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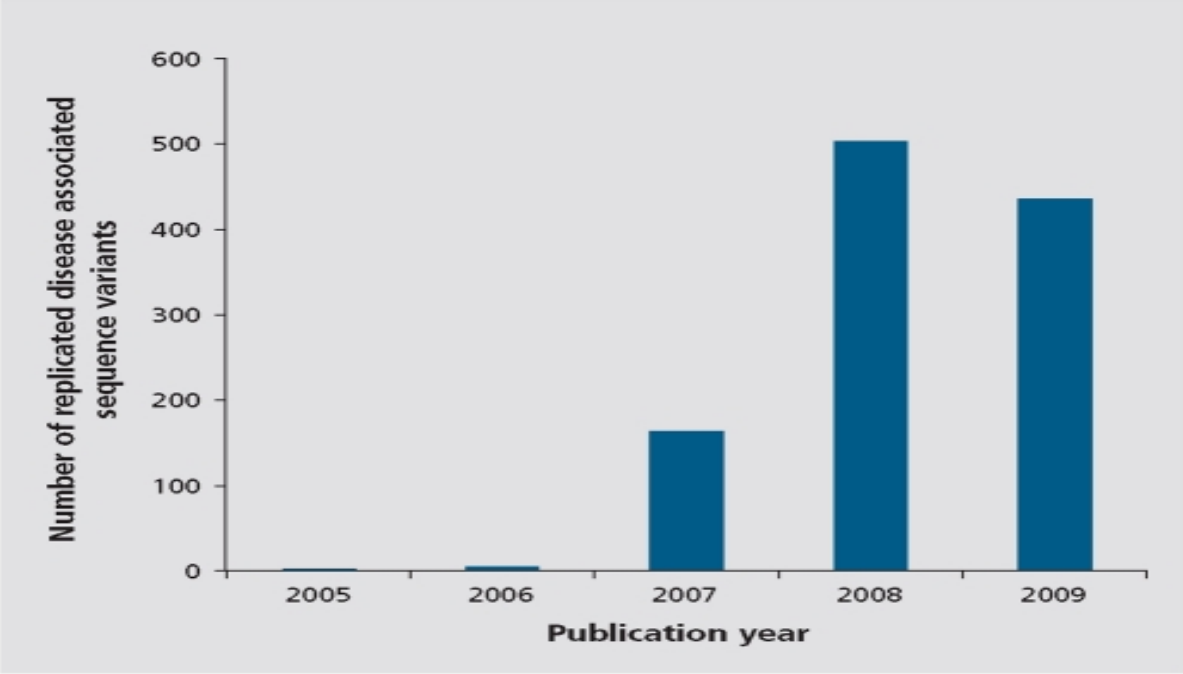
The Practical Reach of Pharmacogenomics: are Custom Drugs a Possibility?

In recent years' researchers have banded together in a concerted effort to try and understand the genome. The Human Genome Project to sequence the entire genome was first conceived in 1986 and initiated in 1990, after 13 years the genome was fully decoded but that's not the end of the process. The first genome cost millions to sequence but after numerous scientific discoveries and technological advancements the cost of sequencing down to as little as $1000. With the price reducing so drastically could we be reaching a point in time where pharmaceuticals can tap into the wealth of knowledge hidden within every person's genome? The reach of pharmacogenomics is ever expanding with new techniques such as SNP searches and GWA studies to analyze drugs but how reliable are these studies and how practical are they? And beyond that what are the ethics involved in analyzing the genome and who should get to know what the genome says? This paper aims to answer some of these questions and get a better picture of just what stands in between medical advancement and achieving custom made drugs to cure devastating diseases.

