Ontology modeling of genetic susceptibility to adverse events following vaccination

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ABSTRACT

Administration of different vaccines triggers a variety of adverse events in some groups of people but not in others. This phenomenon may be due to the variation of genetic factors that affects the susceptibility to vaccine adverse events. In this study, we introduce the development of an Ontology of Genetic Susceptibility Factor (OGSF) that is aligned with the Basic Formal Ontology (BFO). OGSF represents the genetic susceptibility, genetic susceptibility factors and vaccine adverse events using formal ontologies. Two case studies were used to test and validate the model. One case study represents a human gene allele DBR1*15:01 as a genetic susceptibility factor to vaccine Pandemrix related multiple sclerosis. Genetic polymorphisms associated with smallpox vaccine adverse event was analysed as the second use case. A SPARQL query, visualization of extracted data as a network and the social network analysis of the network, further provide insights on the evaluation and application of the ontology.

1 INTRODUCTION

Vaccines have enabled tremendous decreases in infectious diseases and remain among the most effective of our public health initiatives. At the same time, as an ever increasing number of vaccines is administered globally, many vaccine-associated adverse events and reactions have been identified and threaten the public health successes attributable to vaccines [1]. As defined in the Vaccine Adverse Event Reporting System (VAERS) and Ontology for Adverse Event (OAE), a vaccine adverse event is an adverse event following vaccination and does not assume a causal association [2]. Vaccine-related adverse events often occur in some populations but not in others, which has led to the hypothesis of genetic susceptibility to vaccine adverse events [3, 4].

Genetic susceptibility, also called genetic predisposition, is an increased likelihood or chance of developing a particular disease due to the presence of one or more gene mutations and/or a family history that indicates an increased risk of the disease. The allele that confers the increased risk/susceptibility may be inherited but the disease itself will not. The single locus genotype is usually insufficient to cause a disease. For the disease to appear, impaired expressions of alleles at other gene loci and/or environmental factors are often needed [5].

Genetic susceptibility factors are the genetic entities, most likely genetic variations, which influence the susceptibility. The genetic susceptibility factors contributing susceptibility to a disease may not be obvious mutations. It is more likely a combination of subtle changes on several genes, which may be quite common in the healthy population. Moreover, the main determinants of susceptibility may be different in different populations [6]. With current technological advances and new biostatistics approaches to understanding a large number of databases of information, we can now better understand how genetic variations become critical to vaccine-induced positive host responses and adverse reactions.

An Ontology of Genetic Susceptibility Factor (OGSF) was previously developed for our formalization of the definitions of 'genetic susceptibility' and 'genetic susceptibility factor' using the TCF7L2 gene and its susceptibility to Type 2 Diabetes as an example [7]. The entities important for the representation of genetic susceptibility to diseases include: genetic polymorphism, the population and geographical location, the disease entities, and related statistical entities (e.g., odds ratio and p-value). Here we consider that a vaccine adverse event is a pathological bodily process, and we extend the former work to model the genetic susceptibility to adverse event.

Based on previous studies, we have now developed a new version of genetic susceptibility-focused ontology, the Ontology of Genetic Susceptibility Factor (OGSF) by using Basic Formal Ontology (BFO) 2.0 as its upper ontology. OGSF is used to study the susceptibility factors associated with vaccine adverse events.

2 METHODS

2.1 Ontology editing

The format of OGSF ontology is W3C standard Web Ontology Language (OWL2) (http://www.w3.org/TR/owl-guide/). For this study, many new terms and logical definition were added into original OGSF [7] using the Protégé 4.3.0 build 304 OWL ontology editor (http://protege.stanford.edu/).

2.2 Ontology term reuse and new term generation

OGSF imports the whole set of the Basic Formal Ontology (BFO) [8]. To support ontology interoperability, many terms from reliable ontologies are reused. For this purpose, OntoFox [9] was applied for extracting individual terms from external ontologies. For those genetic susceptibility-specific terms, we generated new OGSF IDs with the prefix of "OGSF_" followed by seven-digit auto-incremental digital numbers.

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2.3 Evaluation of OGSF

Use case studies were designed based on literature survey. SPARQL was performed using the SPARQLquery plug-in embedded with Protégé 4.3.0 build 304. Graphed data was extracted using the OntoGraf plug-in [10] Gephi 0.8.2 beta (http://gephi.org)[11] was used to conduct social network data analysis and visualization based on the extracted graph data from instances of OGSF.

