hh signaling activation were recruited to wounding sites and give rise to tumors in the newly formed epidermis. These data indicate that identification of the BCC cell origin becomes more difficult due to the changing tumorigenic potential during cell migration.

The different models used for cell origin investigation of BCC are shown in Figure 1.

CONCLUSION

In these recent publications, researchers are trying to address the cell of origin of BCC using a genetically engineered mouse model to activate Hh signaling in different epidermal compartments. All these results are simply based on one mechanism that high-level Hh signaling alone in keratinocytes can produce murine BCC, but these results over simplify the real situation. The cellular origin of BCCs may not be the same cell type in all circumstances, depending on the tissue condition, the targeted component of the Hh pathway for the study as well as the cell population being targeted. The situation becomes further complicated when considering the movement of these mutant cells before tumor formation. It is fair to say these publications bring more curiosity to the field.

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GUIDELINES FOR BASIC SCIENCE

Genetic interactions in translational research on cancer

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Abstract

Genetic interactions are functional crosstalk among different genetic loci that lead to phenotypic changes, such as health or viability alterations. A disease or lethal phenotype that results from the combined effects of gene mutations at different loci is termed a synthetic sickness or synthetic lethality, respectively. Studies of genetic interaction have provided insight on the relationships among biochemical processes or pathways. Cancer results from genetic interactions and is a major focus of current studies in genetic interactions. Various basic and translational cancer studies have explored the concept of genetic interactions, including studies of the mechanistic characterization of genes, drug discovery, biomarker identification and the rational design of combination therapies. This review discusses the implications of genetic interactions in the development of personalized cancer therapies, the identification of treatment-responsive genes, the delineation of mechanisms of chemoresistance and the rational design of combined therapeutic strategies to overcome drug resistance.

INTRODUCTION

Genetic interactions are functional crosstalk among genes of different loci that regulate or compensate for one another in many signaling and/or metabolic pathways, leading to phenotypic changes, including disease status (sickness) or viability alterations (lethality or semilethality). Unlike the dominance caused by interactions between alleles of the same genetic locus, the interactions of different genetic loci may lead to unexpected phenotypic changes that are different from the effects of mutations in each individual gene. An example of a typical phenotypic change caused by genetic interaction is synthetic lethality or synthetic semilethality; in brief, homozygous mutations in two genes result in normal viability in living organisms when the mutations exist separately but become lethal or semilethal (viability reduced but not completely abolished) when they occur simultaneously[1].

Because a lethal phenotype can be easily identified, synthetic lethality has frequently been used as a research tool for identifying interactions among genes. Global gene knockout studies in yeast showed that about 20% of genes in *Saccharomyces cerevisiae* (*S. cerevisiae*) are essential for growth on a rich glucose-containing medium, whereas

about 80% of the approximately 6200 predicted genes are nonessential, suggesting that the genome is buffered from the lethal effects of genetic disorders in more than 4700 genes that may have redundant functions associated with essential processes[2-4]. Thus far, global synthetic lethality analysis in yeast has generated substantial new information on genetic interactions that compensate for one another in biologically essential processes[5]. Information on genetic interactions has been used to predict the function of uncharacterized genes and decipher complex regulatory relationships among biochemical processes or pathways[5]. The principle of genetic interactions is also being exploited by various investigators to identify genes that are crucial to the survival of certain oncogene-transformed cells[6-9] or genes that sensitize cells to chemotherapy[10,11] or to find small molecules that selectively induce cell death in a subset of oncogene-transformed cells[12-14]. Thus, the principles of genetic interaction have become a research platform for characterizing gene functions, discovering novel anticancer agents, identifying molecular biomarkers for personalized therapy and designing effective combination therapies to overcome drug resistance. Applications of genetic interactions in anticancer drug discovery were recently reviewed in several articles[15-17]. This review will discuss potential applications of genetic interaction in personalized therapy and in the rational design of multimodality therapy.

NETWORKS OF GENETIC INTERACTIONS

The functional interactions among genes are more comprehensive than the physical interactions among proteins. Studies in yeast have shown that, on average, each gene may have more than 40 genetic interactions[18-20], whereas yeast proteins may have an average of 8 physical interactions per protein[21]. A study used 74 genes known to be involved in genomic integrity in *S. cerevisiae* to search for genetic interactions with those genes resulted in the identification of a network of 4956 unique pairs of genetic interactions involving 875 genes[19]. Within this network, several novel components and functional modules or minipathways were defined that are important for DNA integrity, including those involved in DNA replication, postreplication repair, homologous recombination and oxidative stress response[19]. More recently, several groups of researchers used a gene knockdown approach to search for genes that are synthetic lethals to the oncogenic *KRAS* gene and identified numerous synthetic lethal partners with mutant *KRAS* gene in various human cancer cells[6-9]. For example, a genome-wide RNAi screening in the isogenic human colon cancer cell line DLD-1 with and without oncogenic *KRAS* led to the identification of 368 lethal interaction candidate genes with a stringent cutoff and 1613 genes with relaxed statistical criteria[8]. Genes involved in the regulation of several biological processes or pathways, including nucleic acid metabolism, ribosome biogenesis, protein neddylation or sumoylation, RNA splicing, the cell cycle, mitosis and proteasome complexes, were found to be required as additional support to maintain the Ras oncogenic state[8]. Thus, genetic interactions are more complicated and comprehensive than physical interactions.

