Databases and ontologies

**SNPnexus: a web database for functional annotation of newly discovered and public domain single nucleotide polymorphisms**

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**ABSTRACT**

**Motivation:** Design a new computational tool allowing scientists to functionally annotate newly discovered and public domain single nucleotide polymorphisms in order to help in prioritizing targets in further disease studies and large-scale genotyping projects.

**Summary:** SNPnexus database provides functional annotation for both novel and public SNPs. Possible effects on the transcriptome and proteome levels are characterized and reported from five major annotation systems providing the most extensive information on alternative splicing. Additional information on HapMap genotype and allele frequency, overlaps with potential regulatory elements or structural variations as well as related genetic diseases can be also retrieved. The SNPnexus database has a user-friendly web interface, providing single or batch query options using SNP identifiers from dbSNP as well as genomic location on clones, contigs or chromosomes. Therefore, SNPnexus is the only database currently providing a complete set of functional annotations of SNPs in public databases and newly detected from sequencing projects. Hence, we describe SNPnexus, provide details of the query options, the annotation categories as well as biological examples of use.

**Availability:** The SNPnexus database is freely available at http://www.snp-nexus.org.

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**1 INTRODUCTION**

Single nucleotide polymorphisms (SNPs) are simple and very common genetic variations in a single base of the four-bases genome sequence. They represent a valuable resource for investigating the genetic basis of diseases and are widely used for fine-scale genetic mapping and genome-wide association studies. It is well established that certain SNPs may predispose to diseases such as diabetes and cancer, as well as affecting disease progression. Based on linkage analysis results and/or knowledge about the disease pathways, genes are selected for sequencing and screening for novel SNPs. Variations that might be functionally relevant, such as those that lead to amino acids changes, affect splicing sites, are found in known regulatory elements or in conserved non-coding sequences are priority targets in disease studies and large-scale genotyping projects.

Functional annotation data for publicly known SNPs are scattered across many different databases, redundant and far from complete. They include a limited set of information and no options to allow functional annotations of newly detected SNP. When dealing with novel SNPs, researchers are faced with exploring many different data sources, deciding which one to use and manually assessing the functional relevance of their variants before selecting the subset to use in future disease genotyping studies. As a result, the task of making a complete assessment of the potential functional consequences of both novel and known SNPs from sequencing or genome-wide association studies is difficult and time consuming. The lack of suitable user-friendly tools for assessing the full impact of SNPs is evident from numerous publications where the potential functional role of SNPs was not properly explored. This could compromise the design and results of any further experimental investigation.

Here, we present SNPnexus, a one-stop solution for novel and publicly known SNPs functional annotation. SNPnexus allows single or batch queries using dbSNP identifiers or SNP genomic coordinates on clones, contigs as well as chromosomes. From our experience, this is particularly needed to complete public SNP annotations. Also, this is very helpful for researchers discovering novel SNPs by using clones or contigs as a reference sequence in their analysis of sequencing data.

Because it is well known that each gene prediction program has its own limitations that often lead to different results, SNPnexus computes a wide range of possible effects for SNPs through the main gene annotation systems: NCBI RefSeq (Pruitt et al., 2007), UCSC Known Genes (Hsu et al., 2006), Ensembl (Hubbard et al., 2007), the Vertebrate Genome Annotation (VEGA) (Ashurst et al., 2005) and AceView (Thierry-Mieg and Thierry-Mieg, 2006). While most other tools and studies mainly focused on the effects of SNPs based on NCBI RefSeq and/or Ensembl genes, SNPnexus offers for the first time the possibility of assessing additional possible roles for SNPs through VEGA, UCSC and AceView annotations. The NCBI RefSeq is a high-quality, manually curated gene set. While the Ensembl gene prediction dataset is computationally derived at the genome level, VEGA's annotations are manually curated on more limited regions. The UCSC set of predictions is moderately conservative, based on data from RefSeq, GenBank (Benson et al., 2005) and UniProt (Bairoch et al., 2005). The AceView gene dataset is produced from public experimental cDNA sequences from the same species. These gene annotation sets have different prediction methods and therefore show different information on alternative splicing. By integrating all these annotated datasets,
SNPnexus gives the broadest view of the potential functional role of SNPs. The functional annotations through SNPnexus are detailed on the different isofoms and should be considered carefully in any SNP experimental functional assay. Furthermore, SNPnexus investigates any potential regulatory role by computing the overlaps with regulatory elements such as conserved transcription factor binding sites (TFBS) (Wingender et al., 2001), microRNA (miRNA) (Griffiths-Jones, 2004; Grimson et al., 2007; Lewis et al., 2003, 2005; Weber, 2005) and promoter predictions (Davuluri et al., 2001). SNPnexus summarizes any related information from genetic association studies of complex diseases and disorders available from the genetic association database (GAD) (Becker et al., 2004), overlaps with genomic structural variability (Conrad et al., 2006; Hinds et al., 2006; Iafrate et al., 2004; Locke et al., 2006; McCarroll et al., 2006; Redon et al., 2004; Sebat et al., 2005; Sharp et al., 2005; Tuzun et al., 2005), dbSNP (Sherry et al., 2001) as well as HapMap (Frazer et al., 2007) genotype and allele frequency.

