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The Extraction of Pharmacogenomic Data from Whole Genome Sequencing

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Abstract

One area of medicine that is changing fast is clinical genetics. More and more, diagnostic tests are shifting toward genome and exome-wide screenings that are less biased. variations of unclear clinical relevance, difficulties in interpreting variations, and secondary findings are all results of this. In order to better understand uncommon diseases and pharmacogenomics, this research investigated how phenotypic and whole genome sequence (WGS) data may be used. Bardet Biedl syndrome (BBS): a molecular foundation for two cases was attempted to be clarified using WGS. Variants were filtered based on inventiveness, copy number losses or gains were identified using bioinformatics approaches, and known ciliopathy and other genes were examined.

Keywords: Genomes, Pharmacogenomics, Anti-cancer, Medicines, Pharmaceutical, Patients', Drugs

1. Introduction

An integral aspect of precision medicine, pharmacogenomics is finding more and more applications in clinical practice to enhance pharmacological treatment, especially about cancer. The fields of pharmacogenomics and pharmacogenetics refer to the same thing. While genomes get all the attention in the context of precision medicine, the word really encompasses the use of any clinical characteristic to tailor individual patients' medication regimens. Given that heredity sequencing technology have advanced and there is more evidence to suggest gene-drug connections, doctors may use genetic data to personalize treatment plans. Cancer, a disease caused by a mutation in DNA, is one of the most promising new fields for clinical pharmacogenomics research and development. Indeed, tumor profiling (genetic sequencing) has become the gold standard in several cancer centers and for some forms of cancer (e.g., lung, breast, melanoma, colorectal).

There are two genomes involved in cancer pharmacogenomics: the patient's and the tumors. All of these provide useful data for tailoring pharmaceutical treatments to each patient. Standard dosages of certain chemotherapeutic medicines may cause severe toxicity or therapeutic failure in particular patients, and this is because the patient's genome-inherited genetic variation-reveals information about the functioning of essential drug-metabolizing enzymes. Optimizing the selection and dosage of different supportive care drugs may also be possible with an understanding of genetic variances in the patient's genome. The tumor genome, which is a kind of acquired genetic variation, may help pinpoint the mutation(s) that are driving uncontrolled cell development. By targeting these mutations with the right medication, the tumor can be reduced in size. The best course of therapy may be dictated in part by genetic abnormalities found within the tumor genome, which may be associated with prognosis. Compared to conventional cytotoxic chemotherapy, which targets both cancer and healthy tissue, targeted therapies-medications that aim at a particular genetic mutation in the tumor genome-may have fewer side effects. In order to confirm that a targeted treatment is suitable and may have a therapeutic effect, genetic testing must be conducted prior to administration.

Pharmacogenomic testing is still not widely available due to financial concerns and the reluctance of insurance companies to provide coverage for it unless it is absolutely necessary before prescribing a certain medicine. Having said that, more and more people are able to have testing done. Both proactive and reactive strategies are used in pharmacogenomic testing. When considering or beginning a medication therapy, reactive testing may help with drug

selection or dosage for a particular indication, or it might explain why a treatment has failed or what side effects have been encountered. In most cases, a single gene is tested for in reactive testing. Preemptive testing, on the other hand, sometimes entails testing for a panel of genes beforehand; this kind of testing is not reliant on the patient's current or future prescription regimen.

2. Literature Review

He, Shiyu *et al*. (2023) [1] At this time, imatinib is recommended while fighting chronic myeloid leukemia for the first time. Regarding the other hand, customized medicine is lacking in real-world facts pertaining to Chinese patients. The goals of this study are to offer evidence for targeted treatment and dosage reduction by characterizing the studying the pharmacokinetics investigating the effects of imatinib on a group of Chinese patients suffering from chronic myeloid leukemia and effect of several factors on the exposure to this medication. Methods: Participants included 230 people diagnosed with chronic myeloid leukemia; 424 steady-state concentration readings were collected for the purpose of statistics on pharmacokinetics in a population as well as Monte Carlo models run with the Phoenix NLME program. In conclusion, important demographic variables like hemoglobin and estimated glomerular filtration rate may account for variation in imatinib exposure. Significantly impaired renal function patients with high hemoglobin fluctuations need some extra care while being treated.