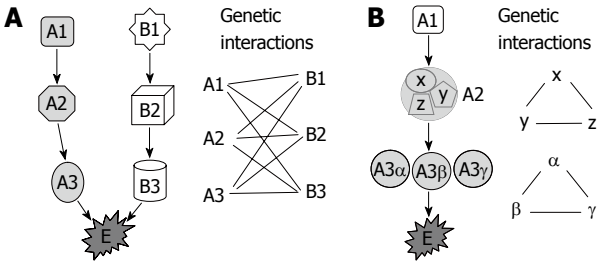

Figure 1 Diagram of genetic interactions. A: The essential biological function E is regulated by pathways A and B. A functional change in either of these pathways, such as a mutation in A1 or B1, is insufficient to induce dysfunction of E. However, the simultaneous presence of a mutation in A1 and a mutation in any of B1, B2 or B3 induces dysfunction of E (or phenotype changes). Thus, A1 has genetic interaction with B1, B2 and B3, and vice versa; B: The essential biological function E is regulated by pathway A alone, in which A2 is a multiprotein complex composed of X, Y and Z, while A3 has homologues of α, β and γ. Genetic interaction may exist among X, Y and Z, and among A3α, β and γ.

Several models have been proposed to account for genetic interactions[21-23], including the components of parallel pathways that together regulate an essential biological function, subunits of an essential multiprotein complex and components of a single linear essential pathway (Figure 1). Synthetic genetic array analysis and synthetic lethality analysis by microarray in yeast revealed that genetic interactions occurred the most frequently between genes with the same mutant phenotype, between genes encoding proteins with the same subcellular localization, and between genes involved in similar biological processes or bridging bioprocesses[5,18]. Although genetic interactions were more frequent than expected between genes encoding proteins within the same protein complex and among gene pairs encoding homologous proteins, relatively few synthetic lethal interactions (only 1%-2%) fall into these two categories[18]. Most of the genetic interactions were identified among functionally related genes or among genes that function in parallel or compensating pathways[2,5,18,24].

STRATEGIES FOR PERSONALIZED CANCER THERAPY

Activating mutations in oncogenes and growth factor receptors are known to play critical roles in tumorigenesis and in the malignant evolution of cancers[25,26]. Several oncogenes or growth factor receptors have been successfully targeted by small molecule inhibitors and/or monoclonal antibodies for cancer treatment. Genetic changes, such as gene amplifications or mutations in the corresponding genes, have been used as predictive biomarkers for identifying patients who would benefit from a particular treatment[27]. Cancers overexpressing HER2 were shown to respond favorably to the monoclonal antibody trastuzumab[28,29]. Similarly, the epidermal growth factor receptor (EGFR) inhibitors erlotinib and gefitinib

were found to be more effective against EGFR mutant cancers[30], whereas imatinib was highly effective against cancer cells with BCR-Abl fusion protein[31].

Therapeutic benefits can also be obtained by targeting oncogenes and tumor suppressor genes indirectly through genetic lethal interactions. Functional alterations in some oncogenes or tumor suppressor genes may render the mutant cells more susceptible to a functional change in another gene. Therefore, the mutant cells can be eliminated through pharmaceutical intervention that leads to synthetic lethality. Selective cytotoxicity of poly (ADP-ribose) polymerase 1 (PARP1) inhibitors in *BRCA1* and *BRCA2* mutant cancer cells is mediated through genetic interaction between *PARP1* and *BRCA*s. *PARP1* is required for DNA single-strand break (SSB) repair because PARP1$^{-/-}$ mice have defective DNA SSB repair and increased homologous recombination, sister chromatid exchange and chromosome instability[32,33]. On the other hand, *BRCA1* and *BRCA2*, whose loss-of-function mutations predispose carriers to breast, ovarian and other types of cancers[34,35], are required for homologous recombination of DNA double-strand break (DSB) repair[36,37]. *PARP1* may not be directly involved in DSB repair and homologous recombination since PARP1$^{-/-}$ embryonic stem cells and embryonic fibroblasts exhibited normal repair of DNA DSBs[32]. Nevertheless, concurrent blockage of DNA DSB repair, resulting from a mutation in *BRCA* genes and DNA SSB repair due to PARP1 inhibition, is fatal to a cell[38,39]. As a result, *BRCA* mutant cells are 1000 times more sensitive to PARP1 than are *BRCA* wild-type cells[39]. Clinical trials also showed that cancer patients with *BRCA1* or *BRCA2* mutations responded favorably to an orally active PARP1 inhibitor, olaparib (AZD2281)[40-43].

Functional changes in several genes involved in DNA DSB repair pathways, such as *ATM*[44], *RAD54*[45] and *BRIT1*[46] genes, have been found to be highly associated with susceptibility to radiotherapy and the DNA cross-linking agent mitomycin C, suggesting that mutations in those genes may be used as biomarkers of susceptibility to radiotherapy or DNA-damaging chemotherapeutic agents. The *ATM* gene encodes the ataxia telangiectasia mutated (ATM) protein kinase that is rapidly activated when DNA DSBs occur in eukaryotic cells[47]. Activated ATM phosphorylates a variety of proteins involved in cell cycle checkpoint control, apoptosis and DNA repair pathways, including p53, CHK2, BRCA1, H2AX and FANCD2[47,48]. A recent study indicated that interactions of ATM and p53, two commonly mutated tumor suppressor genes, should be explored to determine their ability to predict clinical response to genotoxic chemotherapies[49]. In p53-deficient tumor cells, inactivation of ATM or of its downstream molecule CHK2 was sufficient to sensitize the cells to the genotoxic chemotherapeutic agents cisplatin and doxorubicin[49]. Interestingly, inhibition of ATM or of CHK2 resulted in a substantial survival benefit in p53 wild-type cells. Several clinical trials of CHK1/CHK2 inhibitors in combination with genotoxic agents for cancer treatment are currently under way[50]. The p53 inactivation that occurs in about 50% of human cancers because of genetic mutations[51] may serve as a biomarker for the efficacy of combination therapies containing cisplatin and doxorubicin plus inhibitors of ATM and CHK2.

