A computational method for the extraction of pharmacogenomic relationships from text

Adrien Coulet[1,2], Nigam Shah[2], Yael Garten[2], Mark Musen[2], Russ Altman[2]

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2 Stanford University

The NCBO and PharmGKB

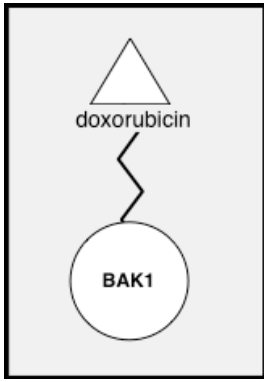
- A joint project

NATIONAL CENTER FOR BIOMEDICAL ONTOLOGY & PharmGKB

- Content of PharmGKB
  - Current:

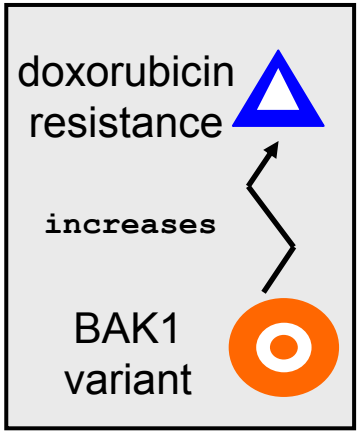
    pharmacogenomics (PGx) relationships

    Gene – Drug ; Gene – Disease ; Drug – Disease



  - Goal:

    to provide more precise relationships



Population of PharmGKB

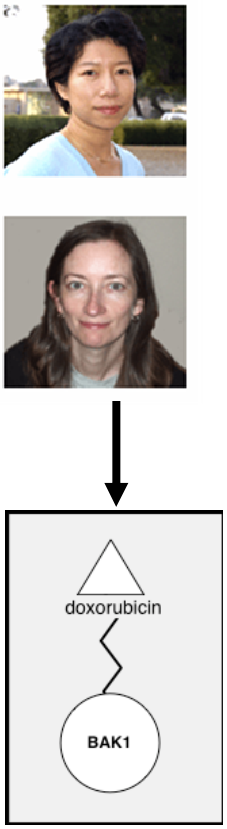
Sentence 1 : Doxorubicin induces BAK1 activity.

Sentence 2 : Doxorubicin transcriptionally activates BAK1.

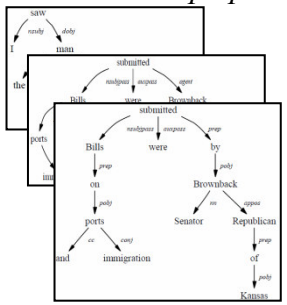
Sentence 3 : BAK1 gene polymorphism affects doxorubicin resistance.

Scientific literature

PharmGKB curators

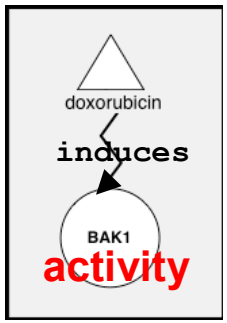


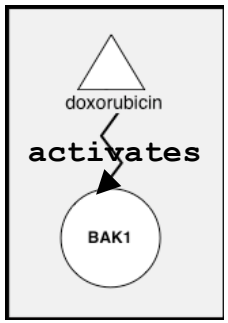
Dependency Graph parsing

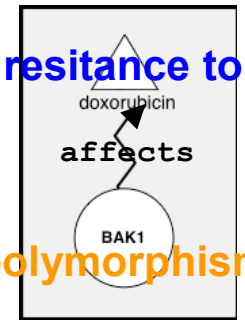


Dependency Graphs of sentences

Relation extraction







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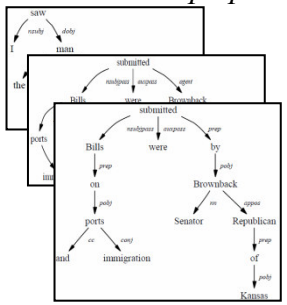

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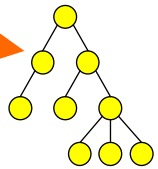
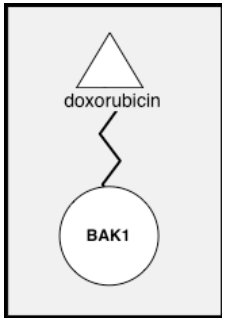
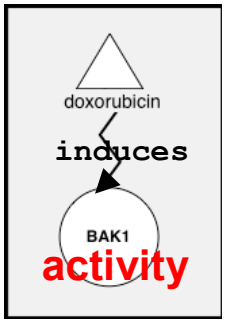
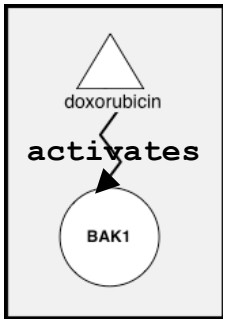


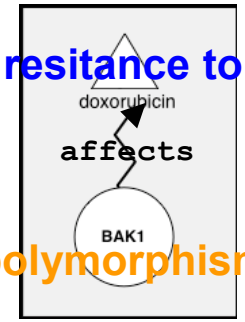
ontology

Relation extraction









Outline

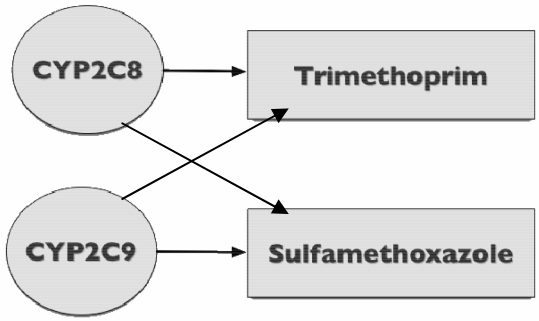
1. Limitations of co-occurrences

2. Construction of semantic network
    1. Algorithm to extract raw relationships
    2. Semi-automated ontology building
    3. Comprehensive knowledge network from 1 & 2

Limitations of co-occurrence (that we wanted to solve)

1. Avoid false positive connections

"Trimethoprim inhibits activity of CYP2C8 while sulfamethoxazole inhibits CYP2C9 activity."



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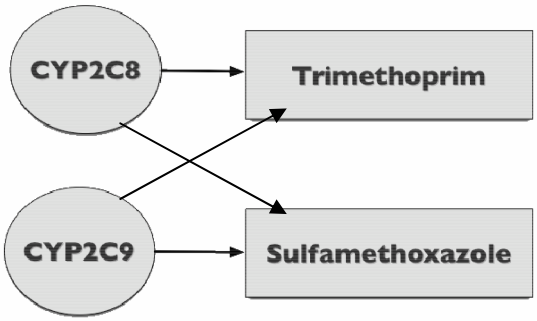

2. Characterize fine-grain semantics of relationships

"CYP3A4 mRNA expression was increased significantly by rifampicin exposure in human hepatocytes."