2.4 Availability and access

The website for OGSF project is available at http://code.google.com/p/ogsf/. The source of the ontology is also available in the NCBO Bioportal: http://bioportal.bioontology.org/ontologies/3214.

3 RESULTS

3.1 OGSF is aligned with BFO

The development of OGSF follows the OBO Foundry principles, including openness, collaboration, and use of a common shared syntax [12]. The early version of OGSF was not well aligned with BFO. To align OGSF with BFO 2.0 Graz version, we started with key terms and render them using BFO's terms as parent terms.

There are two core terms in OGSF: 'genetic susceptibility' and 'genetic susceptibility factor'. The OGSF term 'genetic susceptibility' (OGSF_0000000) is a subclass of 'disposition' (BFO_0000016). The alternative term for 'genetic susceptibility' is 'genetic predisposition'. Note that in BFO 2.0 the term 'predisposition' is not included, so we put genetic susceptibility directly as the child term of 'disposition'. The first level child terms of 'genetic susceptibility' include: 'genetic predisposition to disease of type X' (OGMS_0000033), 'genetic susceptibility to pathological bodily process' (OGSF_0000001), and 'genetic susceptibility to biological process' (OGSF_0000002). The term that reveals our use case is 'genetic susceptibility to adverse event following vaccination' (OGSF_0000010) and it is the third level child term of 'genetic susceptibility'.

Another core OGSF term 'genetic susceptibility factor' (OGSF_0000004) is a subclass of 'material entity' (BFO_0000040). An allele, gene, genotype, and haplotype can be genetic susceptibility factors. The relation: 'material basis of at some time' (BFO_0000127), is used to link genetic susceptibility factor and genetic susceptibility.

3.2 Modeling genetic susceptibility to adverse event following vaccination

The genetic susceptibility to vaccine adverse events is used as a use case for OGSF redesign.

Genetic susceptibility reflects the relation between a genetic factor (e.g. allele) and risk of condition, disease or responses to vaccines or drugs. Different levels of genetic association studies, such as family studies, genetic linkage studies, and population-based studies are conducted in order to determine whether or not a genetic variation mediates the diseases outcome such as a vaccine adverse event.

Fig. 1 shows how we use OGSF terms and BFO relations to represent genetic susceptibility to vaccine adverse event.

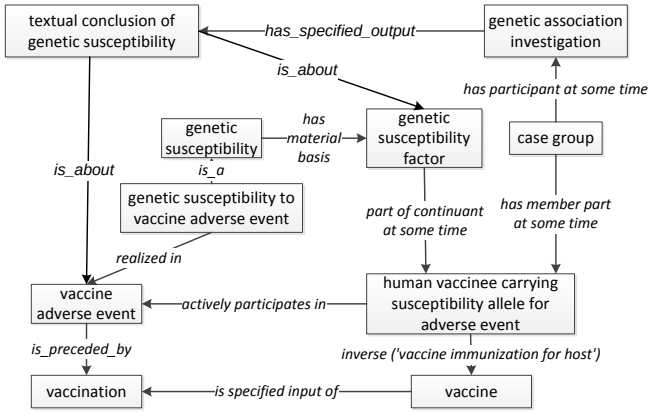

Fig. 1. Design pattern for representing genetic susceptibility to a vaccine adverse event (VAE).

The set of core terms representing the whole topic are ‘genetic susceptibility factor’, ‘genetic susceptibility’, ‘adverse event’ and ‘textual conclusion of genetic susceptibility’. In Fig.1, the 'genetic susceptibility factor' is the material basis of 'genetic susceptibility', which has a subclass ‘genetic susceptibility to vaccine adverse event’. The genetic susceptibility is realized in the process of ‘vaccine adverse event’. The ‘genetic susceptibility factor’ is the part of a 'human vaccinee carrying susceptibility allele for adverse event’, which ‘actively participates in’ the ‘vaccine adverse event’. On the other hand, a ‘genetic association investigation’ has participant ‘case group’ with the ‘human vaccine carrying susceptibility allele for adverse event’ as its member. The ‘genetic association investigation’ has ‘textual conclusion of genetic susceptibility’ as its specified output, and the conclusion ‘is about’ both ‘genetic susceptibility factor’ and ‘vaccine adverse event’. An inverse of VO relation: ‘vaccine immunization for host’ interlinks the human vaccinee and ‘vaccine’. ‘Vaccine’ is a specified input of the process of ‘vaccination’. Relation ‘is preceded by’ linking ‘vaccination’ and vaccine adverse event’ indicates that ‘vaccination’ happens before the ‘vaccine adverse event’.