Another indirect approach is targeting a downstream component in a single linear essential pathway. Evidence has shown that *BRAF* mutant cancer cells can be selectively killed by inhibitors of mitogen-activated protein (MAP) kinase (MEK), a substrate of Raf protein kinases[52]. The RAS/RAF/MEK/Erk pathway is one of the critical signal transduction cascades of most growth factor receptors and is pivotal in oncogenesis[53,54]. RAF kinases are activated by RAS upon the stimulation of extracellular ligands, such as growth factors, cytokines and hormones. Activated RAF phosphorylates and activates the dual-specificity protein kinase MEK, which in turn phosphorylates both tyrosine (Tyr185) and threonine (Thr183) residues of extracellular-signal-regulated kinase (ERK) proteins[55], leading to activation of ERK1/ERK2. Various constitutively active mutations of the *BRAF* gene have been identified in human cancers, including 60%-70% of malignant melanomas, 36%-50% of thyroid cancers, 5%-22% of colorectal cancers, 30% of serous ovarian cancers and lower percentages of other cancers[56]. The strong dependence of *BRAF* mutant tumors on MEK activity may provide a personalized therapeutic strategy for patients with this type of cancer[52].

Overexpression of the *MYC* oncogene was reported to upregulate the expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) death receptor DR5, thereby sensitizing tumor cells to TRAIL-induced apoptosis[57]. An analysis of the knockdown of 510 genes encoding known and predicted kinases, proteins with known functions in TRAIL-mediated signaling pathways, or proteins with unknown functions also revealed that siRNA against *PAK1* and *AKT1* strongly enhanced TRAIL activity, whereas siRNA against *MYC* or the WNT transducer *TCF4* inhibited TRAIL-induced apoptosis, indicating that the MYC and WNT pathways are required for TRAIL-mediated apoptosis[58]. On the other hand, deficiency of the tumor suppressor gene adenomatous polyposis coli (APC) was found to cause accumulation of β-catenin in the nucleus, which interacts with TCF4 and promotes TCF4's binding to c-MYC promoter and overexpression of c-MYC[59]. Deletion of the *MYC* gene rescued the phenotypes caused by deletion of the *APC* gene, despite the presence of high levels of nuclear β-catenin[60]. Thus, *MYC* overexpression is a critical component in the malignancy of APC-defective cancers. A recent study showed that the combination of TRAIL and all-trans-retinyl acetate, another death receptors inducer, significantly enhanced apoptosis induction in *APC* gene-defective tumor cells and premalignant cells[61], indicating that this combination can be useful for chemoprevention and personalized therapy in patients with APC-defective cancers.

SYSTEMATIC ANALYSIS OF GENES ASSOCIATED WITH TREATMENT RESPONSE

Genetic interaction has been exploited as a research tool to identify genes or biomarkers associated with treatment responses. Studies of the Food and Drug Administration (FDA)-approved anticancer agents in a panel of yeast mutants revealed that the DNA cross-linking agent cisplatin displayed high specificity for mutants defective in postreplication repair, whereas the topoisomerase II inhibitor mitoxantrone was highly specific for defects in DNA DSB repair[62]. Because many human disease-related genes are conserved with their yeast counterparts[63,64], yeast has been exploited for mechanistic study of clinically relevant compounds[65,66]. A genome-wide screen of yeast heterozygotes with therapeutic compounds could reveal not only the possible targets but also synthetic lethal partners of the tested compounds[67]. For example, heterozygotes of *TRX2*, a nonessential gene involved in antioxidative stress, were found to be sensitive to camptothecin, whereas heterozygotes of genes involved in exosome rRNA processing were identified as possible lethal partners with 5-fluorouracil[67]. An analysis of more than 1000 structurally diverse compounds, including drugs approved by the FDA and the World Health Organization, in yeast whole-genome heterozygous and homozygous deletion collections showed that genes involved in endosomal transport, vacuolar degradation, aromatic amino acid biosynthesis or encoding of some transcription factors may function as multidrug-resistance genes because their deletion renders yeast sensitive to multiple drug treatments[68]. Nevertheless, information obtained from yeast studies needs to be validated in human cell systems before the results can be translated into clinical applications.

The advent of gene knockdown technology allows us to perform systematic analysis of genes associated with treatment response in human cancer cells. Whitehurst *et al*[10] used a library of more than 84 000 chemically synthesized siRNAs targeting 21 127 unique human genes to screen for gene targets that specifically reduce cell viability in the presence of an otherwise sublethal dose of paclitaxel in the human non-small cell lung cancer line NCI-H1155. Their study identified a set of 87 candidate genes whose knockdown sensitized cells to paclitaxel and some of the genes increased the sensitization of lung cancer cells to paclitaxel by more than 1000 times. Multiple genes encoding core components of the proteasome, proteins involved in the function of microtubules, post-translational modification and cell adhesion, or cancer/testis antigens were found to be associated with the sensitivity of paclitaxel[10]. A similar approach has been used by Astsaturov *et al*[11] for identification of genes associated with response to EGFR inhibitors. Analysis of a siRNA library targeting 638 genes encoding proteins with evidence of functional interaction with the EGFR signaling network, including those transcriptionally responsive to inhibition or stimulation of EGFR, led Astsaturov *et al*[11] to identify 61 genes whose knockdown sensitized the A431 cervical adenocarcinoma cell line to the EGFR inhibitors erlotinib or cetuximab[11]. Most of those genes encode proteins connected in a physically interacting network, including kinases and phosphatases. Nevertheless, a further test in 7 other cell lines for sensitization to erlotinib or cetuximab showed that none of the tested genes sensitized all cell lines, although several of them sensitized 3-5 of the cell lines[11], suggesting that genetic interactions are highly dependent on cell context.