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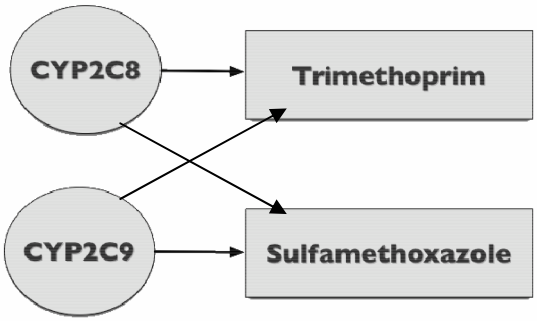

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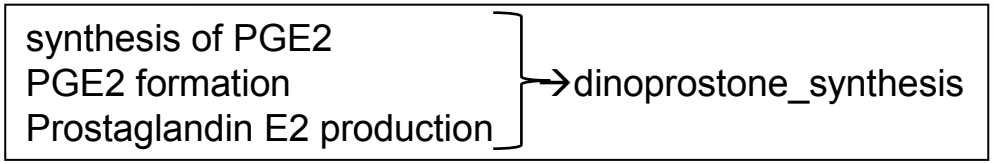
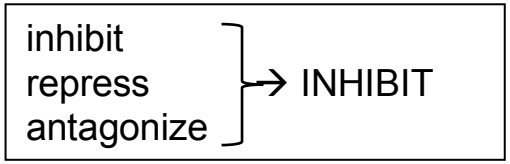
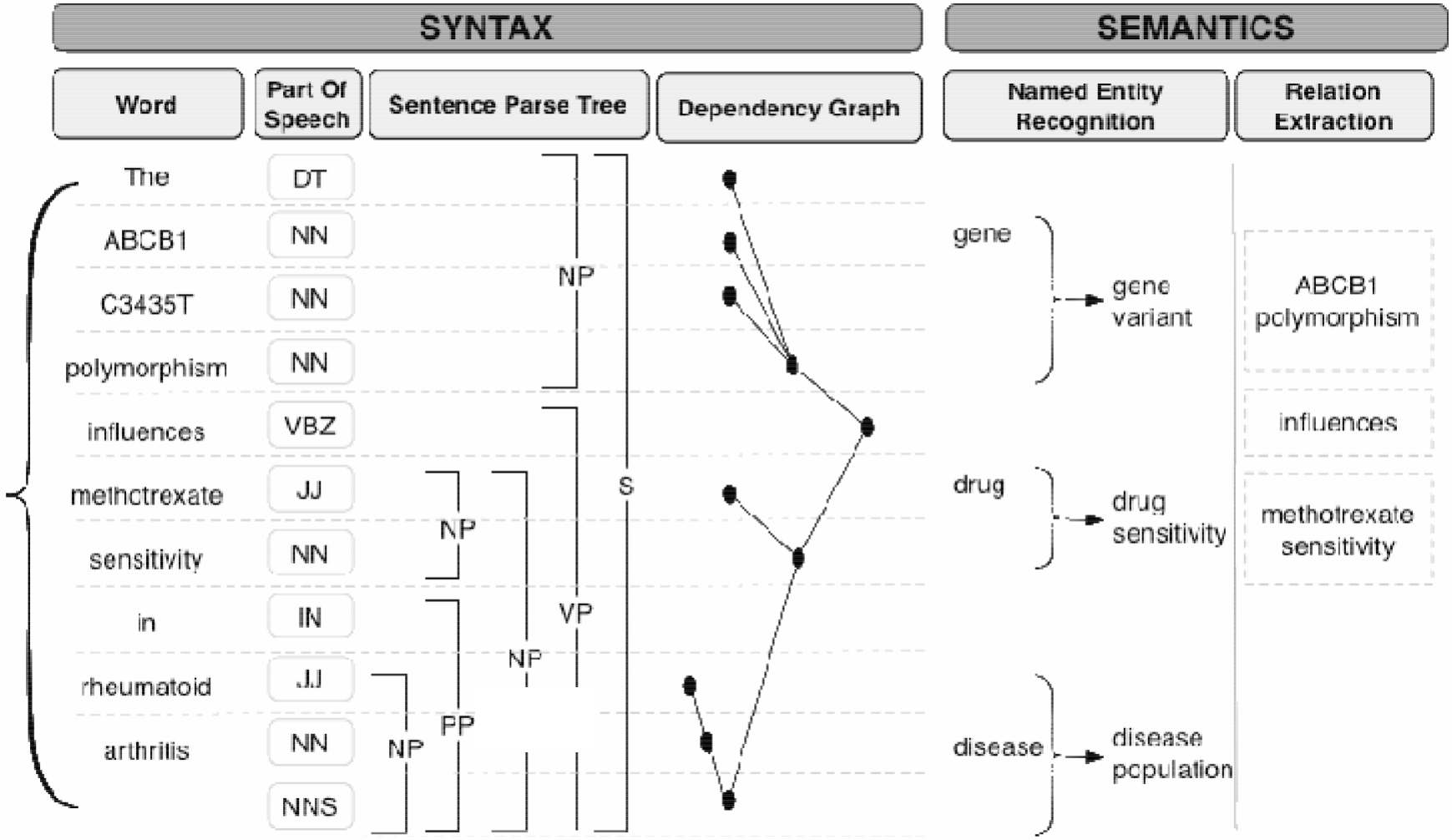
3. To consolidate synonyms (normalize):
   - Between complex entity names:



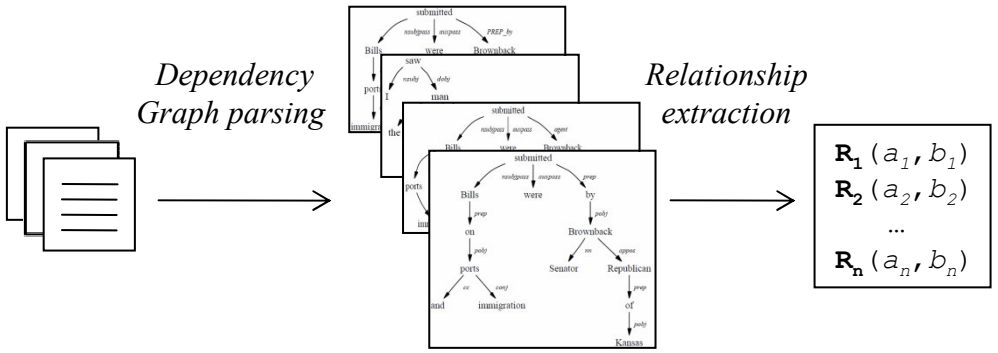
   - Between relationships:



Several steps of text processing enable extracting relationship semantics



The method extracts high quality typed relationships



MEDLINE abstracts

~17,000,000 abstracts

Dependency Graphs of sentences

~87,000,000 dependency graphs

Raw relationships

~41,000 raw relationships

Evaluation:
Randomly selected 220 raw relationships: classified into 3

"polymorphisms in VKORC1 are associated with warfarin dose."

•associated(VKORC1_polymorphisms,warfarin_dose)
= true and complete

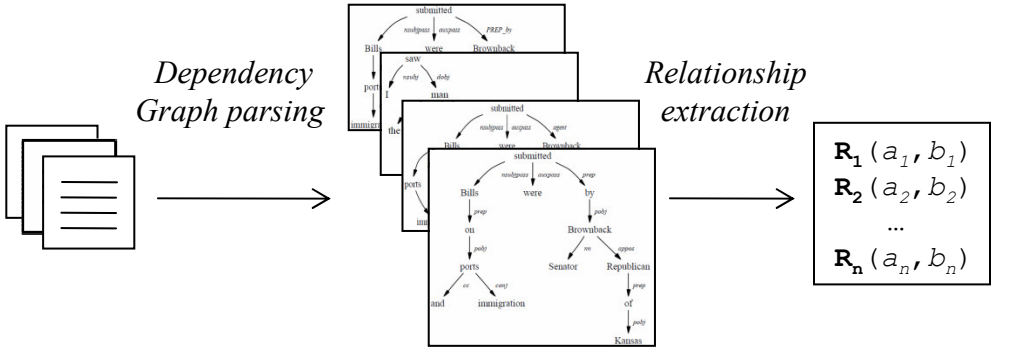
• associated (VKORC1_polymorphisms, warfarin)
= true and incomplete

•polymorphisms (VKORC1, warfarin_dose)
= false

Results:

- 87.7% were complete or incomplete true positives
  - 70% true and complete
  - 17.7% true and incomplete
- 12.3% were false positives