3.3 Modeling genetic association study

Studies have provided many supporting evidences for asserting susceptibility factors to adverse event outcomes. Based on the OBI framework, we specially modeled the genetic association study designs according to our use case. The textual definition of OGSF term 'genetic association investigation' was given as: 'an investigation that aims to test whether single-locus alleles or genotype frequencies (or more generally, multilocus haplotype frequencies) differ

between two groups of individuals (usually diseased subjects and healthy controls)'. Different types of those studies exist, such as 'case-control study', 'GWAS study' (Genome-Wide Association Study) and 'case report'. 'GWAS study' is a type of 'case-control study' and has two subclasses 'initial GWAS study' and 'replicate GWAS study'. The statistical method conducted in a study is modeled as 'data analysis' that is a part of an investigation as asserted in OBI. 'Case group' and 'control group' are subclasses of 'human study subject group'. The 'human study subject group' is the participant of the 'genetic association investigation'.

A statistical analysis of the genetic susceptibility is based on the choice of a statistical study design, which depends on several factors related to the phenotype: the population, the accurate measurement of environmental factors, and known genetic background among other factors. Due to the presence of many different cofounders, it is often difficult to detect and verify genetic susceptibility factors associated with specific adverse event outcomes. Observed statistically significant genetic susceptibilities may be contradictory among different studies [13]. More and consistent observations in different populations may give stronger evidence to support the true causal relation between a 'genetic susceptibility factor' and an observed outcome. Well-designed experiments may be applied to verify the association. In order to store the result from genetic association studies, we use 'textual conclusion of genetic susceptibility' to be asserted as 'specified output of' a 'genetic association investigation'. The 'textual conclusion of genetic susceptibility' is a 'textual entity'. The 'is about' relation was used to link the conclusion with 1) 'genetic susceptibility factor' and 2) ‘vaccine adverse event’ process.

Three terms: 'positive conclusion of genetic susceptibility', 'negative conclusion of genetic susceptibility' and 'neutral conclusion of genetic susceptibility' are asserted as subclasses of 'textual conclusion of genetic susceptibility'. A 'positive conclusion of genetic susceptibility' means that a positive conclusion is drawn based on a significant statistical association of a genetic factor and a vaccine adverse event as studied in this paper. A 'negative conclusion of genetic susceptibility' a denied association between a genetic factor and an adverse event. Sometimes, depending on the data, an investigator may draw a conclusion of a non-significant association but without a clear deny of a possible association. This situation is captured using ‘neutral conclusion of genetic susceptibility’.

3.4 Case study

Case studies are used for two purposes: 1) to validate the modeling, 2) to test possible applications of the ontology.

3.4.1 Case study 1: HLA allele DBR1*15:01 is genetic susceptibility to Pandemrix related multiple sclerosis

Vrethem *et al.* reported the occurrence of severe narcolepsy with cataplexy and multiple sclerosis (MS) in a previously healthy young male in association with Pandemrix vaccination [14]. The investigators found that that those patients carrying HLA allele DBR1*15:01 were associated with MS and those having HLA allele DQB1*06:02 were associated with narcolepsy. It was also concluded that the genetic susceptibility in this patient is a clue that an immune-mediated mechanism and a common etiology for both diseases in this patient.

The DBR1*15:01 as a genetic susceptibility factor responsible for Pandemrix-induced MS was modeled in the class level using OGSF, and the particular study was modeled in instance level using OGSF (Fig 2).

At the class level, 'DBR1*15:01' is an 'allele of HLA gene', which is also the material basis of (BFO 2: 'material basis of at some time') 'genetic susceptibility to vaccine adverse event'. The instance of ‘DBR1*15:01’ is a part of the MS patient instance. In class level, 'multiple sclerosis AE patient' 'actively participates in' the 'multiple sclerosis AE' process. Multiple Sclerosis adverse event is preceded by the 'Pandemrix vaccination'. 'Pandemrix' is a participant of 'Pandemrix vaccination' and it is related to the MS patient using a short relation from Vaccine Ontology (VO): 'vaccine immunization for host', which relates a vaccine with a vaccinee.