MECHANISMS OF RESISTANCE AND RATIONAL DESIGN OF COMBINATION THERAPY

Genetic interactions could be the underlying mechanisms of resistance to targeted cancer therapies. The same concept may allow us to develop strategies to overcome this resistance. Mutation analyses of primary cancers for genes encoding kinases or genes with known associations with cancers have revealed that an individual tumor may harbor 50 or more mutations in such genes[25,69-71]. Several important signaling pathways might cooperatively be involved in the oncogenesis and malignant evolution of cancers[25,69-72]. Thus, cancer itself is a result of genetic interactions. Tumor cells, xenograft tumors and primary tumors may carry multiple concomitantly activated oncogenes or inactivated tumor suppressor genes. As a result, interrupting a single pathway is often insufficient to induce cell death in most cancer cells because redundant input from various pathways drives and maintains downstream signaling; thus, single-agent therapies have limited efficacy[73,74]. Consequently, combinations of targeted agents are frequently required for effective anticancer therapy or for overcoming drug resistance[73]. Numerous combination regimens of targeted agents are currently being investigated at either the preclinical or clinical level[74,75]. The information about networks of genetic interactions may facilitate the rational design of combinatorial therapy to enhance therapeutic efficacy.

The SRC oncogene encodes a nonreceptor tyrosine kinase that interacts with multiple receptor tyrosine kinases (RTKs), including EGFR, vascular endothelial grow factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor, insulin-like growth factor 1 receptor, hepatocyte growth factor receptor and others[76,77]. Recruiting SRC to receptor tyrosine kinases activates SRC and triggers a cascade of downstream signaling promoting cell proliferation, survival and invasion, as well as angiogenesis. Moreover, SRC can interact synergistically with RTKs by phosphorylating RTKS and modulating their activities[78-80]. Increased SRC activity is associated with resistance to conventional anticancer agents, such as cisplatin[81] and gemcitabine[82], and targeted anticancer agents, such as

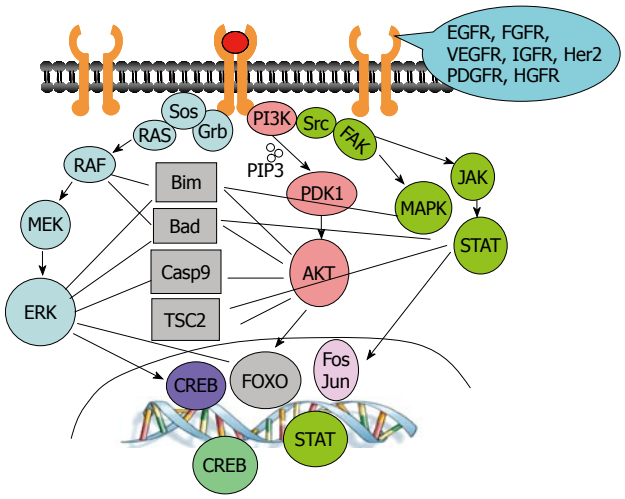

Figure 2 Growth factor activated pathways and their crosstalks. Growth factors, such as epidermal growth factor (EGF), vascular endothelial grow factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF) and platelet derived growth factors (PDGF), interact with their receptors and activate the common downstream pathways, such as PI3K/AKT, RAS/RAF/MAPK and SRC/JAK/STAT pathways. Moreover, there are crosstalks among those pathways in regulating transcription factors and apoptotic/survival proteins. Inhibiting a single target or blocking a single pathway is often not sufficient to induce apoptosis in cancer cells.

gefinitib[83] and trastuzumab[84]. Simultaneous targeting of SRC and Her2 sensitizes multiple trastuzumab-resistant breast cancer cells to trastuzumab *in vitro* and *in vivo*[84]. Inhibiting SRC also sensitized *KRAS* mutant colorectal tumors to cetuximab[85]. Combined inhibition of SRC and EGFR sensitized pancreatic tumor cells to gemcitabine[86]. These results demonstrated that combination therapy consisting of SRC and RTKs inhibitors could be an effective strategy for overcoming resistances to a variety of anticancer agents.

Both EGFR and hepatocyte growth factor receptor (MET)[87,88] play important roles in carcinogenesis[89,90]. Once activated by their ligands, EGF and hepatocyte growth factor, respectively, EGFR and MET activate common downstream pathways, including the PI3K/AKT, RAS/RAF/MAPK and SRC/JAK/STAT pathways (Figure 2). Therefore, elevated activity of MET may negate the effects of anti-EGFR therapeutic agents. Indeed, focal amplification of MET in EGFR-inhibitor-sensitive lung cancer cell lines rendered the cells resistant to anti-EGFR treatment by maintaining ERBB3/PI3K/AKT activity[91]. MET amplification was observed in lung cancer specimens that had developed resistance to gefitinib or erlotinib and in untreated tumors[91,92]. Treatment of resistant cells with a tyrosine kinase inhibitor for either MET or EGFR could not induce cytotoxicity in resistant cells, whereas combined targeting of MET and EGFR resulted in substantial growth inhibition of resistant cells and complete suppression of ERBB3/PI3K/AKT activity[91,92]. Such a therapeutic combination strategy overcame resistance to the EGFR inhibitor erlotinib in an *EGFR* mutant lung cancer tumor model, both *in vitro* and *in vivo*[93].

