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Genetics in Clinical Trials

James F. Meschia[a] and **Katrina Gwinn**[b]

[a]Cerebrovascular Division, Department of Neurology, Mayo Clinic, Jacksonville, Fla., USA

[b]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Tex., USA

Clinical trials provide the 'evidence' in evidence-based medicine. Despite their cost and complexity, clinical trials save society billions of dollars [1]. Recent advances have enabled genome-wide analyses of single nucleotide polymorphisms in complex diseases. Such analyses require large sample sizes and thus depend on collaborative efforts. Genetics ancillary to clinical trials benefit from recruitment by numerous investigators at diverse institutions. Additionally, clinical trial subjects are well characterized via trial eligibility screening, and baseline characteristics and outcomes are collected via validated, standardized measures. This allows genotype-phenotype, genotype-outcome and treatment-response analyses. Banking DNA only marginally increases costs relative to the cost of the trial itself.

The disadvantages to ancillary genetic studies in clinical trials are also clear. Typically, trials do not recruit disease-free individuals necessary for genetic controls. As a result, historical control subjects, who may have incomplete, differentially acquired phenotypes, are frequently used. Trial eligibility criteria result in collections that are not representative of the disease-affected population. For example, PROACT II, a study of intra-arterial thrombolysis, randomized subjects representing 1.5% of those screened [2]. Such small samples can render subcollections useless, even in the absence of recruitment bias.

Although pharmacogenetics is subject to hyperbole, the underlying concepts are traditional. Clinicians consider treatment based on ethnicity, gender and other factors, all of which are the result of gene expression. Malignant hyperthermia [3], long QT syndrome [4], venous thromboembolic disease [5] and tardive dyskinesia [6], among others, have associated underlying genetic risk factors. New tools including microarray technology [7], high-throughput screening and bioinformatics, when combined with large simple trial infrastructure, allow a better understanding of pharmacogenetics.

Finding the High-Responder Subgroup in Clinical Trials

Defining subgroups of high responders in clinical trials might allow more cost-effective treatment. However, the subgroup must represent a substantial proportion of the disease-affected population and testing must be practical. Subgroup analyses are often underpowered because the parent study test is powered to the primary hypothesis. High-responder subgroups might not be easily identified via purely clinical criteria. For example, it was hypothesized that those with cardioembolic stroke represented a subgroup responsive to acute anticoagulation [8]. Subsequent studies failed to confirm this [9]. Determining genotypes associated with adverse outcomes may be useful in planning or monitoring treatment. For example, about 20% of Whites carry different CYP450 mutations causing warfarin sensitivity, suggesting that CYP2C9 genotypes may be helpful in deciding warfarin dosing [10].

James F. Meschia, MD, Department of Neurology, Cannaday Building 2E, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224 (USA), Tel. +1 904 953 2623; Fax +1 904 953 7233, meschia.james@mayo.edu.

Alzheimer's Disease

The epsilon 4 allele of apolipoprotein E (*APOE*) is a well-established, prevalent risk factor for Alzheimer's disease. *APOE* testing has been used to determine subgroup responsiveness to acetylcholinesterase inhibitors, with mixed results (table 1). *APOE* genotyping has also been used to explore novel classes of treatment agents. This strategy allows useful data on therapeutic targets to emerge, even from negative trials. For example, a randomized trial of the peroxisome proliferator-activated receptor-γ agonist rosiglitazone in subjects with mild to moderate Alzheimer's disease [11] demonstrated no significant treatment effect on cognition overall, but an exploratory analysis showed improvement in cognition for the *APOE4*-negative, but not for the *APOE4*-positive group. Results of such a finding will need to be confirmed in further trials.

Pharmacogenomics in Antiepileptic Drugs

About 30% of patients with epilepsy are refractory to therapy, despite the availability of numerous antiepileptic drugs. Two hypotheses have emerged regarding how genetics influence refractoriness: transporter and target [12]. In testing the transporter hypothesis, much attention has focused on P-glycoprotein, encoded by the *ABCB1* gene. An early association study found a significant relationship between refractory epilepsy and the *ABCB1* single nucleotide polymorphism C3435T [13], but attempts at replication yielded mixed results. The target hypothesis, less appealing from a clinical perspective because it assumes that genetic variation in responsiveness is drugspecific, argues that refractoriness occurs due to variations in genes encoding for drug targets such as sodium channels and GABA receptors. Currently, no definitive genotype-response relationship has been discovered [14]. Despite intensive research, no molecular basis for pharmacoresistance to antiepileptic drugs has been identified yet.