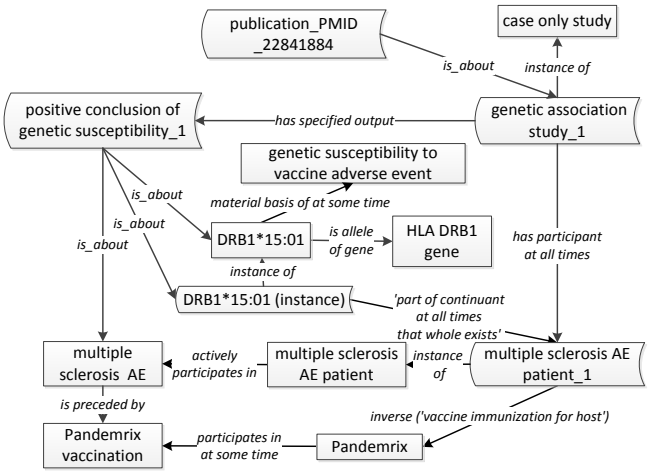

Fig. 2. OGSF modeling of vaccine-associated multiple sclerosis

Since it is a case report, this study gives one specific positive supporting evidence to the genetic susceptibility of DBR1*15:01, which is asserted at the instance level. We use 'genetic association study_1' to represent the study, which gives a specific output 'positive conclusion of genetic susceptibility_1'. This specific conclusion is about the entity 'DBR1*15:01' and the 'multiple sclerosis AE'.

3.4.2 Case study 2: genetic polymorphisms associated with adverse events after smallpox vaccination

Reif e*t al.* reported that genetic polymorphisms in an enzyme methylenetetrahydrofolate reductase (MTHFR) and an immunological transcription factor (IRF1) were associated with AEs after smallpox vaccination [15]. In this study, two independent clinical trials were conducted as initial and replicating genetic association studies separately. The Odds Ratio was used to measure the association between genotypes and systematic adverse event. Only strong association supported by a statistically significant Odds Ratio in both studies was considered and asserted as a true positive genetic association.

In this case, the important information to be stored is the susceptibility allele of the SNPs and the statistical power in two studies. Those information was curated and summarized in Table 1.

Table 1. Statistical summary of genetic susceptibility factors with systematic adverse event following smallpox vaccination

GSF[&]	Allele	Gene	Odds Ratio	P-value	Study 1 or 2
rs1801133 SNP	T	MTHFR	2.3 (1.1–5.2)	0.04	1
rs1801133 SNP	T	MTHFR	4.1 (1.4–11.4)	0.01	2
rs9282763 SNP	G	IRF1	3.2 (1.1–9.8)	0.03	1
rs9282763 SNP	G	IRF1	3.0 (1.1–8.3)	0.03	2
rs839 SNP	A	IRF1	3.2 (1.1–9.8)	0.03	1
rs839 SNP	A	IRF1	3.0 (1.1–8.3)	0.03	2
Haplotype 1[*]	G,A	IRF1	3.2 (1.0–10.2)	0.03	1
Haplotype 1[*]	G,A	IRF1	3.0 (1.0–9.0)	0.03	2
Haplotype 2[#]	T,C,A	IL4	2.4 (1.0–5.7)	0.05	1
Haplotype 2[#]	T,C,A	IL4	3.8 (1.0–14.4)	0.06	2

Notes:
& GSF stands for Genetic Susceptibility Factor
* Haplotype 1 contains G allele of rs9282763, A allele of rs839 in IRF1 gene.
# Haplotype 2 contains T allele of rs2070874,C allele of rs2243268, A allele of rs2243290 in IL4 gene.

The class level assertion is similar to case study 1. For example, the constrains representing one of the genetic susceptibility factors, A allele of rs839, are as follows:

1. *'material basis of at some time' some 'genetic susceptibility to adverse event following vaccination'*
   This axiom denotes that the A allele of rs839 is the material basis of the genetic susceptibility to AE induced by vaccination

2. *'part of continuant at all times that whole exists' some ('human vaccinee experiencing systemic adverse event' and inverse('vaccine immunization for host') some 'Smallpox virus vaccine')*
   This axiom denotes that the 'A allele of rs839' is part of some human who is experiencing systemic adverse event and had vaccinated by Smallpox vaccine

3. *isContainedIn some 'IRF1 gene'*
   This axiom denotes that the 'A allele of rs839' is contained in IRF1 gene

4. *'alternative allele of SNP'*
   This axiom denotes that the 'A allele of rs839' is an alternative allele

5. *'susceptibility allele' (inferred)*
   This axiom denotes that the 'A allele of rs839' is a susceptibility allele, so it is a genetic susceptibility factor.