Polillo *et al*. (2015) [2] It has been almost fifteen years since imatinib was initially used as an individualized strategy in order to treat chronic myeloid leukemia, the first blood cancer. In the time after, many investigations on the pharmacodynamics and pharmacokinetics of BCR-ABL1 TKIs were conducted. with an emphasis on genes, polymorphisms within them, and the proteins encoded by these genes. Transmembrane transporters seem to function at both the cellular and systemic levels via substantial role in determining the fate of TKIs, particularly imatinib.

P Jadhav, Prof *et al*. (2023) [3] Improving treatment effectiveness while lowering medication toxicity is the ultimate objective of customized medicine. At the correct moment, the right medication was administered to the right patient, as this demonstrates. Advancements in molecular diagnostics and individualized drug treatment plans for patients determined by their distinct genetic makeup. Evaluating the benefits, downsides, and implications of customized medicine for healthcare is the major objective of this research. Prospective views and real-world clinical applications. The potential for personalized medicine to detect, halt, and cure illness is great. Research into the role of heredity in the pharmacological response is known as pharmacogenomics (PGx). It is the most recent subspecialty in medicine, and it is growing at a fast pace. The pharmaceutical industry is slowly but surely figuring out how to use data, incorporate it into medication development, and meet the high expectations of doctors and patients.

Rasmussen *et al*. (2024) [4] Patients Thanks to tyrosine kinase inhibitors (TKIs), hematopoietic hSCT is no longer the primary therapy choice for Ph+ individuals with CML or ALL, who have chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL). A subtype of ALL known as Philadelphia chromosome-like (Ph-like) has recently found relief with TKIs.. Unfortunately, a lot of patients move away from imatinib, a first-generation TKI, because of side effects or because it doesn't work. To overcome these obstacles and maybe achieve higher cost-effectiveness, a more tailored strategy for TKI therapy is required. Adult chronic myeloid leukemia (CML) has benefited more from therapeutic drug monitoring (TDM) in terms of response rates and treatment-related toxicity, whereas ALL and juvenile CML are uncommon indications for its usage.

Alarcón-Payer *et al*. (2022) [5] The majority of cancerous blood diseases have their origins in mutations or changes to cell replication pathways that have been acquired throughout time. Acquired genetic and epigenetic changes in hematopoietic progenitor cells give birth to the clinically and molecularly diverse disease known as acute myeloid leukaria (AML). Our understanding of the pathogenesis of the illness has improved, yet the high recurrence rate means that patients still have an extremely poor chance of survival. With the help of pharmacogenetics and large-scale sequencing studies, we have discovered novel recurrent mutations in AML that have high prognostic implications. In order to diagnose this entity and monitor the efficacy of treatment, research on it is essential. Onomatology patients are now treated with tyrosine kinase inhibitors (TKIs), which has modified the usual technique of treating chronic myeloid leukemia (CML). orally, which target the BCR: ABL1 protein.

3. Pharmacogenomic Evaluation and Recommendations

3.1 Instructions for prescribing

Manual extraction of prescribing recommendations was carried out in September 2015 from www.pharmGKB.org. In order to reflect any changes or additions to the guidelines, a review was conducted in January 2018 and the findings were revised appropriately. There were a few suggestions made by clinical pharmacogenetics implementation and the Dutch pharmacogenomics working group Consortium (CPIC), with some input from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). The extraction of 100 separate rules pertaining to 72 distinct medications. A thorough comparison publication was used to compare the recommendations, and they were double-checked thereafter (87). Supplemental Information S2.1 (CD-ROM) has a table that organizes instructions according to haplotype and medication, making analysis easier.

3.2 Haplotype and genotype data

For every pharmacogene with related recommendations in September 2015, genotype and haplotype information was extracted from the haplotype defining tables hosted on www.pharmGKB.org.Any changes to haplotype definitions were the subject of a review in January 2018.

3.3 Genomics and haplotype extraction using whole genome sequencing data

Section 3.2.1 states that only haplotypes or genotypes that were accompanied by pharmacogenomic prescription guidelines were examined. As mentioned before, this was accomplished via IGV. We logged all SNPs and calculated the haplotypes and diplotypes. Everyone in the cohort-all

eighty-four people-had their data taken. The CFTR gene was not included since it may be a carrier test. We also did not include since HLA-B *44 and HLA-B *58:01 are based on sequences instead of SNP-based. further pharmacogenes were added to the Congenica panel as further data was retrieved.