Crosstalk among downstream pathways of growth factors is also common. The RAS/RAF/MEK/ERK and PI3K/AKT pathways crosstalk and regulate many common downstream targets (Figure 2), such as forkhead transcription factors[94-96], the TSC2/mTOR complex[97-101], BAD[102-104] and caspase-9[105,106]. It is expected that high levels of PI3K/AKT activity can negate antitumor activity induced by MEK/ERK inhibition. Indeed, inhibition of MEK/ERK is sufficient to suppress cell growth or induce apoptosis in cells with low levels of AKT activity but is ineffective in cells with high levels of AKT activity[107]. Combination treatment with MEK and AKT inhibitors was more effective than either single agent alone in human non-small cell lung cancer models *in vitro* and *in vivo*[108].

CONCLUSION

Genetic interaction is likely to be involved in every biological process and has been used as a research platform in various areas of biomedical research. It will continue to be a powerful research tool for both basic and translational studies. Knowledge of the networks of genetic interactions is expected to be translated into clinical applications, in particular for the treatment of cancers.

Note that genetic interactions may be highly dependent on cell context. For a particular gene, genetic interaction may vary in different cell lines. Therefore, it is not unexpected that different candidate genes were obtained when the same oncogenic *KRAS* gene was used to query its genetic lethal interactions in various cell lines[6-9], or that a candidate gene identified in one cell line may not necessarily be applicable to another cell line[11]. Therefore, individualized therapeutic interventions will be required for patients with cancer, even though their cancers may harbor the same oncogene or tumor suppressor gene mutations. Nevertheless, it is possible that certain key nodes may exist in the networks of genetic interactions that will allow us to develop a common strategy to overcome resistance derived from different genetic interactions[84].

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REVIEW

Genome-wide association studies: Where we are heading?

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Abstract

We have witnessed tremendous success in genome-wide association studies (GWAS) in recent years. Since the identification of variants in the complement factor H gene on the risk of age-related macular degeneration, GWAS have become ubiquitous in genetic studies and have led to the identification of genetic variants that are associated with a variety of complex human diseases and traits. These discoveries have changed our understanding of the biological architecture of common, complex diseases and have also provided new hypotheses to test. New tools, such as next-generation sequencing, will be an important part of the future of genetics research; however, GWAS studies will continue to play an important role in disease gene discovery. Many traits have yet to be explored by GWAS, especially in minority populations, and large collaborative studies are currently being conducted to maximize the return from existing GWAS data. In addition, GWAS technology continues to improve, increasing genomic coverage for major global populations and decreasing the cost of experiments. Although much of the variance attributable to genetic factors for many important traits is still unexplained, GWAS technology has been instrumental in mapping over a thousand genes to hundreds of traits. More discoveries are made each month and the scale, quality and quantity of current work has a steady trend upward. We briefly review the current key trends in GWAS, which can be summarized with three goals: increase power, increase collaborations and increase populations.

Key words: Genome-wide association studies; Single nucleotide polymorphisms; Sequencing; Genotype imputation; Meta-analysis; Genetic consortium

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INTRODUCTION

Genome-wide association studies (GWAS) were motivated by new thinking about approaches for mapping traits to genomic regions and several developments in large scientific projects, such as the completion of the *homo sapiens* reference sequence by the Human Genome Project[1] and the cataloging of common genetic variants by the International HapMap Project[2-5]. GWAS are based on the premise that densely genotyped common, or high frequency, alleles will have statistical power to detect causal associations with traits at nearby, ungenotyped common

polymorphisms through short-range linkage disequilibrium (LD). LD is the nonrandom association between pairs of alleles[6]. The basis for this strategy is the common disease common variant (CDCV) hypothesis[7], in which it is proposed that high-prevalence traits are most likely determined by high-frequency genetic variants. This approach has been proven effective in many scenarios for mapping small genomic regions to traits (see the National Human Genome Research Institute Catalog of Published Genome-Wide Association Studies, http://www.genome.gov/GWAStudies/)[8,9]. Many of these newly associated regions would not have been considered good candidates for targeted genotyping studies based on biological knowledge or previous linkage evidence, illustrating the difficulty of improvising a hypothesis based on the molecular biology of a gene and its products.

Since the identification of variants in the complement factor H (CFH) gene associating with the risk of age-related macular degeneration (AMD)[10], GWAS have become ubiquitous in genetic epidemiology and have led to the identification of genetic variants that are associated with a variety of human diseases and traits, such as type 1[11,12] and type 2 diabetes[13-15], inflammatory bowel disease[16], Crohn's disease[17,18], breast cancer[19], human height[20] and body mass index[21], to name a few. It has revolutionized the search for genetic contributions to complex traits[22,23].