The instance level representation representing two independent studies provide the statistical supporting evidence to the genetic susceptibility (Fig. 3).

Fig 3 illustrated that two 'positive conclusions of genetic susceptibility' from clinical trail 1 and trail 2 support the 'T allele of rs1801133 SNP' as the 'material basis of at some time' the 'genetic susceptibility of adverse event following vaccination'. The datatype properties 'hasOddsRatio' and 'hasPvalue' are properties of the 'positive conclusion of the genetic susceptibility'. Using these datatype properties, the real data denotes the statistical power was represented in the ontology.

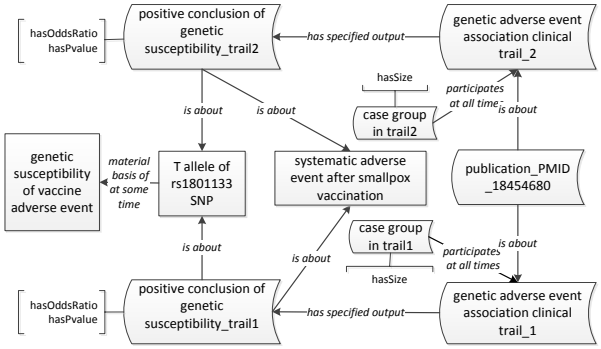

Fig. 3. Modeling Case Study 2 using OGSF

3.4.3 SPARQL query

A SPARQL script was developed to query against inferred OGSF ontology. The query led to the retrieval of the genetic susceptibility factors, as shown in Table 1. (Sparql query script shown in Supplemental material if allowed).

3.4.4 Visualization and social network analysis

In order to give a better view of the terms and links between terms, data from case study 2 was extracted using OntoGraf and visualized using Gephi as following (Fig. 4 and 5).

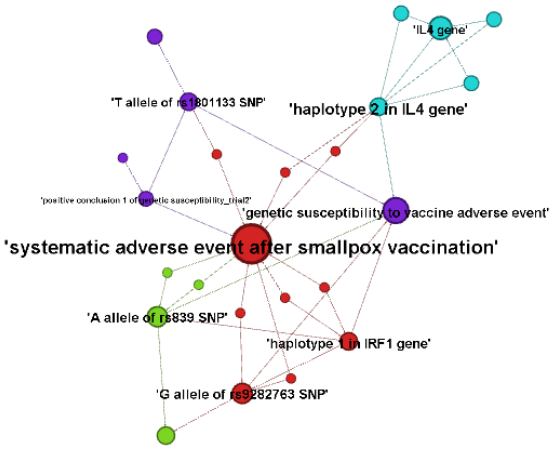

Fig. 4. All related nodes within case study 2.

Fig. 4. shows how the data and terms interlinked with each other in the network of case study2. The most

connected node is ‘systematic adverse event after smallpox vaccine’, since there are 10 conclusions related to it as shown in table1. All the genes, relevant SNP alleles and haplotypes are interlinked with each other, and can be captured as a community within the network, which indicated by colors of the node.

Running Gephi’s ‘filter’ function, two different views of the network of case study 2 were yield as shown in Fig 5.

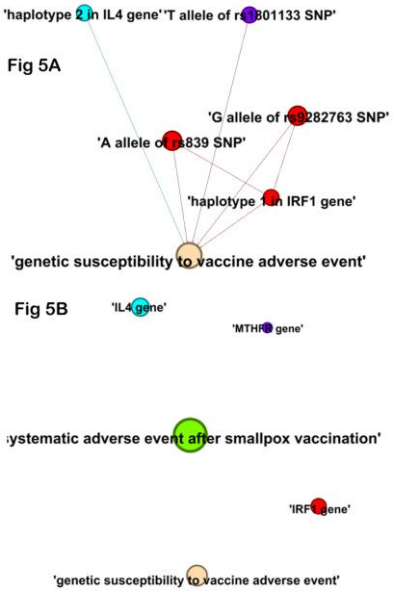

Fig. 5. Two views of the genetic susceptibility network in case study2. (A). EgoNetwork filter view of the network, which shows entities that are directly linked to 'genetic susceptibility to vaccine adverse event'. **(B)** Closeness centrality filtered view of the network. All the dots in the figure have closeness centrality value equal to 0.