Issue: we extracted heterogeneous relationships



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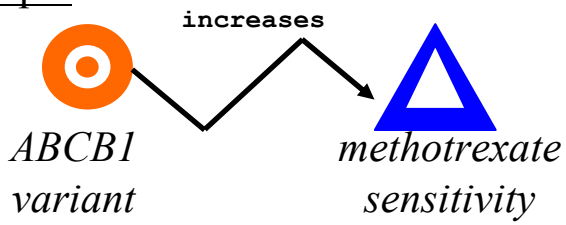
Example:



increase(P-gp_variants, methopterin_intolerance)

augment(ABCB1_SNPs, methotrexate_sensitivity)

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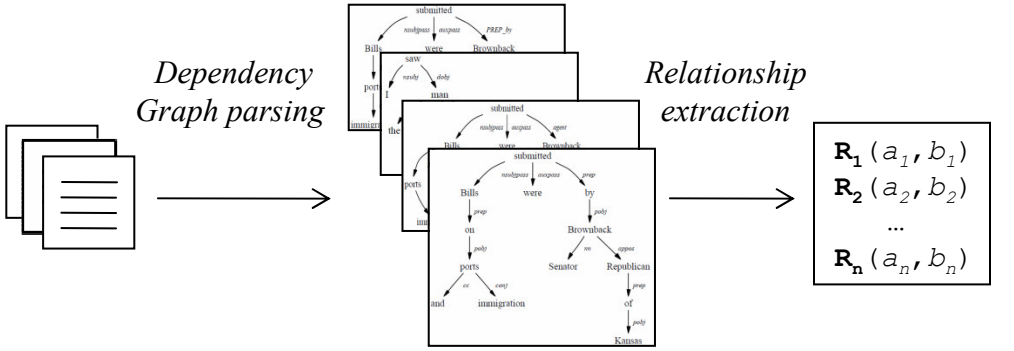

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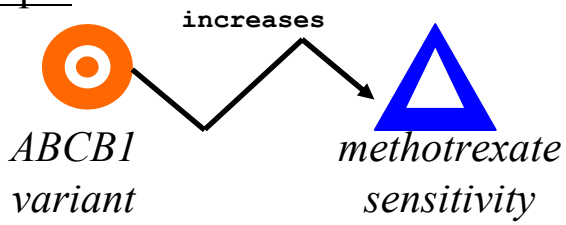

increase(P-gp_variants, methopterin_intolerance)

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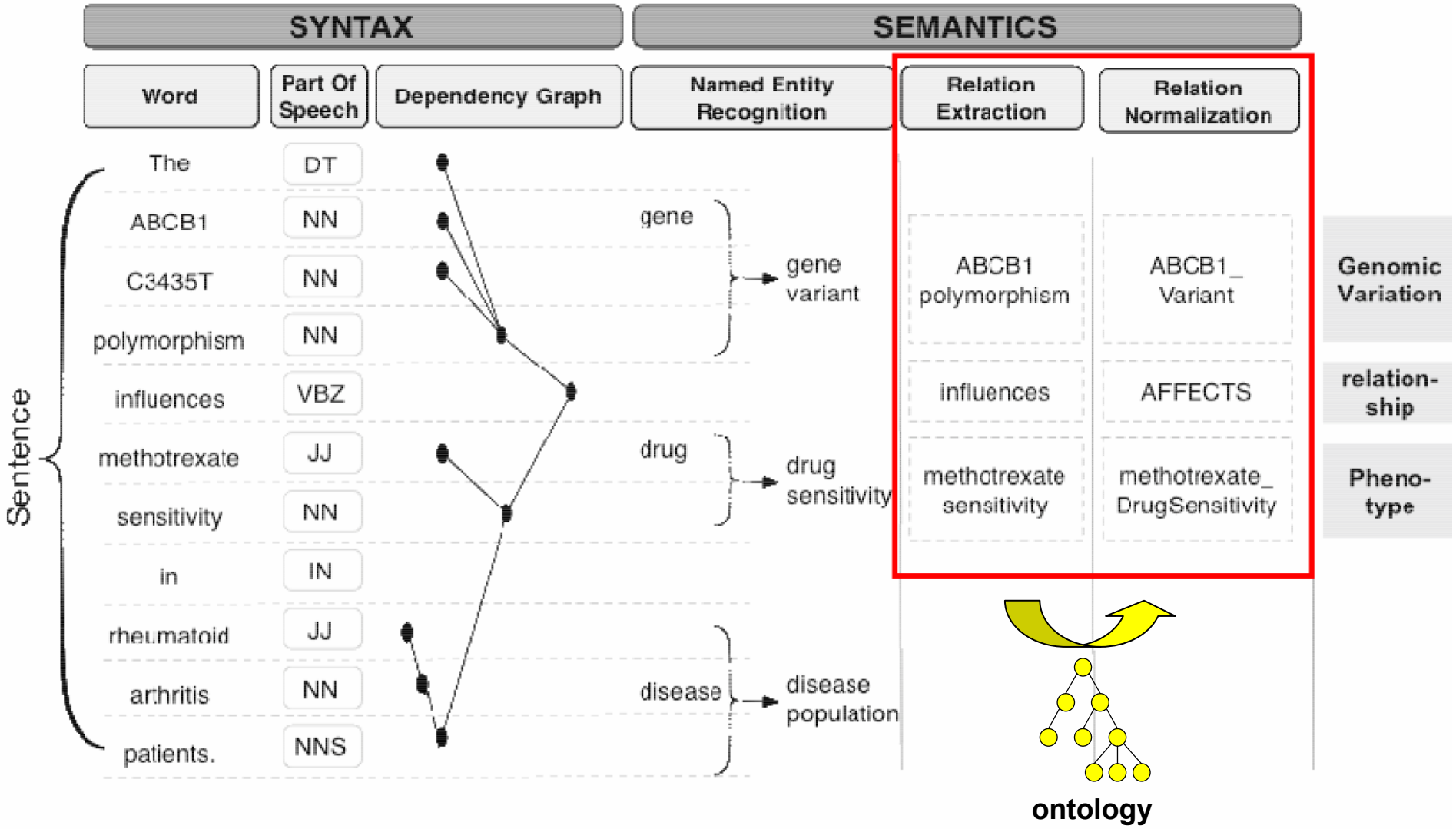
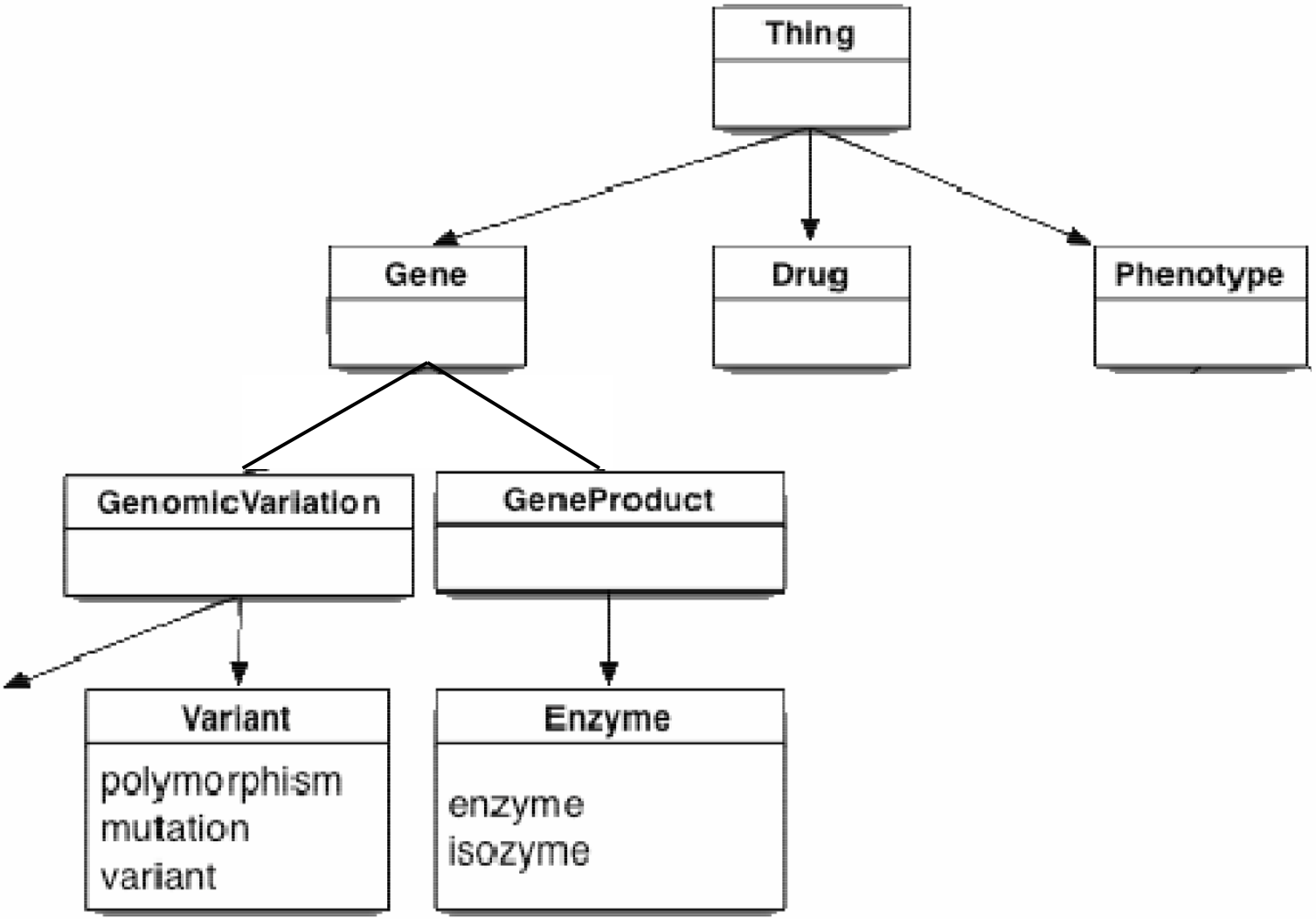
- There is no relation ontology for most of specialized domains
- We created one from extracted relationships

