Pharmacogenomic Profile of a Pakistani Individual

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Abstract

The new era of pharmacogenomics has been raised where we use genetic information of an individual for the development of personalised medicine. Here, we analysed the whole genome sequence of a Pakistani individual to get his pharmacogenomics profile. We found a number of SNPs associated with methotrexate dose response, docetaxel and thalidomide, and several other variants of clinical relevance. The current study provides a workflow example to use personal genomes for developing personalised medicine protocols. The pharmacogenomics association to neurological disorders, depression and hypertension discovered here can provide the most fundamental information for a Pakistani individual to change his way of life and carry out precautionary actions for a better life ahead.

Keywords: Whole-genome; Pakistani; Pharmacogenomics; Personalised medicine; PharmGKB.

Introduction

The personalised genomics study has provided a new set of tools to screen genomic information to investigate disease genes and its correlation with drug responses/efficacy and toxicity to avoid adverse drug reaction associated with drug therapy (Collins et al., 2003; Pereira and Weinshilboum, 2009). The actualisation of individualised drug will need for combining a patient’s conventional medical information with computational-based molecular-assessment profiles.

The main objective of sequencing the ever first human genome was not only to get the entire three billion bases of human DNA, it was also to provide a tool to screen genetic variations to identify disease genes (Venter et al., 2001). Single Nucleotide Polymorphisms (SNPs) are point mutations that occur normally across an individual’s genome. These point mutations have the ability to influence disease risk and drug efficacy and other phenotypes. These genomic variations among individuals that predispose certain people to diseases and elucidate the reasons why some of them react well to certain medicine. Many pharmaceutical companies realise that the new drug development will come from studying the genetic information of diseases and researchers state that there is still a long way to identify genetic susceptibility and developing an effective drug (Langreth and Waldholz, 1999). Researchers and pharmaceutical industries also hope the genetic data will be the basis of simple blood tests that will help the clinicians about the person who will benefit from certain drugs and who get serious side effects. At present, even with the advance technology the best medicines are effective only for 60% of the patients and scientists expect that genetic variants research will raise that percentage (Langreth and Waldholz, 1999). A number of studies have been performed to reveal the importance of genome sequencing in pharmacogenomics research (Ashley et al., 2010; Drögemöller et al., 2011; Mizzi et al., 2014 and Salleh et al., 2013). The analysis of just one sample from a single ethnicity is not enough to obtain sufficient information but it was only to highlight the importance and the applications of genome sequencing in making personalised medicines.

We have analysed and developed the pharmacogenomics profile of a Pakistani individual genome publically available (Azim et al., 2013). We may get more benefits from this research if detailed clinical information of the donor was available. This would help us to discover the novel genes that act as pharmacogenes and also could guide us to find new functions and possibly new treatment options.

Material and Methods

Dataset and ethical approval: The complete genome data of an individual from Pakistan, generated with HiSeq 2000 (Illumina, San Diego, California, USA) was retrieved from NCBI (SRA057506) (Azim et al., 2013). The consent has already been signed by the donor to publicly disclose entire content of his genome.
Mapping and variants calling: All the sequence reads were mapped to hg19 using Burrows-Wheeler Aligner (BWA) software (Li and Durbin. 2009). The alignment was performed using SAMtools software (Li et al., 2009) and the variant calling files VCF were generated by GATK software (McKenna et al., 2010).

Functional annotation: All the SNVs were annotated for functional effects using ANNOVAR (Wang et al., 2010). The variants were mapped against SIFT and Polyphen-2 and the concordant information was filtered for further analysis (Ng and Henikoff, 2003; Adzhubei et al., 2010).

Pharmacogenomics analysis: The uniprot information obtained from ANNOVAR was used to do pharmacogenomics analysis. The Perl program developed by OpenPGx was used to do the study in more detail (Salleh et al., 2013).

Results and Discussion

Approximately three million SNPs were called in the Pakistani genome in which 8,448 were observed as nonsynonymous SNPs. Over 40 nonsynonymous SNVs (nsSNVs) were observed as functionally damaged predicted by Polyphen-2 and SIFT corresponding to 35 genes and more than 100 drugs.