2 METHODS
SNPnexus architecture has two layers: an access layer with a web server and a storage layer with a MySQL database server. We wrote a Perl annotation pipeline to connect the user data to the source database and perform all the calculations displayed in the web interface. Primary data sources are Ensembl and UCSC. We used the MySQL tables from the March 2006 GenBank freeze assembled by NCBI (hg18, Build 36, http://hgdownload.cse.ucsc.edu/goldenPath/hg18/database/) and EnsemblMart_48 (ftp://ftp.ensembl.org/pub/release-48/mysql/ensembl_mart_48). The Genetic Association Database team provided the link to download GAD data file. miRBase data were downloaded from the database FTP site (http://microrna.sanger.ac.uk/sequences/ftp.shtml) Structural variability data were derived from the Database of Genomic Variants (DGV) (http://projects.tcag.ca/variation/) via UCSC. SNPnexus will be updated on a regular monthly basis.

3 RESULTS
3.1 Queries
Queries can be made in both single and batch mode (10 000 SNPs). Users can annotate a novel SNP by providing its position on the genomic clone (clone, contig or chromosome), its alleles and strand. This is particularly useful when SNPs are detected by sequencing many DNA samples and aligning experimental results against a partial clone, contig or chromosome reference sequence. Users can also query SNPnexus for known SNPs by providing the rs# number. This could be used when dealing with reassessment of the functional role of HapMap and dbSNP variants, for example. SNPnexus query options and annotation categories are presented in Figure 1.

3.2 Annotation categories and examples
3.2.1 Gene SNP consequences To the best of our knowledge, SNPnexus is the only tool that provides a comprehensive overview of potential functional consequences of SNPs on alternatively spliced genes by exploring five different transcriptome and proteome models: NCBI RefSeq (Pruitt et al., 2007), UCSC (Hsu et al., 2006), Ensembl (Hubbard et al., 2007), VEGA (Ashurst et al., 2005) and AceView (Thierry-Mieg and Thierry-Mieg, 2006). While the gene annotation from NCBI RefSeq and Ensembl are widely used gene reference systems, they do not properly reflect transcript variation due to alternative splicing. The number of UCSC transcripts is 56 722, which is almost equal to the number of Ensembl transcripts (56 155) and double of the number for RefSeq (25 078). VEGA has over three times more transcript variants than RefSeq (88 828). Gene model in AceView provides more extensive analysis of alternative splicing. Over the entire genome the number of AceView transcripts (258 618) exceeds Ensembl and UCSC by a factor of four, VEGA by a factor of three and RefSeq by a factor of 10. Potential effects of SNPs fall into seven categories: intronic, 5’UTR, 3’UTR, 5-upstream, 3-downstream, splicing site or coding (synonymous or non-synonymous). For intronic SNPs, the distance to the splicing site is reported. For coding SNPs, the coordinates of the position within the cDNA, coding sequence (CDS), amino acid as well as the peptide change produced (if any) are reported. For 5-upstream and 3-downstream, a distance of 2 kb from the UTR start or end is considered appropriate. As a first example, we explored the SNPs of DNA repair genes that were studied in the context of overall survival of pancreatic cancer patients after treatment (Li et al., 2007a). A strong effect of the polymerase β (POLB) gene variants on overall survival was reported. Also, a weak but significant effect on overall survival was demonstrated for 8-oxo-guanine DNA glycosylase (hOGG1), apurinic/apyrimidinic endonuclease 1 (APEX1) and X-ray repair cross-complementing protein 1 (XRCC1) polymorphisms. We considered all the variants in these genes studied in the article (Table 1). The authors reported that POLB A165G and T213C variants were intronic with the dbSNP reference rs2272615 and rs2953993, respectively. Also, the first variant of hOGG1 G2657A was intronic (rs293794) and the second variant C315G was coding non-synonymous (S326C) or 3’UTR (rs1052133). The APEX1 variant D148E (rs3136820) as well as XRCC1 variants R194W (rs1799782) and Q399R (rs25487) were coding non-synonymous. Using SNPnexus, we were able to assess in details the functional consequences of these variants on each isofrom from RefSeq, Ensembl, Vega, AceView and UCSC. First, we noted that hOGG1 variants overlap with isoforms of the neighboring gene calcium/calmodulin-dependent protein kinase 1 (CAMK1). Similarly, APEX1 variant rs3136820 (ID used in the original paper, currently merged to dbSNP rs1130409) could have a 5-upstream effect on the neighboring gene O-sialoglycoprotein endopeptidase (OSGEP) and 3-downstream effect on transmembrane protein 55B (TMEM55B). We also found many additional potential regulatory roles and coding non-synonymous changes leading to additional
Table 1. SNP functional consequences