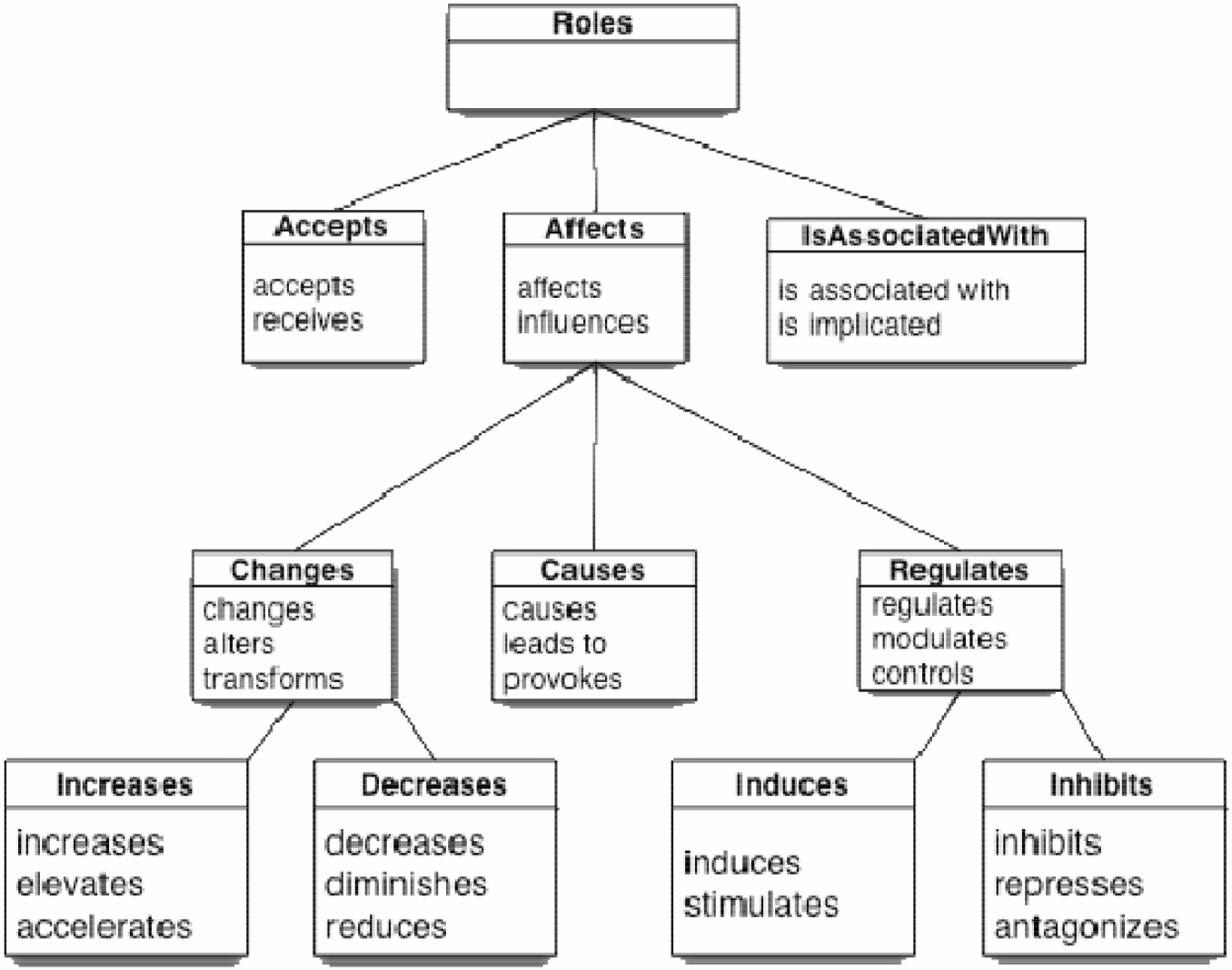
We built and use an ontology to normalize relationships



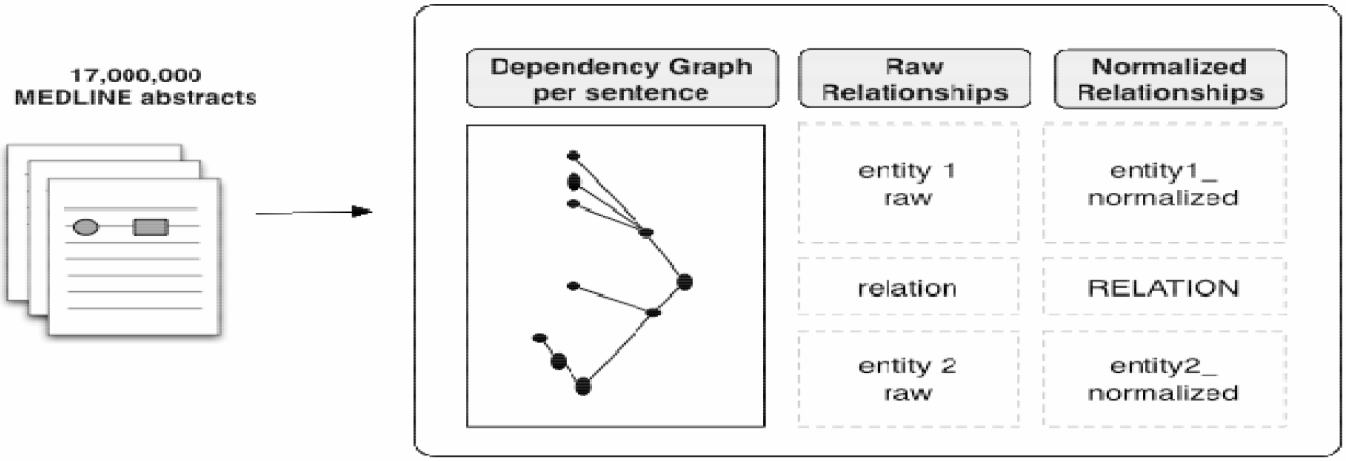
An ontology organizes the "world" into concepts and roles (1/2)