In GWAS, the tests of association with traits are conducted at between hundreds of thousands to millions of densely spaced single nucleotide polymorphisms (SNPs). GWAS require no *a priori* biological knowledge and are therefore an agnostic method for localizing the genetic effects of complex human diseases. These study designs rely on genotyping platforms which are designed by assay manufacturers and genotyping in cases and controls, families that contain multiple affected individuals or random subjects from the population if a quantitative trait is the focus of the investigation. These platforms come primarily from two manufacturers, Affymetrix (http://www.affymetrix.com/) and Illumina (http://www.illumina.com/), and the rationale for the SNPs assayed differs between these companies. The Illumina approach to GWAS design employs haplotype tagging to select SNPs based on local correlation with other nearby SNPs, such that redundant genetic variation containing very similar statistical information is not assayed. The Affymetrix platforms use a different design, where the human genome is saturated with SNPs that are selected based on their location between two restriction enzyme sites. Regardless of platform, the goal of GWAS is to evaluate the majority of common alleles for association with traits through pairwise correlation with assayed SNPs.

Despite the large size of GWAS data, computational tools make GWAS feasible to analyze on standard desktop computer hardware[24]. However, the large number of hypothesis tests in GWAS creates a challenge for statistical testing. An often-cited genome-wide significance level is 5×10^{-8}, based on the assumption of one million independent pieces of genetic information in the human genome[25,26], and less stringent thresholds were also verified[27,28]. Few studies have adequate sample size to maintain the power needed to detect small to moderate effect sizes that predominate in GWAS. The current approach for elucidating genes that influence complex disease is to increase the power in GWAS through increased sample sizes assembled by collaboration among research groups[29,30].

As of June 01 2011, 906 publications have been documented and 4514 SNPs have been associated with human disease and traits at a significance level of 10^{-5} in the Catalog of the Published GWAS (http://www.genome.gov/GWAStudies)[31]. Given the flood of GWAS publications in recent years, this review is not all-inclusive but highlights the key trends in current approaches to GWAS.

INCREASE POWER

Increase sample size

The often-cited first success in GWAS (defined as at least 100K SNPs), the discovery of CFH in AMD, used a small data set (by current standards) of only 96 cases and 50 controls genotyped using the Affymetrix GeneChip Mapping 100K set of microarrays[10]. This study proved the concept of a "brute force" approach to scan the entire human genome for human diseases. Soon after, researchers started using larger sample sizes to augment power in GWAS. In 2007, the Wellcome Trust Case Control Consortium carried out GWAS of seven common diseases using 14000 cases and 3000 shared controls[29]. The need for statistical power (through the incorporation of larger sample sizes) and the requirement for independent replication of association signals also motivated researchers to employ meta-analysis, often with the aid of genotype imputation, to overcome the limitations associated with each individual GWAS analysis.

Early meta-analyses in GWAS reported success in Parkinson's disease[32] and Type 2 diabetes[33,34]. A meta-analysis combines results from multiple independent studies with similar data to address related research hypotheses. It is a more powerful approach to estimate the true effect size than analysis of data from a single study. In recent genetic studies, meta-analysis has led to many successful discoveries of genetic variants with different phenotypes, including type 1 diabetes[35], type 2 diabetes[34], chronic kidney disease[36], retinal microcirculation[37], serum lipid concentrations[38], glucose and insulin response[39], fasting glucose homeostasis[40], blood pressure and hypertension[41], atrial fibrillation[42], Crohn's disease[43], metabolic syndrome[44], human height[20,45], body mass index[21] and blood pressure[41,46]. Meta-analyses of several thousands of samples for human diseases[36,47], and even a quarter-million individuals for common human traits[21], are becoming more common. In addition to increasing sample size, meta-analysis allows researchers to bypass the potential Institutional Review Board (IRB) issues of individual-level data sharing, as meta-data do not increase the risk of

study subjects being re-identified and their personal information made public.

Increase genomic coverage

The density and number of assayed SNPs in GWAS products have improved rapidly, from the Affymetrix 100K array used in the AMD GWAS to the currently often used, the Affymetrix 6.0 (> 1 million markers) and the Illumina Human 1M (> 1 million markers). Leveraging the advances in the HapMap project[2,4,5] and the 1000 Genomes Project (1KGP)[48], the Illumina HumanOmni 2.5 (about 2.5 million markers) is also available and the Illumina HumanOmni 5M (about 5 million markers) will soon become a reality (http://www.illumina.com/). For estimates of genomic coverage for various platforms, see Barrett *et al*[8] and Li *et al*[49].

The recent invention of genotype imputation has become a cost-effective approach to increase genomic coverage in large genomic scans. It not only enables the pooling of GWAS results from different genotyping chips with different SNPs, which meta-analyses have benefited significantly from, but also increases the power of genome scans[50]. Genotype imputation methods utilize haplotypes inferred from a densely genotyped reference panel of subjects with known ethnicity to infer the conditional probabilities of missing genotypes in a study sample genotyped at a subset of SNPs[50,51]. Imputation of genotypes also leverages publicly available resources such as the International HapMap Project data[2,4,5] and resequencing data from the 1KGP[48].

Most of the meta-analyses to date have used the HapMap Phase II reference panels (about 3 million markers). The 1KGP reference panel, with about 16 million variant sites[48], will most likely become the reference panel of choice for future GWAS. This allows researchers to evaluate many more SNPs than are provided by GWAS manufacturers, or to fill-in SNPs that are only in one study in a meta-analysis without increasing the genotyping cost of the study.

The dilemma, that significant GWAS hits so far only explain a small proportion of heritability, has shifted researchers' attention from GWAS genotyping chips to sequencing, with the belief that rare variants might be the culprit for the missing heritability. It was also predicted that DNA sequencing would become a routine tool in genetic research[52].