3.4 Individual prescribing guidance

Individual medication recommendations and published pharmacogenomic prescribing standards were compared with each patient's genotypes and diplotypes. An Excel spreadsheet including the lengthy version of the advice and a summary form were both generated. To determine the frequency of individuals with variations in actionable pharmacogenes, the prescribing recommendations were examined. In order to ascertain the likely impact of this, we queried the phenotyping database to find out if patients had been given any medications that were metabolized by actionable pharmacogenes for which they had variations.

3.5 Haplotype frequency calculations

The literature or Pharm GKB were used to get the haplotype frequencies. In order to get the cohort frequencies, we removed one kid from each set from the SRS trios and monozygotic twins, we have 72 people. The published data was used to compare the frequency of haplotypes or alleles. The complete data for each haplotype or allele was compared using a Fisher's exact test. To compare the frequencies of various haplotypes or alleles, a two-proportion z-test was used, along with 95% confidence intervals (CI). One uses Fisher's exact test while examining contingency tables. The p-value must be less than 0.05. points to the validity of the null hypothesis, which states that the tables are different. If the results do not show a statistically significant deviation from the tables. With 95% certainty, the observed value will fall within a specified range, and that range is given by a 95% confidence interval. If the published frequency were identical to the observed frequency, then the published figure should fall inside the 95% confidence range that was determined for the figure that was seen. To determine whether there is a statistically significant difference (p value less than 0.05), the two proportion z-test compares the observed percentage to each of the two independent variables. one that predicted percentage.

4. Collection and Data Bases for Patients

4.1 Patient data collection

Several sources provided me with patient data. For patients with BBS, IBD, or USH, this included paper and digital patient records kept at Moorfields Eye Hospital, GOSH, and the NHS Foundation Trusts of Guy's and St. Thomas' Hospital. The electronic prescription, imaging, and pathology databases from those medical centers were also a part of it. Summaries of clinical data, including phenotypic descriptors, pathology and imaging findings, and JDM patients' medical histories, were collected from clinicians for this study. Beyond patients' ethnicities, no further clinical data was provided for the SRS group.

4.2 Patient data recording and output

The UCL Data Safe Haven (IDHS) was used to store all patient data. It is permitted to hold sensitive healthcare data belonging to NHS patients. Both the NHS Information Governance Toolkit and the ISO27001 standards were followed in this process. information security standard. Assigning storage space protects the IDHS. to a certain researcher in advance. They can access data securely using a password and a key. Password protection was also implemented for individual IDHS apps.

4.2.1 PhenoTips database

Following clearance by the UCL IDHS committee, With the assistance of UCL IT, the PhenoTips® database was uploaded to the UCL IDHS. personnel. Clinical descriptors, which were obtained from the sources, were input as Human Phenotype Ontology (HPO) words. At semiannual intervals, we reviewed any changes to HPO terms and made the necessary updates to the IDHS version of PhenoTips®. The goal was to identify the most precise HPO word that could characterize the clinical characteristic with each phenotypic description that was entered. Not present were any significant negative aspects. Extra information was also noted, including the subjects' ages, heights, and weights. We were only able to input data into PhenoTips from the USH, JDM, BBS, and IBD groups ® since we did not have any clinical data for the SRS group. A list of essential characteristics of JDM was used to note whether a patient had the disease or not. Along with the recording dates, they were also added to the MS Access database. The data was only collected for patients USH-001 and USH-002. Phenotyping did not include USH-003 since they were unaffected and no clinical data was provided.

You can find the export data option under the "other actions" section of PhenoTips®. It enabled you to export data as either a JSON or text file, which is how the PhenoTips® database was exported. After patients' distinct cohort numbers (e.g., BBS-001) were the sole identifiers, anonymization took place when they were able to choose which data types to export. Not provided were other pieces of information like names and birthdays. The files were anonymized before they were sent out of IDHS. The IDHS file transfer facilities were used to deliver one researcher has access to these documents (including spreadsheets and text files). Among all original researcher was able to deanonymize the data.

4.2.2 Data set created in Microsoft Access (MS Access)

The document describes the development of a customized Microsoft Access database designed to manage clinical data, with a focus on ensuring data privacy and compliance with IDHS regulations. The database comprises a patient information table as the primary data source, supplemented by 15 patient-specific tables and 21 static lookup tables. To facilitate data entry and retrieval, user-friendly forms and queries were implemented, allowing for both anonymized and non-anonymized data outputs. Clinical records related to blood and pathology findings are linked to patient appointments and include reference ranges for various tests. The database employs specific formulas to classify results as normal, high, or low, assisting in highlighting abnormal findings.