Panel A: as reported in previous studies

| dbSNP   | Chrom | Gene   | Functional consequences |
|---------|-------|--------|-------------------------|
| rs293794 | 3     | hOGG1  | I                       |
| rs1052133 | 3     | hOGG1  | 3’UTR, NS (S326C)       |
| rs3136820 | 14    | APEX1  | NS (D148E)              |
| rs2272615 | 8     | POLB   | I                       |
| rs2953993 | 8     | POLB   | I                       |
| rs1799782 | 19    | XRCC1  | NS (R194W)              |
| rs25487  | 19    | XRCC1  | NS (Q399R)              |
| rs2248690 | 3     | AHSN   | Promoter                |
| rs4918   | 3     | AHSN   | Thr/Ser                 |
| rs1071592 | 3     | AHSN   | Thr/Thr                 |

Panel B: computed using SNPnexus

| dbSNP   | Gene   | Source | Transcripts | Functional consequences [peptide shift (if any), number of transcripts] |
|---------|--------|--------|-------------|---------------------------------------------------------------------|
| rs293794 | hOGG1  | RefSeq | 5           | I (1)                                                                |
|         |        |        | Ensembl     | 6                                                                    |
|         |        |        | VEGA        | 6                                                                    |
|         |        |        | UCSC        | 5                                                                    |
|         |        |        | AceView     | 8                                                                    |
|         | CAMK1  | RefSeq | 1           | I (1)                                                                |
|         |        |        | Ensembl     | 2                                                                    |
|         |         |        | VEGA        | 2                                                                    |
|         |         |        | UCSC        | 3                                                                    |
|         |         |        | AceView     | 6                                                                    |
| rs1052133 | hOGG1 | RefSeq | 1           | I (1)                                                                |
|         |        |        | Ensembl     | 11                                                                   |
|         |         |        | VEGA        | 9                                                                    |
|         |         |        | UCSC        | 11                                                                   |
|         |         |        | AceView     | 19                                                                   |
|         | CAMK1  | RefSeq | 1           | 3down                                                                |
|         |        |        | Ensembl     | 2                                                                    |
|         |         |        | VEGA        | 2                                                                    |
|         |         |        | UCSC        | 3                                                                    |
| rs1130409 | APEX1 | RefSeq | 3           | NS (D148E, 3)                                                       |
|         |        |        | Ensembl     | 2                                                                    |
|         |         |        | VEGA        | 3                                                                    |
|         |         |        | UCSC        | 4                                                                    |
|         |         |        | AceView     | 22                                                                   |
|         | NP     | RefSeq | –           | I (1)                                                                |
|         |        |        | Ensembl     | –                                                                    |
|         |         |        | VEGA        | –                                                                    |
|         |         |        | UCSC        | –                                                                    |
|         |         |        | AceView     | –                                                                    |
| rs25987  | OSGEP  | RefSeq | 1           | I (1)                                                                |
|         |        |        | Ensembl     | 1                                                                    |
|         |         |        | VEGA        | 1                                                                    |
|         |         |        | UCSC        | 1                                                                    |
|         |         |        | AceView     | 5                                                                    |
| rs2272615 | POLB  | RefSeq | 1           | I (1)                                                                |
|         |        |        | Ensembl     | 1                                                                    |