Both SIFT and Polyphen-2 gave different number of damaged variants. A consensus of the two tools was generated to get more consistent damaged variants, revealing 531 unique variants in 422 genes. The consensus prediction, employing SIFT and Polyphen-2, was used against a well annotated dataset of genes involved in pharmacologic pathways derived from PharmGKB and Drug Bank (Hewett et al., 2002; Wishart et al., 2008). Our analysis revealed three drug metabolising enzymes and two drug targets harbouring damaging nsSNPs, many of which are involved in the transport, metabolism or targeting of drugs, used as hematological, psychiatric, oncological, analgesic, antiviral and anti-infective agents. A large number of variants were associated with toxic drugs, while other nsSNVs were linked to the efficacy of medicines, used in the treatment of diseases, such as, depression, diabetes mellitus, Alzheimer’s disease, arthritis and so on (Table 1). After discovering the possibly damaged variants found in Polyphen-2 and SIFT, the concordant of both datasets were further analysed in order to find the highest impact of these deleterious variants in terms of drug targeting, transport, and metabolism. We found nsSNVs that affect the function of drugs (three enzymatic and two targets drugs).

Our analysis revealed SNPs (rs1801394 at chr5:7870973 in MTRR) having interaction with methotrexate dose response which increases red blood cell folate in people with Arthritis (Menon et al., 2012). A variant in gene VDR in chromosome 12 was found associated with calcitriol which increases the risk of bone fractures (Morrison et al., 2005). An SNP interaction was reported with docetaxel and thalidomide which increases toxic effect in people with prostatic neoplasms (Deeken et al., 2010). A significant number of variants were observed to be associated with drug toxicity, while many belonged to drugs used in the treatment of diseases such as depression, hypertension, schizophrenia and other neurological disorders.

We have developed an individual’s pharmacogenomics profile in a broad aspect using next generation sequencing data. The protocol developed would help to realise individualised medicine as an extensive tool for whole genomic data on a person and can be applied into clinical practices. Moreover, disease traits and associated drugs information for neurologic and cancer recognised here, would help a Pakistani individual to change his way of life and carry out precautionary actions for a better life ahead.

Competing interests

The authors declare no competing financial interests.

Acknowledgement

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References


Table 1. List of drugs (PharmGKB, Drug Bank) in the Pakistani genome.

<table>
<thead>
<tr>
<th>rsID</th>
<th>Position</th>
<th>Ref.</th>
<th>Alt</th>
<th>AA</th>
<th>Category</th>
<th>Gene</th>
<th>Prot Id</th>
<th>Is Genotyped</th>
<th>Is VIP</th>
<th>PD</th>
<th>PK</th>
<th>Has Variant</th>
<th>Annotation</th>
<th>Drug</th>
<th>Diseases</th>
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<td>G</td>
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<td>Q6NWU0</td>
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<td>TRUE</td>
<td>PD</td>
<td>PK</td>
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<td></td>
<td>amitriptyline; antipsychotics; atomoxetine; carvedilol; chlorpheniramine; chlorpromazine; citalopram; clomipramine; clozapine; codeine; debrisoquine; desipramine; dextromethorphan; doxepin; escitalopram; flecainide; fluoxetine; fluvoxamine; gefitinib; haloperidol; iloperidone; imipramine; maprotiline; metoprolol; mexiletine; mianserin; morphine; nortriptyline; paroxetine; perhexiline; perphenazine; propafenone; propranolol; risperidone; sparteine; tamoxifen; thioridazine; timolol; tolterodine; tramadol; yohimbine; zuclopenthixol</td>
<td>Breast Neoplasms; Cystic Fibrosis; Depression; Depressive Disorder; Hypertension; Neoplasms; Pain; Parkinson Disease; Schizophrenia; tardive dyskinesia</td>
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<td>TRUE</td>
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<td>PK</td>
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<td></td>
<td>antineoplastic agents; antipsychotics; benazepril; busulfan; capecitabine; carboplatin; cisplatin; cyclophosphamide; cyclosporine; dactinomycin; dexamethasone; disulfiram; docetaxel; doxorubicin; fluorouracil; folic acid; gemcitabine; hormonal contraceptives for systemic use; hydroxychloroquine; leucovorin; mercaptopurine;</td>
<td>Alopecia; Alzheimer’s Disease; Arthritis, Juvenile Rheumatoid; Arthritis, Psoriatic; Arthritis, Rheumatoid; Breast Neoplasms; Carcinoma, Non-Small-Cell Lung; Cardiovascular Diseases; Cleft Lip; Cleft Palate; Cocaine-Related Disorders; olonic Neoplasms; Colorectal Neoplasms; Artery Disease; Down Syndrome; Drug Toxicity; Graft vs Host Disease; Hyperhomocysteinemia;</td>
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<td>MTRR</td>
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