DNA Banking

Clinical trials are designed to test the primary hypothesis, and some argue that failing to adequately test the primary hypothesis because of an inadequate sample size is unethical, exposing subjects to risks without the benefits [15]. Excessively powering a study may also be unethical. Clinical trials should maximize the subjects' contribution; genetic studies, of minimal risk, are therefore worthwhile. A genetic substudy allows the possibility of therapeutic target discovery, even in negative studies.

Recent technological advances coincide with increasing recognition of the importance of very large cohorts for studying complex genetics [16]. Genetic studies that rely solely on analysis of samples collected in the trial risk inadequate power. Genomic approaches increase the likelihood that useful information will be gained by an ancillary genetic study, but even phase III trials risk being underpowered for genetic results. The number of subjects needed for gene discovery depends on several factors, including gene number and effect size, disease heterogeneity and study design, but is estimated between 2,000 and 10,000. Moreover, replication depends on the availability of independent populations. Limited access to biomaterials collected by individual projects is a roadblock to genome-wide analyses. In response, efforts in gene banking (NINDS repository: http://ccr.coriell.org/Sections/Collections/NIGMS/?SsId=10) have been undertaken. Underpinning uniform public access are bioinformatics solutions, and DbGaP (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap) offers a resource for genotype-phenotype data.

Summary

Pharmacogenetics is founded on longstanding traditions in clinical practice, where therapies are selected based on history and physical findings in order to maximize benefit and minimize risk. Genetic tools allow increased sophistication in patient profiling and treatment optimization. Pharmaceutical companies are aware of the value of collecting genetic data during their clinical trials [17,18]. Pharmacogenetics research is bidirectional with clinical trials: efficacy data are correlated with genetic polymorphisms, which in turn define subjects for treatment stratification. Currently, pharmacogenetics is in its infancy. Nonetheless, we anticipate that the identification of disease-specific genes will result in earlier diagnostic measures, disease progression markers and targets for therapeutic discovery.

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Table 1

Studies where APOE, status has been used to attempt to identify high-responder populations in Alzheimer's disease trials

Ref.	Drug	Trial design	Findings
[11]	rosiglitazone	randomized, placebo controlled	exploratory analyses demonstrated significant improvement on ADAS-Cog in *APOE* ε4-negative patients treated with 8-mg dose
[19]	galantamine	randomized, placebo controlled	*APOE* ε4 genotype did not affect improvements in cognition, global rating, function or behavior
[20]	tacrine	randomized, placebo controlled	non-*APOE* ε4 carriers on tacrine improved more versus placebo than patients with APOE ε4 on tacrine versus placebo
[21]	metrifonate	pooled analysis of 4 randomized trials	interactions of *APOE* genotype and metrifonate effect on cognition were not significant
[22]	tacrine	prospective case series blinded to genotype	no significant differences in response to treatment were seen based on *APOE* genotype
[23]	sabeluzole and galantamine	pooled analysis of 4 randomized trials	sabeluzole was not effective overall or in any subgroup stratified by ε4 allele count; galantamine produced cognitive and functional improvements that were not affected by ε4 allele count
[24]	rivastigmine	pooled analysis of 2 randomized trials	no significant differences in response to treatment were seen based on *APOE* genotype
[25]	donepezil	prospective case series	*APOE* ε4 carriers had improved or unchanged scores at retesting for visual and verbal memory, visual attention, inductive reasoning and Mini Mental State Examination; these favorable effects were not observed in the ε4-negative group
[26]	donepezil	prospective case series	no significant differences in response to treatment were seen based on *APOE* genotype
[27]	citicoline	randomized, placebo controlled	possible improved response to treatment in the epsilon 4 carriers
[28]	tacrine	randomized, placebo controlled	intention-to-treat analysis of patients with available genotypes did not reveal response differences by genotype
[29]	selegiline	randomized, placebo controlled	*APOE* genotype did not influence therapeutic outcome
[30]	tacrine	prospective case series	*APOE4*-positive patients had declined more than ε4-negative patients on treatment