(continued)
amino acid changes (Table 1). We noted that these effects were also missed in other papers where some of the variants were investigated in additional cancers (Huang et al., 2007; Sangrajrang et al., 2008). SNPnexus enabled discovery of new potential functions that should be considered in any further analysis. As a second example, we considered the 2-Heremans-Schmid glycoprotein (AHSG), a candidate for type 2 diabetes (T2D) susceptibility. Using direct sequencing of the AHSG promoter region and exons, a recent study identified nine common SNPs with a minor allele frequency (MAF) >5%, assessed their consequences using NCBI RefSeq AHSG mRNA sequence (NM_001622) and carried out a detailed genetic association study of their contribution to the genetic susceptibility of T2D in French Caucasians (Siddiq et al., 2005). Their results showed that the major allele of a synonymous coding SNP (rs1071592) presented significant evidence of association with T2D. Also, one promoter variant and one coding non-synonymous variant (rs2248690 and rs4918) in strong linkage disequilibrium (LD) with rs1071592 showed evidence-approaching significance. We reanalyzed the consequences of these three SNPs on all AHSG transcripts using SNPnexus. We confirmed the synonymous coding consequence of rs1071592. However, we found that this SNP can have additional 3-downstream and most importantly synonymous non-coding (H6P) consequences (Table 1). For rs4918, we confirmed the non-synonymous coding S256T and found additional potential effects. We confirmed the promoter location for the SNP rs2248690 in all transcripts annotations (Table 1). Again, these novel potential functional roles should be included in any experimental assay investigating the role of these variants in T2D.

3.2.2 HapMap population data The HapMap Project provides a resource of genotypic data of ~4 million common SNPs in lymphoblastoid cell lines derived from four human populations: African YRI (from Yoruba in Ibadan, Nigeria), Japanese JPT (from Tokyo, Japan), Han Chinese CHB (from Beijing, China) and European CEU (from Utah, USA with ancestry from northern and western Europe) (Frazer et al., 2007). The HapMap genotypic data have proven to be a key resource for researchers investigating the genetic contribution to human diseases, variation in gene expression and drug response (Zhang et al., 2008). The HapMap data could
be used to estimate MAF of SNPs in the different populations. This is essential since common SNPs having a MAF value $\geq 5\%$ or 1% are mainly targeted in genetic studies. This hypothesis has been challenged by studies reporting that rare variants may also influence common diseases (Cohen et al., 2004; Romeo et al., 2007). Rare SNPs might also be useful when the disease-causing variant is also rare. An estimation of the MAF in the different populations could also help in assessing the association between SNPs and a given disease. SNPnexus provides both genotype and allele information, count and frequency. If $f(11)$, $f(12)$ and $f(22)$ are the HapMap frequencies of the three genotypes at a given locus with two alleles (1 and 2), then the frequency $p$ of allele 1 and the frequency $q$ of allele 2 are: $p = f(11) + 0.5 \times f(12)$ and $q = f(22) + 0.5 \times f(12)$. MAF is simply the smaller of these two frequencies. As an example of use, we considered the association between the +1858C>T SNP (rs2476601) in PTPN22 and type 1 diabetes (T1D) that has been reported in separate studies among different populations (Chelala et al., 2007; Smyth et al., 2004). However, the +1858T allele was not found in a large Asian cohort (Kawasaki et al., 2006), which raises the possibility that rs2476601 is not associated with T1D in Asian populations. It is also possible that other potentially functional variants in PTPN22 may be responsible for the susceptibility to T1D in these populations or the PTPN22 locus contains another variant that disrupts gene expression. SNPnexus prioritized BTG2 miRSNP rs1804734 showing that it overlaps with targetscan BTG2:miR-21. Added to the fact that miR-21 was reported to be upregulated in breast cancer (Iorio et al., 2005), the role of rs1804734 in breast cancer is worthy of investigation to see whether it could interfere with BTG2:miR-21 processing, expression and/or binding to target BTG2 mRNA.

3.2.4 Genetic association database GAD is an archive of published scientific papers on human genetic association studies of complex diseases and disorders (Becker et al., 2004). When investigating the role of variants, the user can mine GAD and extract any related information related to the gene of interest.