An ontology organizes the "world" into concepts and roles (2/2)



We manually created a PGx ontology "bottom-up"



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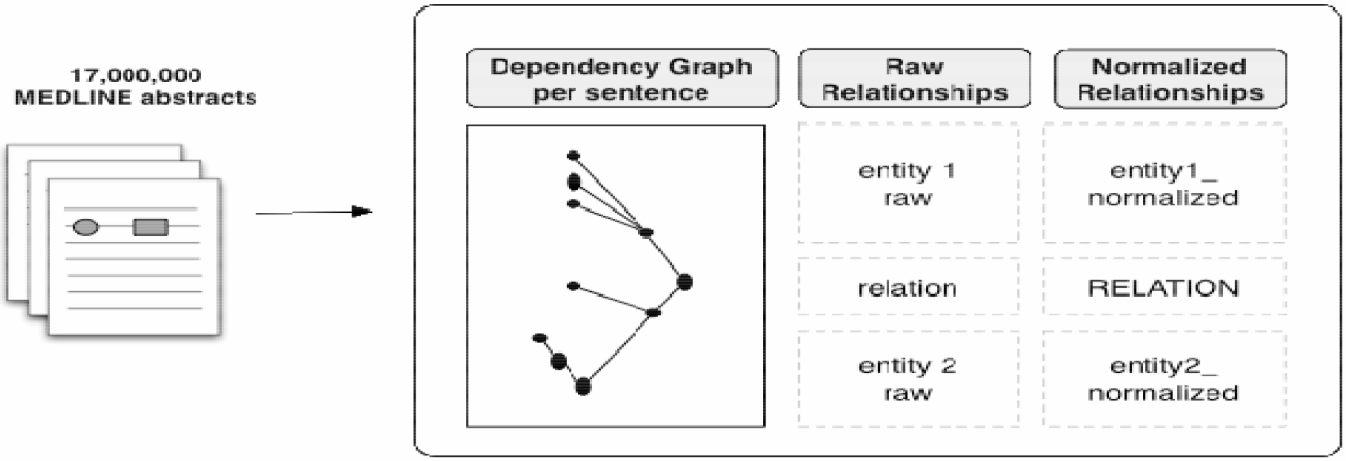

Relationship types	Entities modified by		
	Genes	Drugs	Phenotypes
2538 associate	1237 *gene*	377 *metabolism*	304 *cell*
1017 increase	1000 *inhibitor*	358 *activity*	114 *line*
985 inhibit	935 *polymorphism*	298 *inhibitor*	101 *patient*
825 induce	775 *expression*	267 *effect*	71 *risk*
763 metabolize	773 *activity*	263 *administration*	35 *tissue*
666 involve	689 *mutation*	246 *channel*	34 *specimen*
643 reduce	685 *genotype*	242 *treatment*	33 *case*
547 catalyze	393 *inhibition*	193 *antagonist*	27 *treatment*
515 cause	329 *level*	178 *concentration*	26 *rate*
509 affect	245 *gene_mutation*	172 *dose*	26 *effect*

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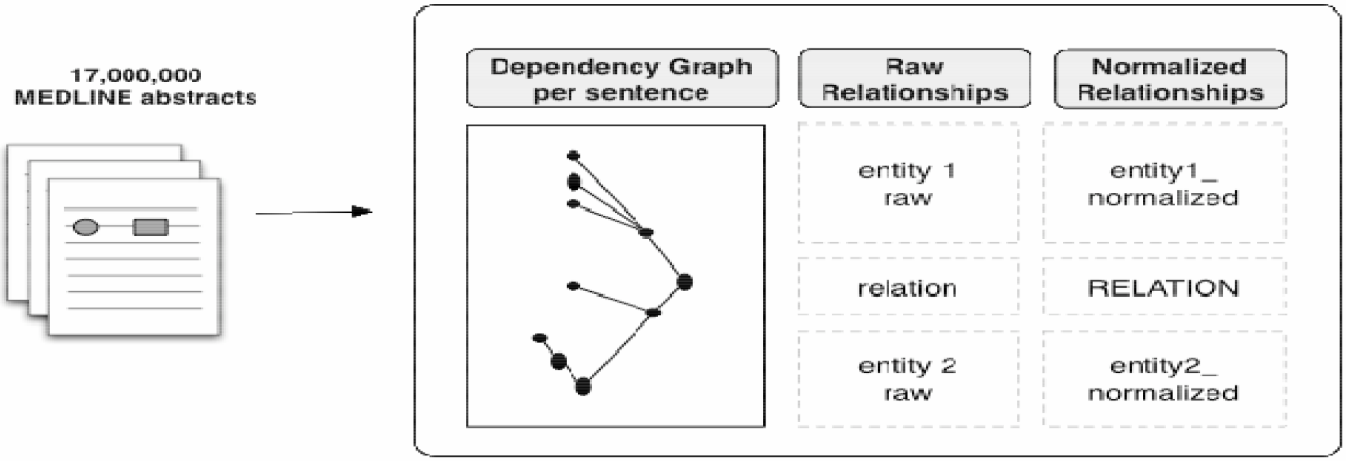