Direct-to-consumer genetic tests has been speculated since the dawn of The Human Genome Project. Pharmaceutics took notice of the potential when a wave of discoveries of common DNA sequences that are associated with risks for diseases such as heart complications (including heart attack and angina), morbidity, and other common illness that account for most

of the health care costs in various nations. Researchers Helgason A, and Stefansson K explored this in their paper "The Past, the Present, and Future of Direct-to-Consumer Genetic Tests." They claim that the predictive power of the genomic sequence, given the sheer amount of associations already discovered with diseases with high incidence would make DTC genetic tests a main goal of pharmaceutics in the future. Indeed the pair postulates that the importance of DTC genetic tests lies in the variations between individuals and how these variations can cause differences in chance and severity of disease, i.e. sex, age, weight, and other biological markers. Be they preventative tests or genomic tests after a disease has sprung up consumer tests have the potential to cure certain disease.

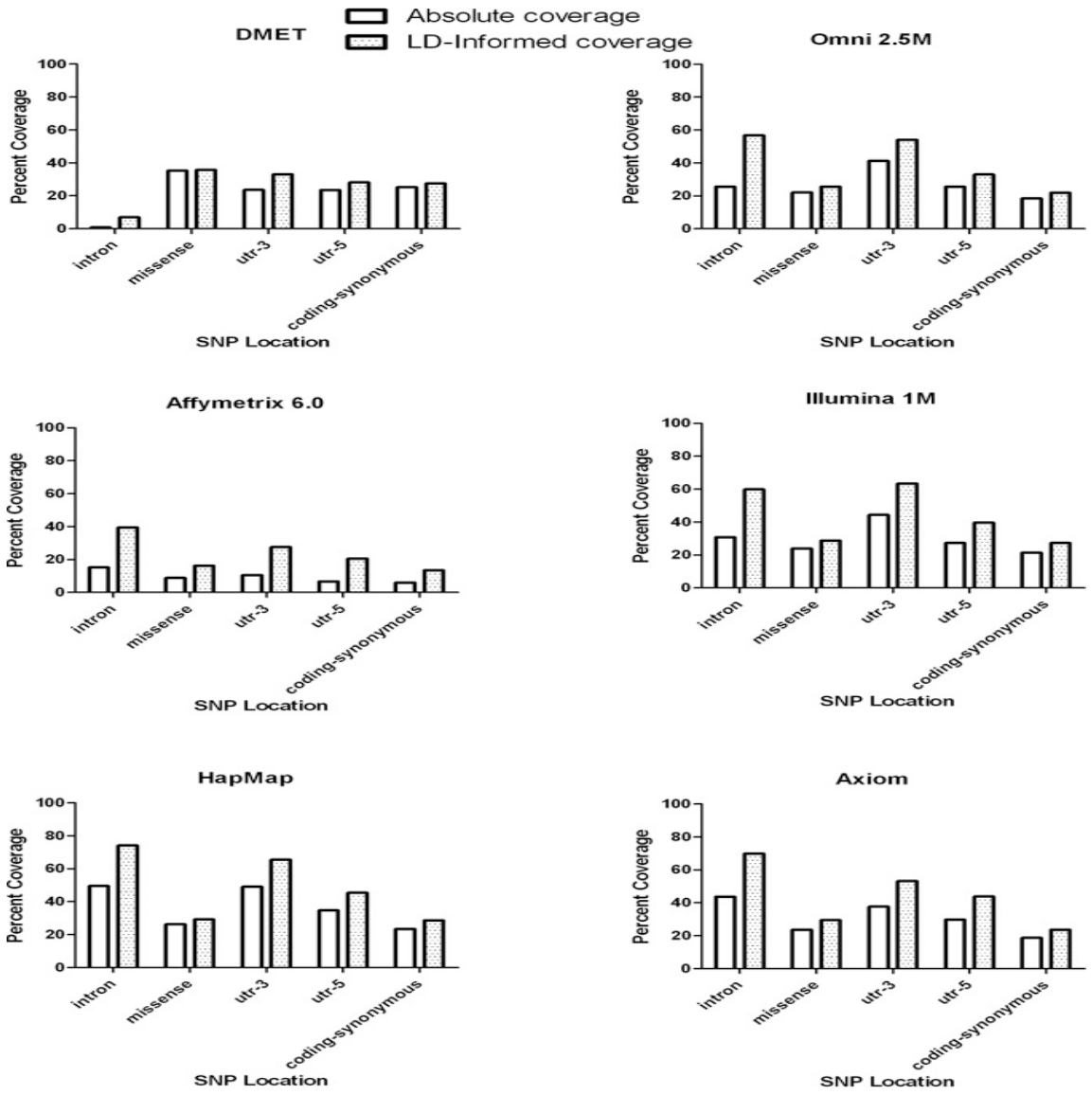
But how has genomics caused such a miraculous turn for disease study? DTC tests can play a transitional role in understanding of disease and by testing individuals who have already contracted a disease researches can find out more and more about what changes in the body lead to the illness. Below is a figure from the study conducted b Helgason and Stefansson:

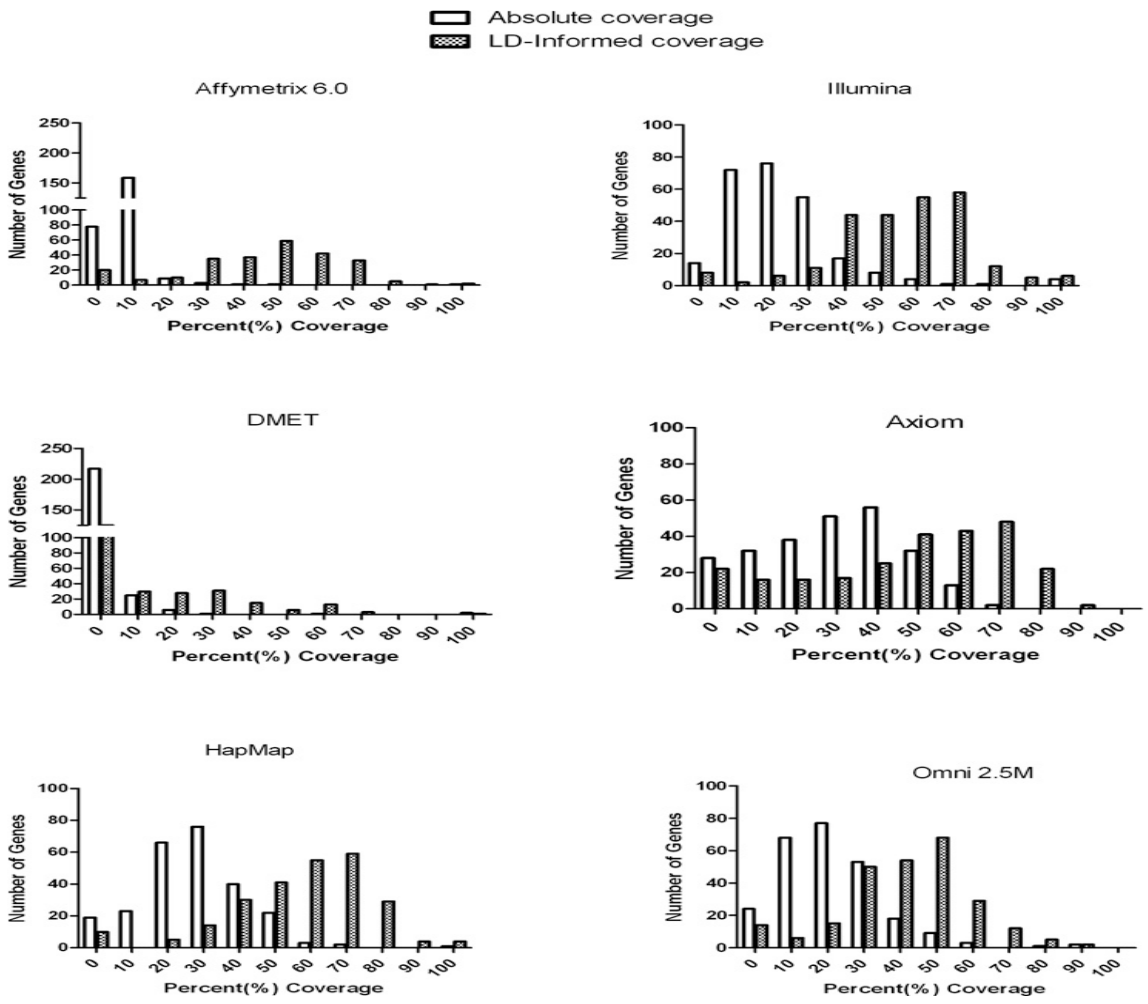


Just two years after studies of the genome the Genome Wide Association studies launched which accounts for the skyrocketing results. Over time with better and better technology more diseases will be discovered and the strength of DTC will only increase. There are three main reasons the GWA studies worked so well and will only continue to work so well. The first is how much information the Human Genome Project made available by providing an example human genome and the ensuing HapMap project that followed up the Human Genome Project. The second are new genotyping technologies that have allowed scientists the ability to analyze thousands of SNPs. And the third is just the sheer amount of DNA samples that can be gathered from individuals inflicted with diseases of interest and control samples of DNA from the same population. These unprecedented results show that their truly is value in continued research of the genome and that maybe one day DTC genome tests can be used by pharmaceuticals to either provide specific patients with drugs to cure their diseases or to provide the vast community with drugs designed to cure complex diseases. While this idea is fantastic in theory, there are limitations to genome studies.