Data anonymization is a critical aspect of this database; it follows IDHS guidelines by removing personal identifiers

such as first and last names, hospital numbers, and dates of birth. Anonymized data is exported in multiple formats, including text files for researchers, with cohort numbers assigned as identifiers. The document highlights the secure transmission of data using the IDHS encrypted file transfer service, ensuring that only authorized individuals can deanonymize the data using a secure system that requires authentication.

Accompanying supplemental materials on a CD-ROM include an anonymized version of the database, containing entries from various medical conditions such as BBS, IBD, JDM, and USH, although specific patient groups were excluded due to inadequate data. The database is designed for long-term usability, integrating additional data relevant to other multiomics studies and maintaining separations for pharmacogenomic data. Its structure uses systematic prefixes for ease of organization-patient data prefixed with "tbl_" (e.g., tbl_BloodTestResults), result searches with "x_" (e.g., x_BBS_PatientInformation), and queries with "qry_" (e.g., qry_BBS_BloodTestResults). The emphasis on usability extends to data entry forms, which simplify input and navigation for users. Overall, the database is a comprehensive tool aimed at facilitating efficient clinical data management while safeguarding patient privacy.

4.3 Data use

Researchers, such as Drs. Rosalind Davies and Jochen Kammermeier, combed through databases to find clinical data in order to compile prescription information for the pharmacogenomics chapter and diagnostics chapter, as well as for assessments of burden, patient stratification, and multiomics.

5. Sifting Through Whole Genome Sequence Data for Pharmacogenomic Insights

Eighty-four people belonging to five cohorts had their whole genome sequenced. This included ten family units consisting of three generations (the two pairs of identical twins (BBS-010 and BBS-011, and BBS-016 and BBS-017), as well as a group of people named Reach.

A. Genotypes and haplotypes

Genomics of single-nucleotide polymorphisms linked to alleles related with prescribing identified one variant in CYP4F2 and one variation in rs12777823, both of which are important in warfarin prescriptions. recommendations that were retrieved. According to clause 5.3.2.3.1, no data were retrieved for CFTR. Furthermore, analysis of Astrolabe data resulted in the modification of many haplotypes. All results for all individuals (except the BBS cohort, which is shown in Tables 1 to 8) are available in Supplementary Information 2.2 (CD-ROM). We were unable to get data because sequence, not single nucleotide polymorphisms, determines the alleles for HLA-B *44 and HLA-B *58:01. Up until now, there has been no conclusive evidence regarding which SNPs are acceptable for individuals to be classified as having these haplotypes. Where applicable, the SNPs that were found were then transformed into diplotypes. Several individuals in the SRS and IBD cohorts did not have DPYD-interpretable haplotypes.

B. Prescribing advice

Future prescribing advice

Prescription recommendations were derived for each patient after genotypes and diplotypes were compared with established standards. There were two types of advice papers made: thorough and summary. Supplementary Information 2.3 (CD-ROM) contains comprehensive long-form and short-form prescription guidance for each person. the genes whose findings may affect recommendations for medication use. Twelve individuals (14%), twenty-seven (23%), fourteen (17%), eight (10%), and two (2%), had a single diplotype or genotype that might cause a shift in prescription recommendations. Every patient had an average of 3.8 actionable variations. What this implies is that every single patient has a genetic mutation that might need a different dosage or closer monitoring if they are given a medication that could affect this.