Combining Fig. 5A and 5B, it indicates that: 1) in OGSF, the genetic susceptibility is directly related with variants, such as SNPs and haplotypes. 2) Gene is indirectly linked to genetic susceptibility via variants. The in-directed connection can be captured by centrality network analysis in the given data set. In our specific case study 2, the closeness centrality calculations of genetic susceptibility, adverse event and genes are the lowest.

4 DISCUSSION

4.1 Representing genetic susceptibility requires the notion of instance level evidence

The purpose of representing the knowledge of genetic susceptibility here is to extend existing beliefs by adding new facts. For example, if in one study A1, the genetic factor SNP B is statistically significant related to an adverse event C, then the SNP B as a genetic susceptibility factor will be represented using the OGSF framework. This knowledge will become an existing belief, when another study A2 reached the same conclusion, this fact will be added into the OGSF knowledgebase and hence provide stronger supporting evidence to the genetic causal association. Another example is that suppose gene G is related with both SNP B and SNP E, when another study A3 gave the conclusion of SNP E statistically significant related with the same adverse event C. To add this fact into OGSF would strengthen the belief that gene G is related to the genetic causal association.

The notion of genetic susceptibility can be expressed using OWL classes, whereas each study is modeled in instance level as data item. To simplify the connections, the relation 'is_about' was used to bridge the individual level 'textual' conclusions from an individual study to a 'genetic susceptibility factor' (class level) and specific vaccine adverse event (class level). The efficiency and applicable aspects of these relations need to be tested using more complicated datasets and SPARQL query.

4.2 The granularity of genetic susceptibility factor is at allele level

Nowadays, thousands of Single Nucleotide polymorphisms (SNPs) can be tested efficiently in large population-based studies. Researchers are using various entities to describe genetic susceptibility bearers, such as genotype, SNP, LD block, haplotype and so on. Except for LD block, other genetic susceptibility factors can be represented by notion of allele. As defined in our previously developed Ontology for Genetic Interval (OGI) [16], ‘allele’ is ‘an alternative form of a genetic interval that is located at a specific position on a specific chromosome’. In OGI, term 'allele' has following subclasses: 'allele of gene', 'allele of polymorphism', 'allele of SNP', 'allele of phenotype', 'allele shared by sibs'. OGSF fully imports OGI, thus inherited the OGI's allele classes and definitions. OGI gives formalized topological relations between alleles and genes, so that the relations between alleles and genes can be logically calculated [14]. Adopting those relations ensure the example discussed in the section 4.1 can be reasoned in OGSF.

4.3 Visualization of sub network of OGSF data

The ontology's instance level data can be visualized as directed graph. The visualization and network analysis results provide deep insights in terms of ontology designing. Representing the genetic susceptibility can be addressed using three layers of information depending on researchers' interest. The first layer is the direct link of types of genetic factors and investigated adverse event. In our representation, it is grounded to allelic variant level. The second layer is the supporting conclusion that provides positive evidence to the direct link. The third layer is the linking between a gene and the investigated adverse event. Since in OGSF, gene and adverse event are not directly linked, the social network analyses shows that this indirect link can be measured mathematically and thus provide the foundation for prediction. It is noted that usually only significant associations were reported in the literature, and many negative results may not be available. The network analysis may be biased.

In conclusion, based on the formalization of genetic susceptibility, OGSF provides a frame work to represent the genetic allelic variants, genes and pathological processes. It requires ontological scientific discourse representations as those developed in SWAN ontology[17]. Furthermore, a large numbers of databases have been established in order to establish the relation between genotypes and phenotypes. Some of them, such as SNPedia [18], Bio2RDF [19], Leiden Open (source) Variation Database (LOVD) [20] and GWAS central [21], support sematic web and open data technology. OGSF is aim to be an intermediate layer between applications and above existing resources.

ACKNOWLEDGEMENTS

This project was supported by a NIH-NIAID grant (R01AI081062). We would like to acknowledge with appreciation Dr. Wei Zhang, a biostatistician expert from University of Michigan School of Public Health, for his advice and consultation.

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