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Drug Array

Introduction

Many kinds of drug targets have been developed in drug research, such as DNA, RNA, and protein targets. Many new targets have emerged over the years, but there are not enough drug-like molecules to match them [1]. In such cases, apart from looking for novel disease-related targets, identifying the new relationships between diseases and existing drug targets is an alternative approach for drug R&D.

BGI thus developed a comprehensive capture Drug Array. Drug Array is an efficient and proficient selection tool which not only helps researchers to advance their studies into disease mechanisms, but also benefits drug repositioning and personalized medicine.

Through the application of Drug Array in target region sequencing and bioinformatics analyses, new relationships between diseases and existing drug targets may be revealed. Alternatively, with respect to the target gene variants, Drug Array could also facilitate the patient stratification and optimization for therapeutic research.

Array design

Drug Array profiles 1,325 target genes related to more than 100 diseases. These target genes are derived from Drugbank (http://www.drugbank.ca/) and have corresponding drugs in the market.

These targets are involved in many different kinds of diseases such as auto-immune diseases, central nervous system diseases, infectious diseases, metabolic diseases, cardiovascular diseases, cancer diseases, and have been classified according to the specific disease types.

Methods

- DNA extracted from 24 peripheral blood samples and YanHuang (YH) sample
- Genomic DNA from 24 samples and YH sample were pooled for one library construction
- Another library was constructed from YH sample
- Both libraries were hybridization-captured with Drug Array
- Paired-end sequencing of libraries on Illumina HiSeq™ 2000 platform
- SNPs of YH samples were validated by comparison with data in YanHuang database (http://yh.genomics.org.cn/)

Figure 1. The work flow of Drug Array target region sequencing

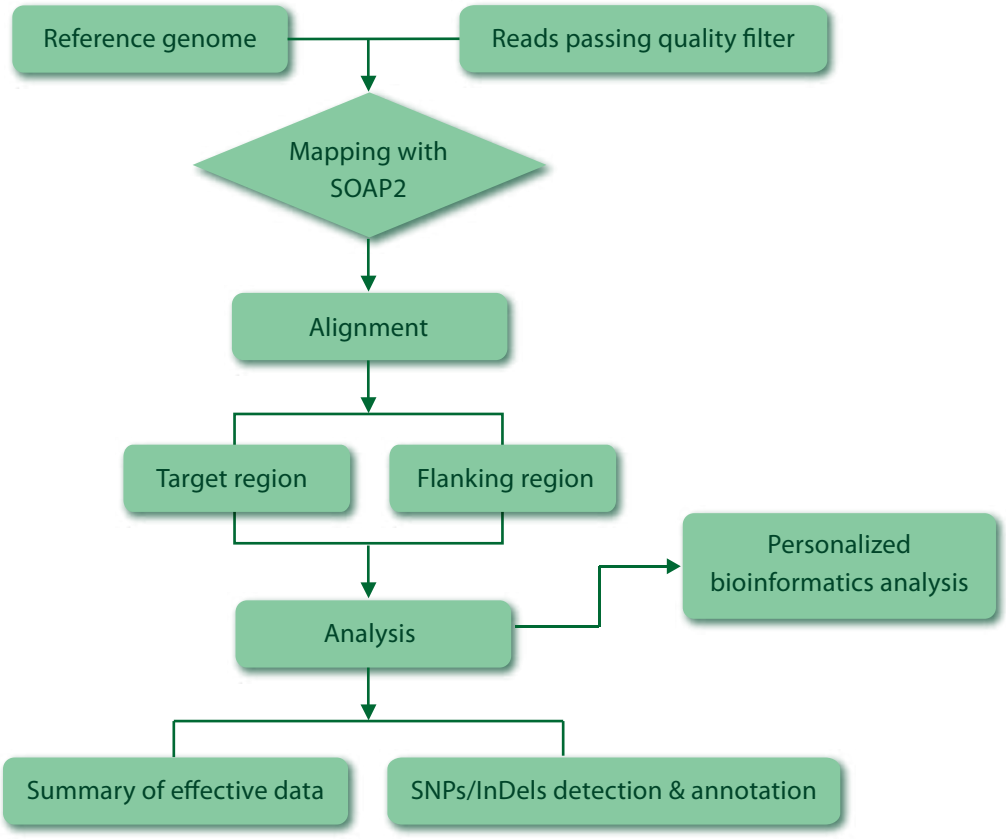

Figure 2. Bioinformatics analysis pipeline

Results

Pooling strategy

To maximize the efficiency of this chip, the sequencing results from the pooled strategy were compared with the results from the single YH strategy. Table 1 shows the depth, coverage, and numbers of SNPs from these two strategies, along with false positive (FP) and false negative (FN) calculated by database comparison.

Table 1. Comparison of YH data in single sample library and YH data from pooling library

YH sample	Depth	Coverage	SNP	Target sites	YH Genotyping sites	Check sites		
						TP	FP (FPR)	FN (FNR)
578X	578	98.41%	1,697	2515067	3,381	795	5 (0.19%)	5 (0.62%)
pooling _70X	76	97.98%	1,713	2515067	3,381	792	6 (0.23%)	7 (0.88%)

Compared to the result of YH genotyping data from the database, the coverage of single YH library and pooling library are approximately 98.41% and 97.98%, respectively. A total of 3,381 sites were selected for comparison to data in the Yanhuang database. The FP and FN of these sites are 0.19% and 0.62% from the single YH library. The FP and FN are 0.23% and 0.88% from YH data in the pooling library. These results show the pooling method is feasible for Drug Array captured target sequencing on Illumina HiSeq™ 2000 platform.

SNP comparison

YH data from pooling library and single YH library shared 97% of SNPs (Fig.3).

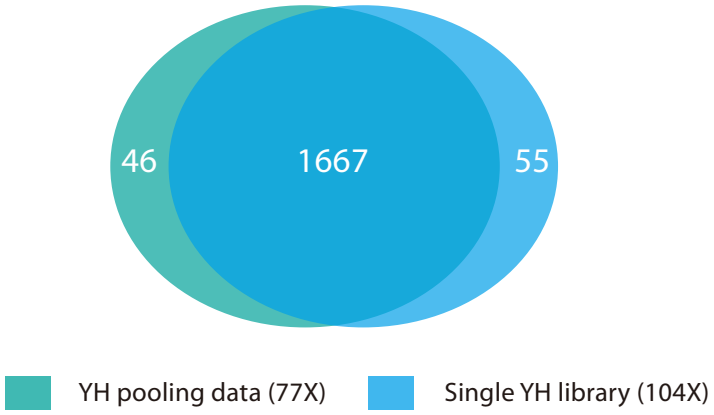

Figure 3. YH data from pooling library and single YH library

Conclusion

Through the comparison of YH data from single YH library and pooling library, pooling method is found to be a feasible way for target region sequencing with the Drug Array chip.

Key Features

- Contain 1,325 drug targets in one chip
- Analyze the relationship between disease and target genes
- Facilitate patient stratification
- Facilitate drug repositioning

Reference

[1] John P. Overington, *et al*. How many drug targets are there? ***Nature reviews***, 2006, (5):993-996.

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