The cost of data generation, storage and processing and bioinformatics analysis add another level of difficulty to whole-genome sequencing experiments in large samples. The per-subject cost for generating individual-level genotype data from GWAS is still much less than the cost of resequencing at a depth that is sufficient for making genotype calls throughout the genome. As a result, especially for traits for which GWAS have not yet been conducted on a large-scale, we believe that array-based GWAS assays will continue to be important, especially with the aid of genotype imputation and new design of high-density GWAS chips.

Some recent research has shown that association testing from sequence data may provide slightly more statistical power than variant-based genotyping on a per-subject basis[53] using two recently developed tests of association[54,55]. However, we note that due to the large difference in the cost of resequencing to the cost of variant-based genotyping, on a per-unit of resources basis, many more subjects could be genotyped with variant-based methods than could be resequenced. As a result, the statistical power to detect an association might be better in a large sample of variant-based genotypes than in a small sample of sequence-based genotypes, utilizing the same resources.

Furthermore, once GWAS have elucidated novel regions, targeted resequencing for direct association of alleles in implicated regions can be performed at a fraction of the cost of whole-genome or whole-exome resequencing. Therefore, the use of GWAS can offer benefits at subsequent stages of an investigation and reduce the overall costs of novel locus discovery compared to an approach that relied exclusively on resequencing. The marriage between GWAS arrays and sequencing is likely to be the future, e.g. GWAS arrays followed by targeted sequencing or whole genome sequencing followed by GWAS custom arrays. Regardless of the strategy taken, good coverage of important loci and sufficient sample size to detect associations with rare alleles are indispensable.

INCREASE COLLABORATIONS

The requirement for large sample sizes and replications have motivated massive scientific collaborations. Many new genetic consortia have arisen due to the challenges of conducting successful investigations with GWAS, e.g. the Diabetes Genetics Replication And Meta-analysis Consortium[34], the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium[30], the Meta-Analyses of Glucose and Insulin-related traits Consortium[40], the Genetic Investigation of ANthropometric Traits consortium[20], the Genetics of Obesity-related Liver Disease consortium[56], the Chronic Kidney Disease consortium[36], the Global Blood Pressure Genetics consortium[57], the Candidate-gene Association Resource consortium[58] and the Coronary Artery Disease (C4D) Genetics Consortium[59]. Genetic consortia targeting Asian populations have also been formed, e.g. the Asian Genetic Epidemiology Network consortium[46], which includes 12 GWAS studies of Asian participants (http://agenconsortium.org/). By using prospective cohort studies, the CHARGE consortium has been very successful in producing numerous high-impact publications on a variety of phenotypes. Publications from these consortia sometimes are co-authored by over a hundred researchers, illustrating the collaborative nature of modern genetic epidemiology. This trend is unprecedented in the field and is likely to continue as technology matures and the cost of experiments using the latest tools in-

creases beyond the ability of any single research group to afford highly-powered studies.

INCREASE POPULATIONS

A rare trait allele may not be annotated in the databases of common variants maintained by the HapMap project or the National Center for Biotechnology website dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/), thereby excluding the possibility of detecting that SNP through imputation and subsequent association analysis. The genetic determinants for a trait may also be unique for each population of human subjects, where sensitive functional gene or regulatory regions are perturbed by independent sets of rare mutations that occurred after geographic or cultural barriers led to increased genetic distance[60]. Thus, the same associated allele from GWAS across multiple ethnic groups does not necessarily imply the same underlying architecture of causal alleles in LD and it should not be expected that a causal allele in one population will have the same association in another population with a distinct demographic history.

Recent studies show that multi-ethnic GWAS can improve the power for novel locus discovery[61]. A recent example of the association of the variants in KCNQ1 with type 2 diabetes in East-Asian population samples[62,63] were not identified in earlier GWAS in European samples[64]. The associated SNP, rs2283228, has a minor allele frequency (MAF) of about 40% in East-Asian samples. However, the MAF in European samples is only about 5%. At this level of MAF, there is simply not enough power at the GWAS significance level of 5×10^{-8} to detect association in European samples conducted earlier than the two East-Asian samples[13-15,33,65]. Moreover, some risk alleles may be population-specific, which also highlights the importance of conducting GWAS in samples of non-European ancestry[46].

Early GWAS conducted in Parkinson disease's (PD) did not yield results that reached genome-wide significance[66-68]. Associations with PD have been replicated in the candidate gene and GWAS contexts, including those described early in PD association studies, such as α-synuclein (*SNCA*)[69-75] and the microtubule-associated protein tau (*MAPT*) inversion region on chromosome 17 in European-ancestry subjects[76-89], as well as ubiquitin-specific protease 24[90-92], ELAV-like 4[90,93,94], monoamine oxidase B[95], Apolipoprotein E[96] and the mitochondrial haplogroups[97-104]. The consistency of results, particularly for *SNCA* and *MAPT*, suggest that the failure to reach genome-wide significance in previous studies is due to the relatively small GWAS datasets. More recently, GWAS-based investigations into the genetic determinants of PD have been more fruitful, definitively identifying several associated regions in the genes *MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK* and *LRRK2, ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11*, and *CCDC62/HIP1R* in both Caucasian and Asian patients, although the *MAPT* association seems to be the result of a chromosomal inversion only present in Europeans[105-110].