3.2.5 Structural variability Human DNA-level variation ranges from bi-allelic SNPs to large-scale structural variation [such as deletions, duplications, insertions, inversions and large-scale copy-number variants (CNVs)] also called copy-number polymorphisms (CNPs)]. Structural variants can have a direct effect on gene dosage or an indirect effect on expression of a gene by changing its position on the genome (Feuk et al., 2006). They can predispose to additional damaging structural changes or function as susceptibility alleles in complex genetic diseases (Feuk et al., 2006). A recent study showed the importance of CNVs in complex phenotypes, and the need to assess it independently from SNPs (Stranger et al., 2007). Also, the analysis of SNPs within genes with CNV could be technically challenging. Furthermore, it is important to distinguish abnormal genetic lesions from normal CNP since some of the genetic differences in tumor genomes when analyzed in comparison to an unrelated normal genome could be due to germline CNPs. SNPnexus allows integration of both types of variation and assessment of the hypothesis cited above. This could be useful for genes and SNPs located within a CNV. In this case, both gene copy number and the genotyping of relevant SNPs should be investigated in order to understand the phenotypic impact of genome variation on the disease of interest. SNPnexus assesses overlaps with putative CNPs and sites of intermediate-sized structural variation (ISV) determined by various methods. This covers deletions from genotype analysis using the HapMap Phase I data, release 16a (McCarroll et al., 2006), HapMap Phase I data, release 16c.1, CEU and YRI samples (Conrad et al., 2006) and from haploid hybridization analysis in 24 unrelated individuals from the Polymorphism Discovery Resource, selected for SNP LD study (Hinds et al., 2006). This also include CNP from BAC microarray analysis in a first population of 55 individuals (Iafrate et al., 2004), a second population of 47 individuals (Sharp et al., 2005) as well as in the HapMap Phase II data (Redon et al., 2006). Further CNP regions are identified using array CGH in the HapMap populations (269 individuals) (Locke et al., 2006) and using representational oligonucleotide microarray analysis (ROMA) in a population of 20 normal individuals (Sebat et al., 2004). ISV sites are detected by mapping paired-end sequences from a human fosmid DNA library (Tuzun et al., 2005). As an example, we reused AHSG SNPs rs1071592, rs2248690 and rs4918 (Table 1). SNPnexus found an overlap with a CNV region thus suggesting that the genotypes of rs1071592 and rs4918 as well as the overlapping CNV should both be investigated in order to understand the phenotypic impact of these genome variations on T2D in French Caucasians. Similarly, rs2476601 in PTPN22 overlaps with a CNV that should be also studied in T1D.
4 DISCUSSION AND CONCLUSION

Both focused candidate-gene and whole-genome studies require the selection of an optimal number of tagSNPs. This is an important, challenging task that will affect the study outcome and cost, especially for complex diseases where the number of candidate genes is expected to be large. SNPnexus could help in the selection of tagSNPs with potential functional effect, which could be used to complement the selection based on the haplotype information and therefore increase the sensitivity and efficiency of large-scale genotyping projects (Jorgenson and Witte, 2006; Wiltshire et al., 2006).

SNPnexus is the most comprehensive resource currently available for assessing the functional consequences of novel and public domain SNPs on the major transcriptome, proteome, regulatory and structural variation models. We provide examples on how it allows researchers, through a user-friendly web interface, to work on novel and publicly available SNPs to extract important annotation and genotyping information. SNPnexus data should be considered in the design of experimental functional assays so as to prioritize the list of SNPs or CNVs to be investigated in further association studies.

To the best of our knowledge, there are no tools or databases that provide the same information as SNPnexus. Therefore, we can only review other tools to provide an evaluation of our system. SNPnexus has a gene/protein annotation category allowing the users to view and navigate through large sets of high-dimensional data from five major annotation systems (Ensembl, RefSeq, VEGA, AceView, UCSC). Out of these, only Ensembl is mainly used by other tools, such as PupaSNP (Conde et al., 2006) and SNAP (Li et al., 2007b). SNPnexus offers more query options than PolyPhen (Ramensky et al., 2002) and SNAP. While these tools in their current versions allow queries for one SNP at a time, SNPnexus allows single and batch queries. Most importantly, SNPnexus is the only tool providing annotations for novel and publicly known SNPs, while all other tools focus on already known variants from dbSNP. Thus, SNPnexus is complementary to existing tools, such as Polyphen, SNAP and PupaSNP by allowing researchers to connect novel annotated SNPs to these tools. One could get further functional annotation of non-synonymous SNPs using PolyPhen, SNAP that disrupt exon splicing enhancers using PupaSNPs or redesign PCR primers to re-sequence individual variants using SNAP.

The recent technological advances in next-generation sequencing enable comprehensive screening of genome variation. One of the main promises and challenges lies with the analysis of these variations and the selection of those who contribute to the phenotype. Although designed initially to annotate novel SNPs from candidate gene sequencing studies, SNPnexus query option for novel SNPs could also be used to assess the potential significance of candidate variants detected by next-generation sequencing, point to the gene/protein isoform that might be phenotypically important and guide future experimentation. SNPnexus is freely available and will be updated regularly. We welcome feedback from the user community on new annotation systems that could be added to SNPnexus.

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