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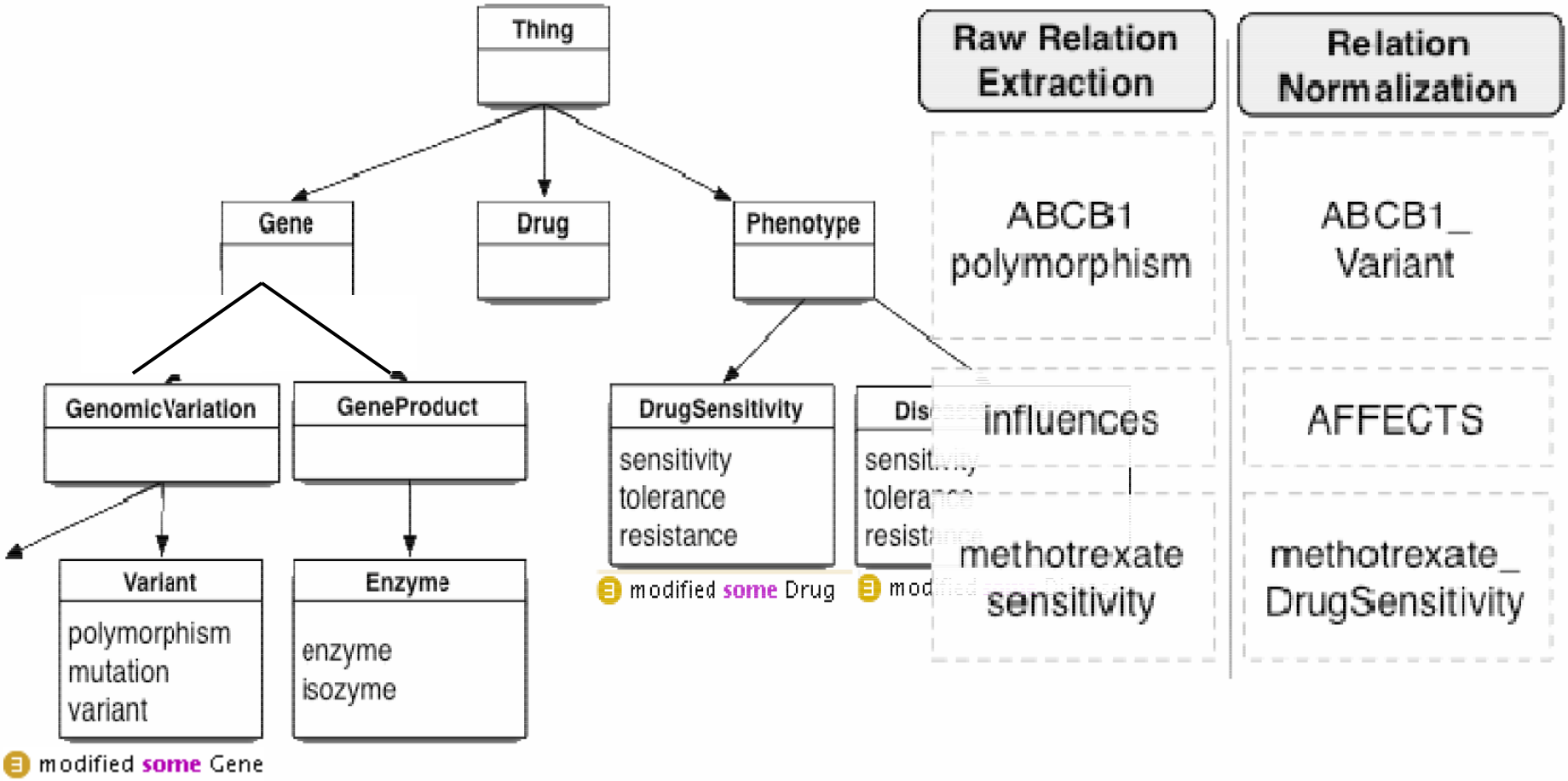
237 concepts
76 roles

We use the ontology to normalize the raw relationship (subject, relation and object)



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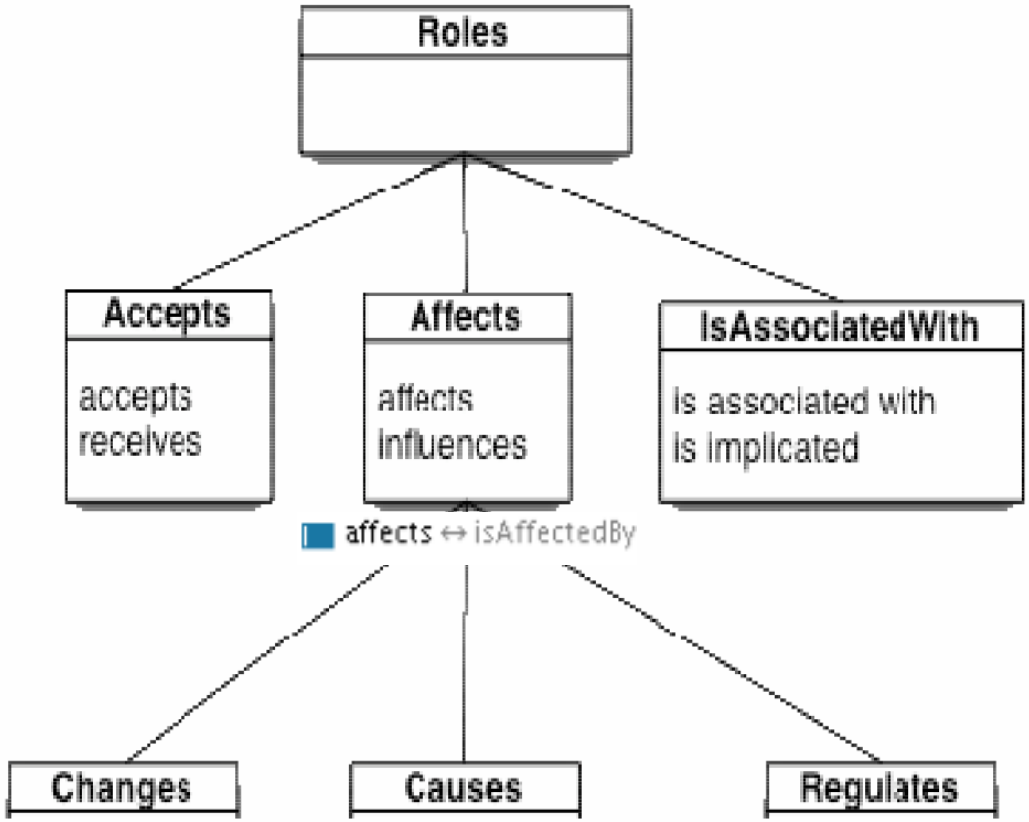
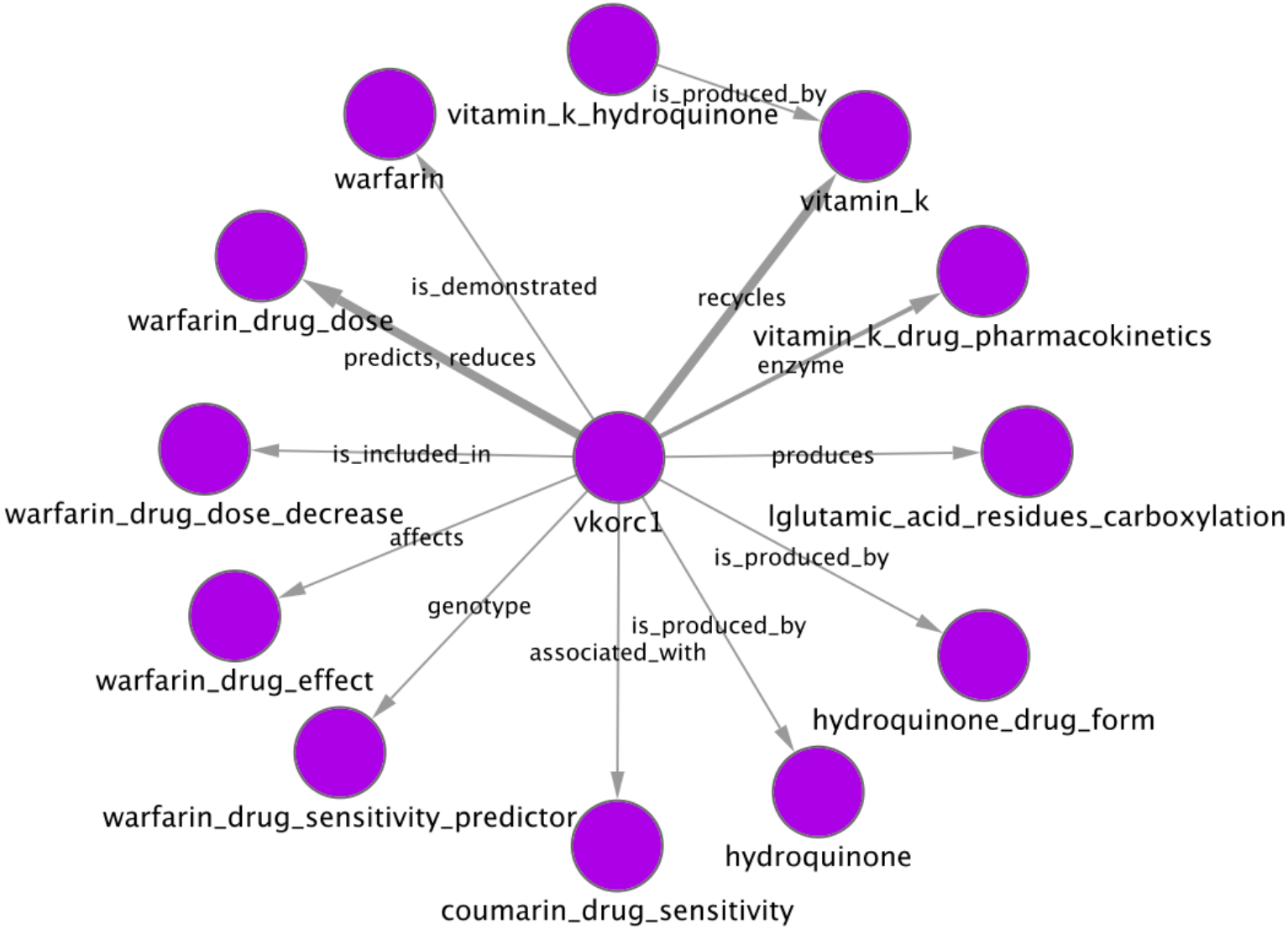