The public health impact and economic burden of obesity is substantial as obesity is associated with increased risks for type 2 diabetes mellitus, cardiovascular disease, dyslipidemia, hypertension, sleep apnea and several forms of cancer[111,112]. In the US, the obesity epidemic disproportionately affects certain ethnic minorities, including Mexican and African-Americans[113]. Mexican Americans are the fastest growing minority group in the US and are expected to represent 18% of the US population by 2025 (http://www.census.gov/). Obesity and comorbid conditions such as diabetic retinopathy have higher prevalence in Mexican Americans than in European Americans[114-116], which will introduce significant social and economic costs if the corresponding genetic research is left far behind.

The PAGE network (Population Architecture using Genomics and Epidemiology) is a National Human Genome Research Institute funded initiative designed to characterize GWAS-identified variants in cohorts, including individuals of ancestral groups other than European-decent, to determine if the variants identified are globally associated with various complex traits[117]. Investigators in PAGE are exploring traits that have undergone extensive evaluation in GWAS including lipids, obesity, type II diabetes, stroke, and various cancers. More information about the PAGE network can be found at http://www.pagestudy.org/.

CONCLUSION

The study of epidemics of heritable diseases and knowledge about the genetic architecture of complex human traits has developed rapidly in the last two decades. These advances have been primarily due to improvements in genotyping technology and a commensurate increase in the amount and availability of data with which to describe and understand the nature of genetic variation in human populations. During this period, genetic studies of human traits have moved away from a focus on assaying a small number of loci to identify regions of linkage to traits in family studies to samples of hundreds of thousands of study subjects assaying millions of SNPs for statistical association with traits using a variety of study designs. There is perhaps no better example of this than GWAS, a fundamental tool that has reshaped the way that studies are designed, collaborations are forged and thinking about the architecture of complex human traits.

Because of the rapid pace of discoveries resulting from GWAS and the promise of many more from newer technologies, it seems reasonable to look forward to a time when patients have their genomes genotyped or sequenced and analyzed to provide a personal profile of disease susceptibilities, drug compatibilities and other heritable traits. Approaches continue to rapidly evolve for employing GWAS but it is likely that the approach will be a viable way to discover the connections between inter-individual genetic variation and phenotypes for the foreseeable future.

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2nd joint scientific meeting: Progress In Quality Assurance And Technical Developments In Genetic Testing
Nijmegen, The Netherlands

January 20, 2012
Exploiting bacteriophages for bioscience, biotechnology and medicine
Welwyn Garden City,
United Kingdom

January 26, 2012
An Introduction to miRNA and siRNA
The Nowgen Centre,
Manchester, United Kingdom

February 2-4, 2012
6émes Assises de Génétique Humaine et Médicale
Marseille, France

February 2-5, 2012
International Congress on Personalized Medicine: Up Close and Personalized (UPCP 2012)
Florence, Italy

February 16, 2012
The 2012 London Regenerative Medicine Event
London, United Kingdom

March 9, 2012
Cell culture technology: recent advances, future prospects
Welwyn Garden City,
United Kingdom

March 23, 2012
Mycobacterium tuberculosis.....can we beat it?
London, United Kingdom

March 27-31, 2012
2012 American College of Medical Genetics Annual Clinical Genetics Meeting
Charlotte, North Carolina,
CA, United States

March 29, 2012
Regulatory Cells in Autoimmunity event: Analysing and moderating function
London, United Kingdom

March 30, 2012
Histopathology: Advances in research and techniques
London, United Kingdom

April 15-24, 2012
Exome Sequencing
Hinxton,
Cambridge, United Kingdom

April 19, 2012
Strategies for commercial success of biosimilars
London, United Kingdom

May 11-12, 2012
4th International Course on Fluorescence in sity Hybridization
Jena, Germany

May 17, 2012
Biomarker discovery: Driving technologies
London, United Kingdom

May 23, 2012
Taking the heat out of chaperokine function
London, United Kingdom

May 30 – June 1, 2012
Capita Selecta in Complex Disease Analysis - CSCDA2012
Liège, Belgium

June 11-13, 2012
ICHG 2012: International Conference on Human Genetics
Copenhagen, Denmark

June 13-22, 2012
Functional Genomics and Systems Biology
Wellcome Trust Genome Campus,
Hinxton,
Cambridge, United Kingdom

June 21-23, 2012
Satellite Meeting: The Biological Future of Man. Continuities and Break in the History of Human Genetics before and after 1945
Nürnberg, Germany

June 23-26, 2012
European Human Genetics Conference 2012
Nürnberg, Germany

July 1-4, 2012
28th Annual Meeting - ESHRE 2012
Istanbul, Turkey

July 22-25, 2012
Human Genetics Society of Australasia 36th Annual Scientific Meeting
Canberra, Australia

November 6-10, 2012
Annual Meeting of the American Society of Human Genetics
San Francisco,
CA, United States

December 5-8, 2012
10th Asia-Pacific Conference on Human Genetics 2012
Kuala Lumpur, Malaysia

World Journal of Medical Genetics

Online Submissions: http://www.wjgnet.com/2220-3184office
wjmg@wjgnet.com
www.wjgnet.com

World J Med Genet 2011 December 27; 1(1): I-V
ISSN 2220-3184 (online)

GENERAL INFORMATION

World Journal of Medical Genetics (*World J Med Genet*, *WJMG*, online ISSN 2220-3184, DOI: 10.5496) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 103 experts in medical genetics from 28 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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Name of journal

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Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pres-

sure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2220-3184/g_info_20100725073806.htm.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
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Guidelines for basic research: http://www.wjgnet.com/2220-3184/g_info_20100725072344.htm

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