In truth studying diseases is not as simple as running a GWA study and analyzing the SNPs, the actual path to finding cures for diseases is still well off. In Gamazon ER, Skol AD, and Perera MA's paper "The Limits of Genome-Wide Methods for Pharmacogenomic Testing" the researchers go into the problems with GWA analysis. The ultimate goal of pharmacogenomics is the transition from DNA sequence and genomic discovery to individualized patient care, but the problem with this goal is that GWA studies and genomic discovery in general are a far way off from actually providing cures to disease. In their words GWA's "Systematically evaluate high-throughput genotyping technologies for their ability to assay variation in pharmacogenetically

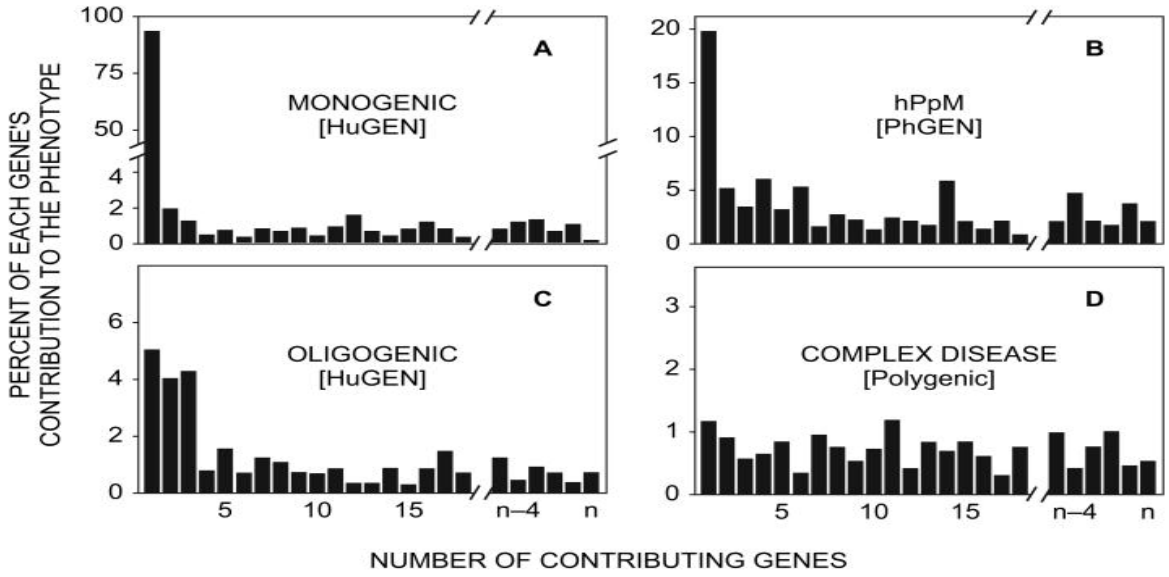
important genes (pharmacogenes).” The researchers proceeded to analyze 253 of their “pharmacogenes” found through GWA studies and found that not a single gene showed more than 85% ownership of it’s respective disease. Indeed, pharmacogenomics is forced to rely more heavily on SNP genotyping to find associations since GWA do not provide coverage of all chromosomal regions. The graphs below account for the coverages shown using different interfaces:





The main goal of pharmacogenics would be to study the HapMap and other high-throughput genotyping platforms for sufficient genotypic information to successfully capture all the variation found in re-sequencing so that researchers and medical practitioners know exactly how to treat a disease. The problem is that if the platforms cannot sufficiently capture all of the variations those very same researchers and medical practitioners would fail to identify some of the causative variants that lead to phenotype expression. The figures above show just how few diseases are covered more than 50%, and with such little information on these diseases cures found through DTC genomic tests aren't yet very practical.

So far its been shown that the potential for genomics on a practical level is immense but the reality of its use with today's technology is bleak. While researchers are very hopeful for the outcome of future processing its still very clear that with today's knowledge on disease its just not enough to find cures. There are monogenic, oligogenic, and complex diseases coded in the human genome. Researchers Nerbert D, Zhang G, and Vesell E dove into just how complex it is to find and treat diseases as they get to be more and more complex. In their paper "From Human Genetics and Genomics to Pharmacogenetics and Pharmacogenomics: Past Lessons, Future Directions" They set off their paper highlighting the differences in fully understanding these three different forms of disease:



This graph reveals that the main issue with finding a cure for complex diseases is the fact that the number of genes that directly cause phenotypic expression are wide and their isn't one major cause. It could be that these genes are pleiotropic or under epistasis for other genes. While monogenic disease are rather easy to find a cure for since there is one gene that has an outlandish contribution to the phenotype, other forms of disease are harder to sift through.

That being said there are still ways of finding those many genes that contribute to complex diseases. With current technologies its still possible to a few of the genes that have a high P-value of significance for certain complex disorders:

Partial list (limited to two dozen examples) of recent GWA studies in which one or a few SNPs are associated with a complex disease or *multiplex phenotype* (note highly significant *P*-values of $<1 \times 1(10^{-6})$).

Phenotype	Gene(s)	*P*-value	Reference
Risk of inflammatory bowel disease	*IL23R*	1.60×10^{-9} to 3.36×10^{-13}	(Duerr et al.,2006)
Risk of type-2 diabetes	Four loci plus *TCF7L2*	3.2×10^{-17}	(Sladek et al.,2007)
Risk of breast cancer	Nine previous genes plus *CASP8*	1.1×10^{-7}	(Cox et al., 2007)
Susceptibility to Crohn disease	*IL23R, CARD15, PTGER4* [a]	10^{-7} to 10^{-9}	(Libioulle et al.,2007)
Risk of prostate cancer	Chr 8q24 (two independent loci)	1.41×10^{-11}; 6.62×10^{-10}	(Yeager et al.,2007)
Risk of prostate cancer	Chr 8q24 (two independent loci)	1.4×10^{-10}; 1.6×10^{-14}	(Gudmundsson et al., 2007a)
Association with body mass index and predisposition to obesity	*FTO*	3×10^{-26}	(Frayling et al., 2007)
Susceptibility to Crohn disease	*IL23R, CARD15, ATG16L1, PHOX2B, NCF4, FAM92B*, and intergenic region on 10q21.1 [b]	$< 10^{-10}$	(Rioux et al., 2007)

