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Meeting Highlights

Pharmacogenetics Research Network and Knowledge Base: 1st Annual Scientific Meeting

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The National Institute of General Medical Sciences of the National Institutes of Health recently established a collaborative group of scientists, called the Pharmacogenetics Research Network. Central to the network is a shared, state-of-the-art data repository, the Pharmacogenetics Knowledge Base (PharmGKB), which is housed at Stanford University. Network investigators deposit pharmacogenetic data into PharmGKB, after all individually identifying information has been removed. Contents of PharmGKB will be freely accessible to the scientific community, with the goal of forging new links between gene variation and drug response. An open scientific meeting was held recently to introduce the research community to the network and to invite academic and industry-based researchers to deposit data into PharmGKB. Featured at the meeting were summaries of research progress to date, as well as discussions of issues intimately related to pharmacogenetics research, namely ethics and relations with the biotechnology and pharmaceutical industries.

Keywords: *database, ethics, genotype, National Institutes of Health, phenotype*

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1. Introduction

To foster pharmacogenetics research, the National Institute of General Medical Sciences established the Pharmacogenetics Research Network in April 2000 (see [101]). Other NIH components participating in the initiative include the National Cancer Institute; the National Heart, Lung and Blood Institute; the National Human Genome Research Institute; the National Institute of Environmental Health Sciences; and the National Library of Medicine. The formation of the network was born of discussions (see [102]) between NIGMS and a working group that met in June 1998 [1]. The network, presently comprised of nine teams of scientists across the United States, is collectively investigating how genes affect the responses of individuals to a range of different medications, including antidepressants, asthma drugs and chemotherapy treatments. It is anticipated that four to five new research teams will join the network in late summer 2001. Central to the network is a shared, state-of-the-art data repository, PharmGKB, which is housed at Stanford University (see [103]). A major impetus for forming the network was the desire to provide free and open access to pharmacogenetic data to academic researchers whose access might

otherwise be limited by the existence of an increasing number of proprietary databases. An open scientific meeting was recently held to introduce the research community to the network and to invite academic and industry-based researchers to deposit data into PharmGKB.

Network investigators deposit pharmacogenetic data into PharmGKB after individually identifying information has been removed. Contents of PharmGKB will be freely accessible to the scientific community, with the goal of forging new links between gene variation and drug response and for serving as a stimulus for the generation of novel hypotheses. PharmGKB is expected to become a rich information resource of maximum utility for storing, co-ordinating, linking and interpreting complex information. The design and curation of PharmKGB is a challenging bioinformatics enterprise [2], necessitating careful thought with regard to technical aspects, such as compatibility with a variety of extant databases and literature archives, and to transforming a collection of pharmacogenetics research projects into a larger, potentially predictive pharmacogenomics endeavour [3]. Equally challenging, however, is the prospect of adequately addressing issues related to privacy and confidentiality, issues which inevitably arise during genetics and genomics investigations. Any research enterprise involving and aiming to improve the ultimate health of human subjects poses special problems in maintaining the privacy and confidentiality of the individuals and groups that contribute significantly to the data pool. An increased public awareness surrounding these issues has stemmed in part from the possibility that the propensity to disease may be inferred from genetic make-up, potentially leading to discrimination (of either or both individuals and populations). The ultimate ramifications of the outcomes of pharmacogenetics research relating to healthcare delivery are unknown, but nevertheless invite consideration.

2. Pharmacogenetics Research Network: research in progress

In the first session, principal investigators from each of the network research groups provided a status report of research progress to date. R Weinshilboum (Mayo Foundation, Rochester, Minnesota, USA) described efforts to resequence genes encoding hepatic Phase II metabolising enzymes, including histamine N-methyltransferase (HNMT), thiopurine methyltransferase (TPMT), various hydroxysteroid sulfotransferases (SULT), phosphoadenosine 5′-phosphosulfate synthetase (PAPS synthetase I) and catechol-O-methyltransferase (COMT), with the goal of identifying and characterising genetic polymorphisms. Significant differences in allelic frequency have been identified that varied according to ethnicity [4]. Weinshilboum, in addition to several other meeting participants, identified a need for haplotype determination algorithms. K Giacomini (University of California, San Francisco, USA) presented a comprehensive allele detection and analysis for two candidate transporter genes associated with neuropsychiatric phenotypes: the serotonin transporter SCL6A4 and the monoamine transporter SLC18A2 [5]. Unique, non-synonymous, non-common variants were found using the complete 450-sample DNA Polymorphism Discovery Resource [6]. A clinical study was also described in which 500 DNA samples derived from Parkinson's disease patients displayed a widely variable frequency in the frequency of SNPs in the transporters organic cation transporter 2 (OCT2), multi-drug resistance transporters (MDR), vesicular monoamine transporter 2 (VMAT) and serotonin transporter (SERT). S Weiss (Brigham and Women's Hospital, Boston, Massachusetts, USA) discussed ongoing clinical studies aiming to stratify (by genotype) responses to current asthma therapeutic regimens targeting each of the leukotriene, β-agonist and steroid pathways. J Licinio (University of California, Los Angeles, USA) described pilot studies investigating genetic underpinnings in the response of Mexican-Americans to the predominantly serotoninergic and the other predominantly noradrenalinergic antidepressant medications Prozac™ (fluoxetine) and Norpramin™/Pertofrane™ (desipramine), respectively.