Raw Relation Extraction	Relation Normalization
ABCB1 polymorphism	ABCB1_ Variant
influences	AFFECTS
methotrexate sensitivity	methotrexate_ DrugSensitivity

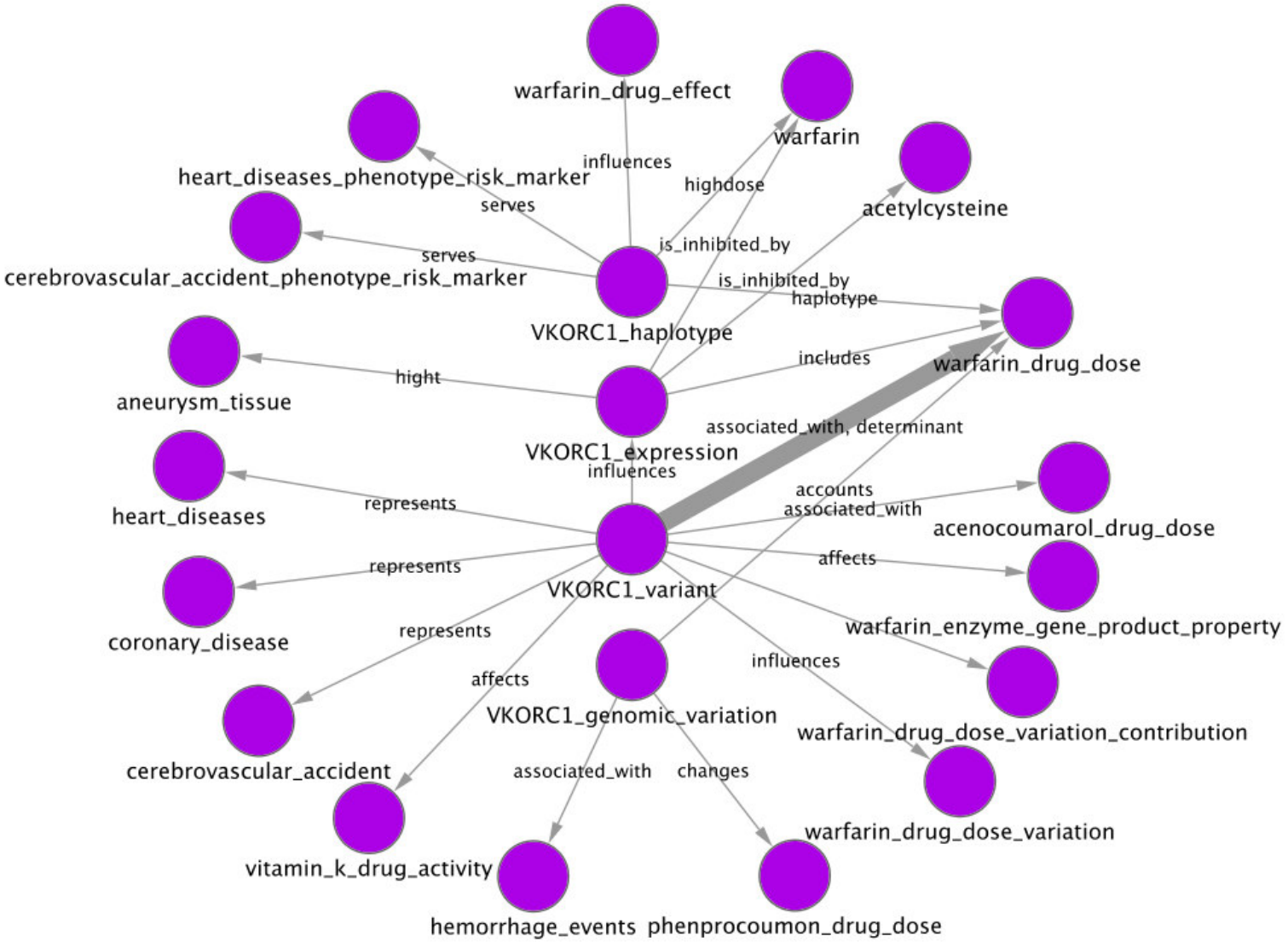
Example: two sentences but one fact

raw text	sentence	The ABCB1 C3435T polymorphism influences methotrexate sensitivity in rheumatoid arthritis patients.	A variant C3435T allele of the MDR1 gene affects methotrexate tolerability.
raw relationship	entity 1	ABCB1 polymorphism	allele of the MDR1 gene
	relationship	influences	affects
	entity2	methotrexate sensitivity	methotrexate tolerability
normalized relationship	entity 1	ABCB1_Variant	ABCB1_Variant
	relationship	AFFECTS	AFFECTS
	entity2	methotrexate_DrugSensitivity	methotrexate_DrugSensitivity