Partial list of recent publications in which one or very few SNPs "are associated with" a *complex disease*, also termed *multiplex phenotype* (*P* values between <0.05 and 0.001).[a]

Phenotype	Gene	*P* value(s)	Reference
Lung cancer and smoking	*NQO1*	0.048	(Rosvold et al., 1995)
Induced CYP1A2 metabolic activity	*CYP1A2*	<0.05	(Nakajima et al., 1999)
Risk of colorectal cancer	*SULT1A1*	0.009	(Bamber et al., 2001)
Myocardial infarction	*GCLM*	<0.001	(Nakamura et al., 2002)
Ethnic differences in risk of heart failure	*ADRA2C, ADRB1*	<0.001, 0.004	(Small et al., 2002)
Successful weight reduction by sibutramine	*GNB3*	0.031, 0.004	(Hauner et al., 2003)
Vulnerability to illegal drug abuse	*HTR2B*	0.0335	(Lin et al., 2004)
Caffeine metabolism	*CYP1A2*	0.036, 0.038	(Chen et al., 2005)
Risk of young onset, late onset Parkinson disease	*NAT2*	0.003	(Chaudhary et al., 2005)
Coffee intake and risk of myocardial infarction	*CYP1A2*	0.04	(Cornelis et al., 2006)
Smoking and obesity in prostate, lung, colorectal and ovarian cancer patients	*DRD2*	0.02, 0.007	(Morton et al., 2006)
Antidepressant efficacy in depression patients	*GNB3*	0.02, 0.03	(Wilkie et al., 2007)
Risk of aspirin-intolerant asthma	*PTGER2, PTGER3, PTGIR, TBXA2R*	0.023, 0.038	(Kim et al., 2007)
Gefitinib responsiveness in non-small-cell lung cancer	*EGFR*	0.014, 0.029	(Han et al., 2007)
Risk of atherosclerosis	*CYP2J2*	0.036	(Lee et al., 2007)
Risk of toxic liver injury	*ABCC2*	0.04	(Choi et al., 2007)
Risk of primary lung cancer	*ERCC1*	0.034	(Ma et al., 2007)
Induction of extrapyramidal symptoms by antipsychotics	*RGS2*	0.003, 0.009	(Greenbaum et al., 2007)
Fracture risk (bone mass) after estrogen treatment	*P2RX7*	<0.01, 0.02	(Ohlendorff et al., 2007)
Glatiramer acetate therapy for multiple sclerosis	*TRB@* locus	0.049	(Grossman et al., 2007)

Phenotype	Gene(s)	*P* value	Reference
Risk of Alzheimer disease	*APOE*	<0.00001	(Saunders et al., 1993)
Risk of deep vein thrombosis	*F5*	$<10^{-15}$	(Bertina et al., 1994)
Risk of type-2 diabetes	*PPARG*	0.002	(Altshuler et al., 2000)
Risk of Crohn disease	*NOD2*	2×10^{-5}; 6×10^{-6}	(Hugot et al., 2001)
Type-1 diabetes	*PTPN22*	6.0×10^{-4}	(Bottini et al., 2004)
Rheumatoid arthritis	*PTPN22*	6.6×10^{-4}; 5.6×10^{-8}	(Begovich et al., 2004)
Type-2 diabetes	*TCF7L2*	2.1×10^{-9}	(Grant et al., 2006)

Results like these are what give researchers the drive to continue parsing through complex diseases. Even though these are just one or two of the several genes that directly contribute to phenotypic expression its hope that more still can be found.

In conclusion, DTC genetic tests are not a reality quite yet but with increasing results with each study that passes the reality may come soon. GWA studies and SNP reviews reveal the genes that effect diseases and can ultimately lead to pharmaceutical advancement to develop drugs to combat illness.

Works Cited:

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