Table 1: Variants of CYP2C9 in the BBS group

Patient ID	Diplotype	rs1799853	rs1057910	rs28371686	rs9332131	rs7900194	rs28371685
		10:94942290	10:94981296	10:94981301	10:94949282	10:94942309	10:94981224
		g.94942290 C>T p.Arg144Cys	g.94981296 A>C p.Ile359Leu	g.94981301 C>G p.Asp360Glu	g.94949282 delA p.Lys273Argfs	g.94942309 G>A p.Arg150His	g.94981224 C>T p.Arg355Trp
	*1	C	A	C	A	G	C
	*2	T	A	C	A	G	C
	*3	C	C	C	A	G	C
	*5	C	A	G	A	G	C
	*6	C	A	C	del A	G	C
	*8	C	A	C	A	A	C
	*11	C	A	C	A	G	T
BBS-001	*1/*1	CC	AA	CC	AA	GG	CC
BBS-002	*1/*2	CT	AA	CC	AA	GG	CC
BBS-003	*1/*1	CC	AA	CC	AA	GG	CC
BBS-004	*1/*2	CT	AA	CC	AA	GG	CC
BBS-005	*1/*1	CC	AA	CC	AA	GG	CC
BBS-006	*1/*2	CT	AA	CC	AA	GG	CC
BBS-007 BBS-008	*1/*1 *1/*3	CC CC	AA AC	CC CC	AA AA	GG GG	CC CC
BBS-009	*1/*1	CC	AA	CC	AA	GG	CC
BBS-010	*1/*1	CC	AA	CC	AA	GG	CC
BBS-011	*1/*1	CC	AA	CC	AA	GG	CC
BBS-012	*1/*1	CC	AA	CC	AA	GG	CC
BBS-013	*1/*2	CT	AA	CC	AA	GG	CC
BBS-014	*1/*2	CT	AA	CC	AA	GG	CC
BBS-015	*1/*1	CC	AA	CC	AA	GG	CC
BBS-016	*1/*3	CC	AC	CC	AA	GG	CC
BBS-017	*1/*3	CC	AC	CC	AA	GG	CC
BBS-018	*1/*1	CC	AA	CC	AA	GG	CC

Table 2: Variants of CYP2C19 in the BBS group

Patient ID	Diplotype	rs4244285	rs4986893	rs28399504	rs56337013	rs72552267	rs72558186	rs41291556	rs12248560
		10:94781859	10:94780653	10:94762706	10:94852738	10:94775453	10:94781999	10:94775416	10:94761900
		g.94781859G>A. Pro227=	g.94800653G>A p. Trp212Ter	g.94762706A>G p. Met1Leu	g.94852738C>T p. Arg433Trp	g.94775453G>A p. Arg132Gln	g.94781999T>A	g.94775416T>C p. Trp120Arg	g.94761900C>T
	*1	G	G	A	C	G	T	T	C
	*2	A	G	A	C	G	T	T	C
	*3	G	A	A	C	G	T	T	C
	*4A	G	G	G	C	G	T	T	C
	*4B	G	G	G	C	G	T	T	T
	*5	G	G	A	T	G	T	T	C
	*6	G	G	A	C	A	T	T	C
	*7	G	G	A	C	G	A	T	C
	*8	G	G	A	C	G	T	C	C
	*17	G	G	A	C	G	T	T	T
BBS-001	*1/*2	GA	GG	AA	CC	GG	TT	TT	CC
BBS-002	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC
BBS-003	*1/*2	GA	GG	AA	CC	GG	TT	TT	CC
BBS-004	*1/*2	GA	GG	AA	CC	GG	TT	TT	CC
BBS-005	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC
BBS-006	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC
BBS-007	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC
BBS-008	*1/*17	GG	GG	AA	CC	GG	TT	TT	CT
BBS-009	*1/*17	GG	GG	AA	CC	GG	TT	TT	CT
BBS-010	*1/*17	GG	GG	AA	CC	GG	TT	TT	CT
BBS-011	*1/*17	GG	GG	AA	CC	GG	TT	TT	CT
BBS-012	*17/*17	GG	GG	AA	CC	GG	TT	TT	TT
BBS-013	*1/*17	GG	GG	AA	CC	GG	TT	TT	CT
BBS-014	*1/*2	GA	GG	AA	CC	GG	TT	TT	CC
BBS-015	*1/*2	GA	GG	AA	CC	GG	TT	TT	CC
BBS-016	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC
BBS-017	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC
BBS-018	*1/*1	GG	GG	AA	CC	GG	TT	TT	CC