M Ratain (University of Chicago, USA) reported on current investigations examining the role of sequence variability in UDP-glucuronosyltransferase 1A1 (UGT1A1) in the therapeutic response and side effect profile of the cancer therapy irinotecan (CPT-11) [7]. Extensive sequence variation was found in the non-coding, intronic regions of the UGT1A1 gene. D Flockhart (Georgetown University, Washington, DC, USA) reported recent data from a small, ongoing Paxil™ (paroxetine)/Nolvadex™ (tamoxifen) trial of 24 women. Preliminary data suggest that paroxetine's effects in reducing the incidence of hot flashes may

negate the efficacy of tamoxifen, possibly through competition for a common drug receptor/transporter.

Discussion following the research session focused on the process of melding pharmacogenetic research studies into pharmacogenomic projects, combining and integrating data sets into and between metabolic pathways. There is a recognisable need for statisticians and informatics specialists to move pharmacogenetic research pursuits into the genomic realm. Other comments addressed strategies for choosing sample sources, notably the relative value of using ethnically anonymised DNA samples for SNP discovery purposes.

3. Pharmacogenetics Knowledge Base

R Altman (Stanford University, Stanford, California, USA) identified pharmacogenetics as an area especially challenging yet opportune for bioinformatics research. Policies for submitting data to PharmGKB were described and are posted on the Internet [103]. At present, all data received are displayed in a simple format; however, the design and development of more sophisticated query tools is ongoing. Topics discussed relating to PharmGKB included the modelling complexity (for genotypes, phenotypes), XML infrastructure of the database, surveillance of related databases, modelling three-dimensional sequellae of polymorphisms, mining of the published literature and cross-species, comparative sequence analyses. P Nadkarni (Yale University, New Haven, Connecticut, USA) discussed the development of query tools to extend the utility of PharmGKB. Entity-Attribute-Value (EAV) databases can be useful for aggregating and submitting to PharmGKB data from investigators in the wider scientific community. Challenges inherent in distinguishing implicit and explicit descriptors were noted.

4. Issues of ethics in the Pharmacogenetics Research Network

M Rothstein (University of Louisville, Louisville, Kentucky, USA) contrasted perceived promises and challenges offered by pharmacogenetics and pharmacogenomics research. Among the potential benefits presented are the promise of more effective medications with fewer side effects and the potential to rescue orphan drugs [8]. Potential downsides were described as subdividing populations and generating disparities in healthcare access. A telesurvey to poll the US public about attitudes toward the purposes and effects of pharmacogenetics research is currently in process.

A panel discussion considering the constellation of ethical issues that intersect with research in the area of genetics in general and of pharmacogenetics in particular followed the research presentations. Questions posed to the ethics panel included the following. What are the potential benefits and risks to individuals associated with pharmacogenetics research? What are the benefits, risks and potential implications for larger communities and identified groups? P Ossorio (University of Wisconsin, Madison, Wisconsin, USA) led the panel discussion, suggesting that new ethical methodologies may be needed to accompany research that inevitably involves communities and larger populations. Defining the notion of community and who best represents it may be less important than determining the recipients of the greatest impact of pharmacogenetics research and then seeking consultation accordingly. V Ota Wang (Arizona State University, Tempe, Arizona, USA) urged the scientific community to take on the responsibility to describe data in sufficient depth, warning against the potential hazards of removing so much identifying information from data that the research, ultimately, may have little to do with people. W Burke (University of Washington, Seattle, USA) made the distinction between genetic/pharmacogenetic tests that may be developed that have high clinical utility *versus* those that may have uncertain clinical utility. Making these characterisations may involve considerable time and effort, shifting healthcare costs from drug development to patient care. P Sankar (University of Pennsylvania, Philadelphia, USA) spoke on the topic of sample anonymity, suggesting that there is a great need to establish a clear nomenclature for the various terms used to describe how samples are identified.

5. Opportunities for industry-academic interactions

Following the discussion on ethical issues, a panel convened to address interactions of the network with the biotechnology and pharmaceutical industries. P Manasco (GlaxoSmithKline, Research Triangle Park, North Carolina, USA) emphasised that the pharmaceutical industry is interested in pharmacogenetics,

citing an average rate of efficacy of 50% for most therapeutic drugs. Speaking on the issue of sample identification, B Spear (Abbott Laboratories, Abbott Park, Illinois, USA) outlined a newly defined set of definitions regarding sample classification, developed by the recently established industry consortium, the 'Pharmacogenetics Working Group.' Standard definitions to describe samples ranging from fully identified to fully anonymous have been developed by this group of industry representatives [9]. Also emphasised during the industry panel discussion was the need for extensive public education efforts. A Houston (Variagenics, Cambridge, Massachusetts, USA) noted that while all the pharmacogenetic success stories to date have arisen from academic pursuits, the cost of the large-scale trials that will be necessary to validate the general utility of most pharmacogenetic applications will be prohibitive to academic institutions, ranging from an estimated US$20 - 60 million per trial. Future linkages between academia and industry will be necessary.

6. Expert opinion and conclusions

Pharmacogenetics and pharmacogenomics hold great promise for bettering human health by increasing the efficacy of therapeutic medications, reducing unwanted side effects and potentially streamlining the drug target selection process. It will be extremely important for academia and industry to consolidate efforts in the conduct and application of pharmacogenetics and pharmacogenomics and these units must work together co-operatively in areas where synergistic effects may be anticipated. Forging unexpected links between genotypes and phenotypes (perhaps not always in a one-to-one relationship) can form the basis for the timely, cost-effective development of new therapeutics but should also lay the foundation for the formulation of new scientific hypotheses. Maximal usage of data repositories with full and unrestricted access to all members of the scientific community will greatly enhance this process. Finally, the pharmacogenetics research community must not forget that individuals and communities – each with particular questions, needs and concerns – are integral to the research process. Ethical concerns facing individuals and groups must be confronted as the pharmacogenetics revolution marches on.

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