Table 3: Varieties of CYP2D6 in the BBS study group

Patient ID	Diplotype	rs16947	rs1135840	rs3574268 6	rs1065852	rs3892097	rs5030655	rs5030656	rs2837170 6	rs2837172 5	rs769258	Notes
		22:42127941	22:42126611	22:42128242	22:42130692	22:42128945	22:42129084	22:42128174-42128176	22:42129770	22:42127803	22:42130761	
		g.42127941G>A p.Arg296Cys	g.42126611C>G p.Ser486Thr	g.42128242delta p.Arg259Glyfs	g.42130692G>A p.Pro34Ser	g.42128945C>T	g.42129084delA p.Trp152Glyfs	g.42128174_42128176delCTT p.Lys281del	g.42129770G>A p.Thr107Asn	g.42127803C>T	g.42130761C>T p.Val11Met	
*1		G	C	T	G	C	A	CTT	G	C	C	
*1xN												
*2		A	G									
*2xN		A	G									
*9x2								delCTT				
*10			G		A							
*10x2			G		A							
*17		A	G						A			
*17x2		A	G						A			
*35		A	G								T	
*41		A	G							T		
*41x2		A	G							T		
Patient ID	Diplotype	rs16947	rs1135840	rs3574268 6	rs1065852	rs3892097	rs5030655	rs5030656	rs2837170 6	rs2837172 5	rs769258	Notes
BBS-001	*1/*4	GG	GC	TT	GA	CT	AA	CTT/CTT	GG	CC	CC	
BBS-002	*1/*41	GA	GC	TT	GG	CC	AA	CTT/CTT	GG	CT	CC	
BBS-003	*1/*41	GA	GC	TT	GG	CC	AA	CTT/CTT	GG	CT	CC	
BBS-004	*1/*1	GG	CC	TT	GG	CC	AA	CTT/CTT	GG	CC	CC	
BBS-005	*1/*1	GG	CC	TT	GG	CC	AA	CTT/CTT	GG	CC	CC	
BBS-006	*1/*9	GG	CC	TT	GG	CC	AA	CTT/delCTT	GG	CC	CC	
BBS-007	*4/*4	GG	GG	TT	AA	TT	AA	CTT/CTT	GG	CC	CC	

BBS-008	*4/*4	GG	GG	TT	AA	TT	AA	CTT/CTT	GG	CC	CC	
BBS-009	*1/*41	GA	CG	TT	GG	CC	AA	CTT/CTT	GG	CT	CC	
BBS-010	*1/*41	GA	CG	TT	GG	CC	AA	CTT/CTT	GG	CT	CC	
BBS-011	*1/*41	GA	CG	TT	GG	CC	AA	CTT/CTT	GG	CT	CC	
BBS-012	*1/*41	GA	CG	TT	GG	CC	AA	CTT/CTT	GG	CT	CC	
BBS-013	*4/*4	GG	GG	TT	AA	TT	AA	CTT/CTT	GG	CC	CC	
BBS-014	*1/*2	GA	CG	TT	GG	CC	AA	CTT/CTT	GG	CC	CC	
BBS-015	*2/*35	AA	GG	TT	GG	CC	AA	CTT/CTT	GG	CC	CT	Astrolabe
BBS-016	*2/*2	AA	GG	TT	GG	CC	AA	CTT/CTT	GG	CC	CC	
BBS-017	*2/*2	AA	GG	TT	GG	CC	AA	CTT/CTT	GG	CC	CC	
BBS-018	*1/*4	GG	CG	TT	GA	CT	AA	CTT/CTT	GG	CC	CC	

Table 4: Variants of the CYP3A5 gene in the BBS group

Patient ID	**Diplotype**	**rs28365083**	**rs776746**	**rs56411402**	**rs55965422**	**rs10264272**	**rs41303343**	**rs55817950**	**rs28383479**
		7:99652613	7:99672916	7:99665237	7:99666950	7:99665212	7:99652770	7:99676198	7:99660516
		g.99652613 G>T p.Thr398Asn	g.99672916 T>C	g.99665237 T>C p.Gln200Arg	g.99666950 A>G	g.99665212 C>T, p.Lys208=	g.99652770_71insA p.Thr346Tyrfs	g.99676198 G>A p.Arg28Cys	g.99660516 C>T p.Ala337Thr
	*1	G	T	T	A	C	_	G	C
	*2	T	T	T	A	C	_	G	C
	*3	G	C	T	A	C	_	G	C
	*4	G	T	C	A	C	_	G	C
	*5	G	T	T	G	C	_	G	C
	*6	G	T	T	A	T	_	G	C
	*7	G	T	T	A	C	ins	G	C
	*8	G	T	T	A	C	_	A	C
	*9	G	C	T	A	C	_	G	T
BBS-001	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-002	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-003	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-004	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-005	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-006	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-007	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-008	*1/*3	GG	TC	TT	AA	CC	_/_	GG	CC
BBS-009	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-010	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-011	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-012	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-013	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-014	*1/*3	GG	TC	TT	AA	CC	_/_	GG	CC

BBS-015	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-016	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-017	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC
BBS-018	*3/*3	GG	CC	TT	AA	CC	_/_	GG	CC

Table 5: Genotypes for rs12777823, CYP4F2 and VKORC1 in BBS cohort

Patient ID		CYP4F2	VKORC1	VKORC1
	rs12777823	rs2108622	rs9934438	rs9923231
	10:94645745	19:15879621	16:31093557	16:31096368
	g.94645745 G>A	g.15879621 C>T p. Val433Met	g.31093557 G>A	g.31096368 C>T
BBS-001	GA	CT	GG	CC
BBS-002	GG	CT	GG	CC
BBS-003	GA	CC	GA	CT
BBS-004	GA	TT	GG	CC
BBS-005	GG	CC	AA	TT
BBS-006	GG	CT	GG	CC
BBS-007	GG	CT	GA	CT
BBS-008	GG	TT	GG	CC
BBS-009	GG	CT	AA	TT
BBS-010	GG	TT	GA	CT
BBS-011	GG	TT	GA	CT
BBS-012	GG	CC	GA	CT
BBS-013	GG	CT	GA	CT
BBS-014	GA	CC	GG	CC
BBS-015	GA	CC	GG	CC
BBS-016	GG	CC	GA	CT
BBS-017	GG	CC	GA	CT
BBS-018	GG	CC	GA	CT

Table 6: Family structures for DPYD in the BBS group. (all reference sequences are not presented) rs1801267, rs1801268, rs72539306, rs80081766, rs78060119, and rs55886062.

Patient	Diplotype	rs3918290	rs1801159	rs72549303	rs1801158	rs1801160	rs72549309	rs1801266	rs1801265
		1:97450058	1:97515839	1:97450066	1:97515865	1:97305364	1:97740415-18	1:97691776	1:97883329
		g.97450058 C>G	g.97515839 T>C p. Ile543Val	g.97450066 delG p. Pro633Glnfs	g.97515865 C>T p. Ser534Asn	g.97305364 C>T p. Val732Ile	g.97740415_18delATGA p. Phe100Serfs	g.97691776 G>A p. Arg235Trp	g.97883329 A>G p. Cys29Arg
	*1	C	T	G	C	C	ATGA	G	A
	*2A	T	T	G	C	C	ATGA	G	A
	*2B	T	C	G	C	C	ATGA	G	A
	*3	C	T	_	C	C	ATGA	G	A
	*4	C	T	G	T	C	ATGA	G	A
	*5	C	C	G	C	C	ATGA	G	A
	*6	C	T	G	C	T	ATGA	G	A
	*7	C	T	G	C	C	_/_/_	G	A
	*8	C	T	G	C	C	ATGA	A	A
	*9A	C	T	G	C	C	ATGA	G	G
	*9B	C	T	G	C	C	ATGA	G	G
BBS-001	*1/*6	CC	TT	GG	CC	CT	ATGA/ATGA	GG	AA
BBS-002	*5/*9A	CC	TC	GG	CC	CC	ATGA/ATGA	GG	AG
BBS-003	*6/*9A	CC	TT	GG	CC	CT	ATGA/ATGA	GG	AG
BBS-004	*1/*5	CC	TC	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-005	*1/*5	CC	TC	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-006	*1/*1	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-007	*1/*1	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-008	*5/*9A	CC	TC	GG	CC	CC	ATGA/ATGA	GG	AG

BBS-009	*5/*9A	CC	TC	GG	CC	CC	ATGA/ATGA	GG	AG
BBS-010	*1/*1	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-011	*1/*1	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-012	*1/*9A	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AG
BBS-013	*1/*9A	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AG
BBS-014	*1/*1	CC	TT	GG	CC	CC	ATGA/ATGA	GG	AA
BBS-015	*5/*9A	CC	TC	GG	CC	CC	ATGA/ATGA	GG	AG

6. Conclusion

Among the benefits is the possibility of routinely reviewing these genomes in light of newly discovered genes or advances in our knowledge variety that does not depend on coding. Improved data quality and data accessibility are two further advantages. reusability for applications like pharmacogenomic variation or screening for additional disease risk factors. Cost, analytical challenges, and data storage costs are some of the disadvantages. The capacity to examine data when new genes or disease pathways are discovered and the ability to detect secondary variations of clinical importance are two further problems that may be considered as either benefits or drawbacks.

7. References

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