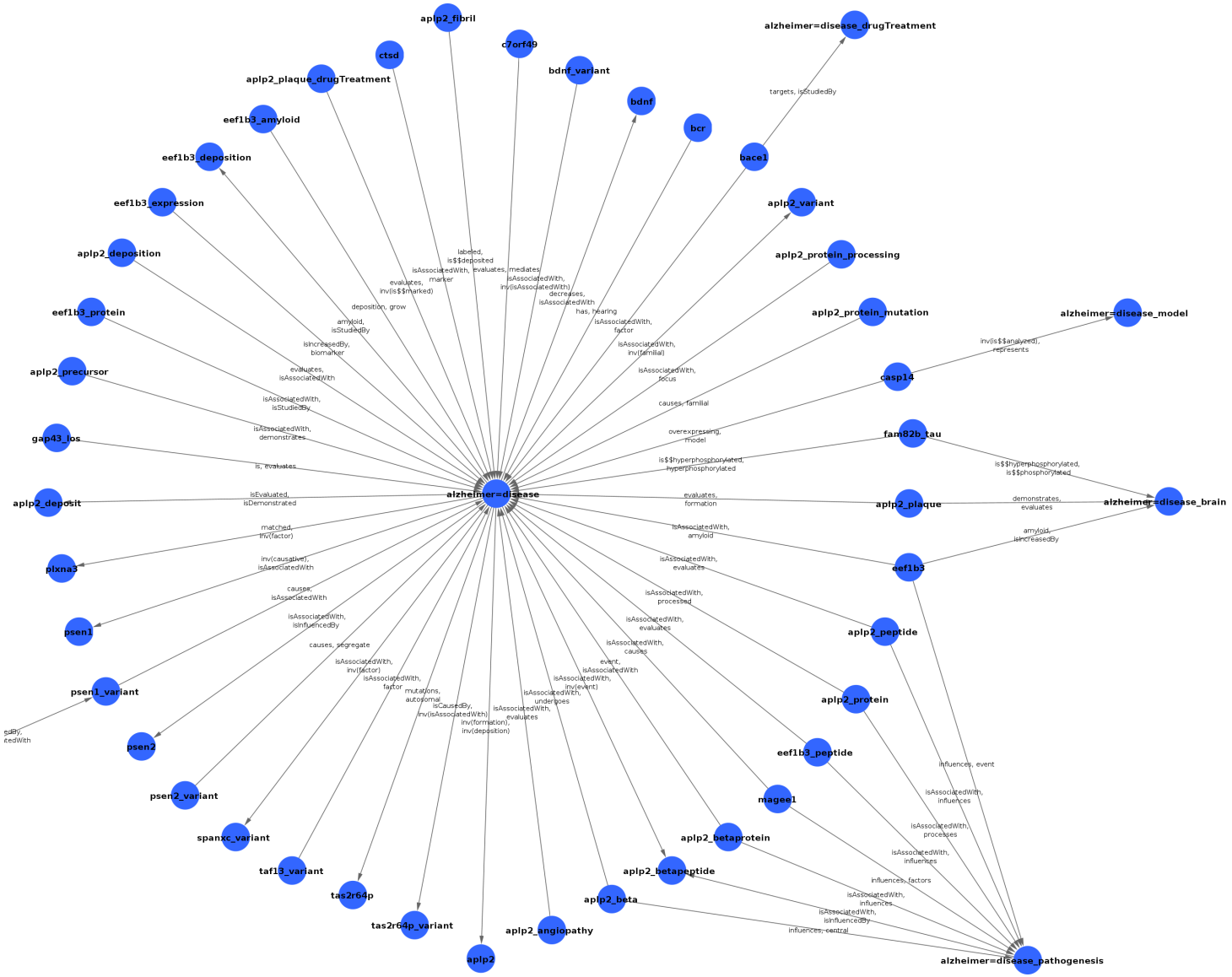
Example of network (1/3): VKORC1



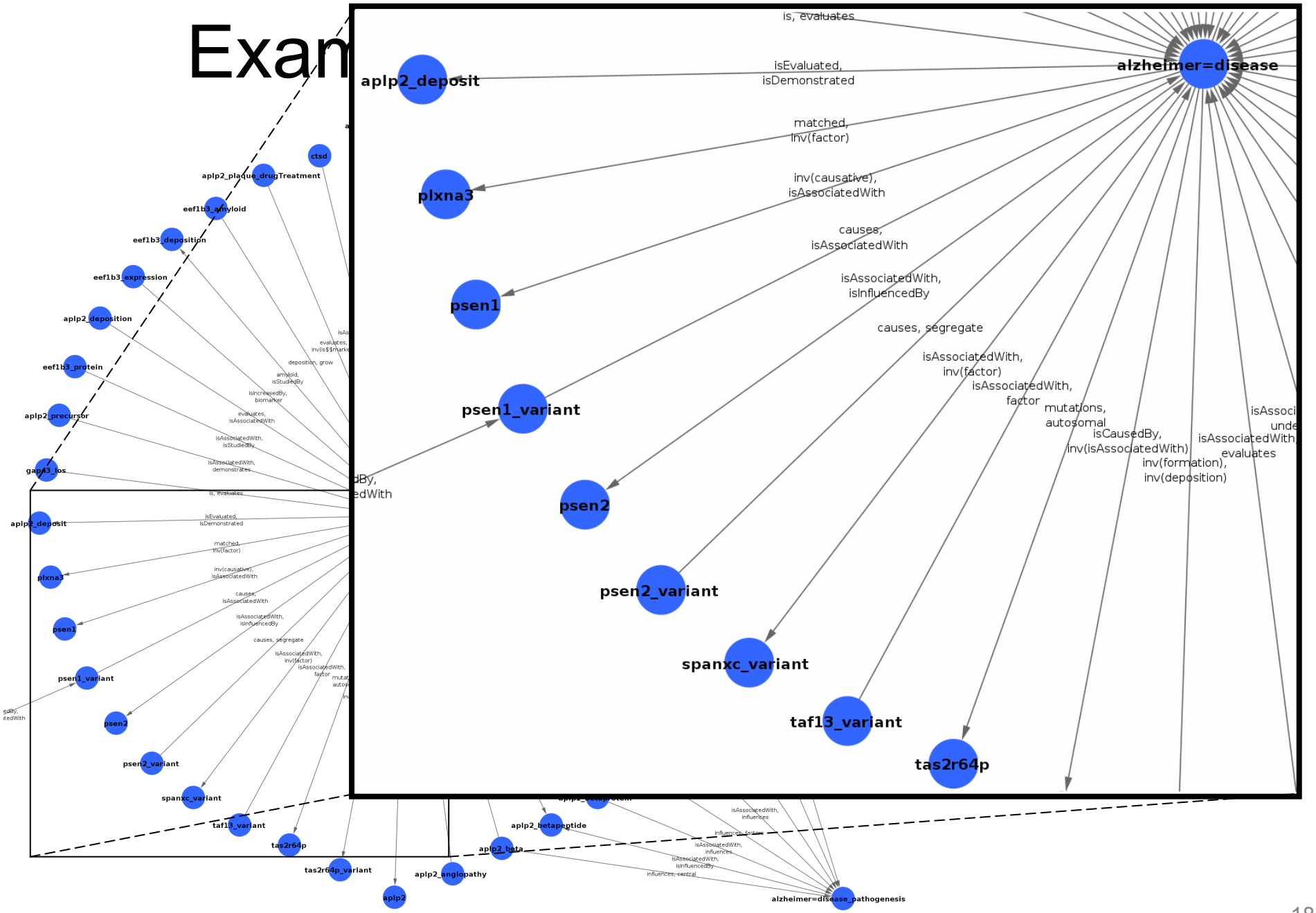
Example of network (2/3): VKORC1 something



Example of network (3/3): AD



Exam

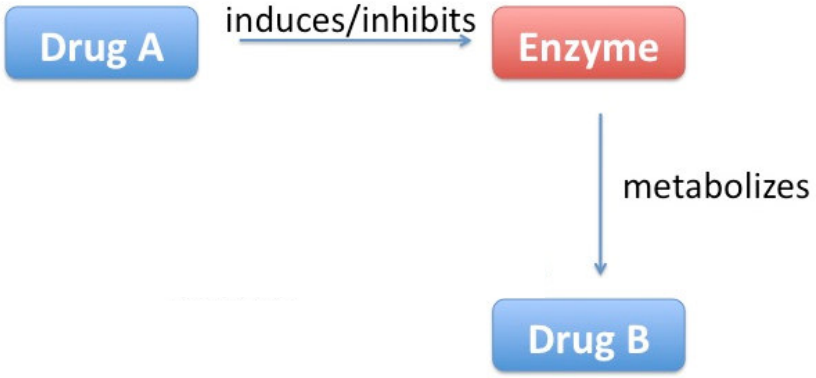

alzheimer=disease
is, evaluates
isEvaluated,
isDemonstrated
matched,
inv(factor)
inv(causative),
isAssociatedWith
causes,
isAssociatedWith
isAssociatedWith,
isInfluencedBy
causes, segregate
isAssociatedWith,
inv(factor)
isAssociatedWith,
factor
mutations,
autosomal
isCausedBy,
inv(isAssociatedWith)
inv(formation),
inv(deposition)
isAssociatedWith,
evaluates
aplp2_deposit
plxna3
psen1
psen1_variant
psen2
psen2_variant
spanxc_variant
taf13_variant
tas2r64p
ctsd
aplp2_plaque_drugTreatment
eef1b3_amyloid
eef1b3_deposition
eef1b3_expression
aplp2_deposition
eef1b3_protein
aplp2_precursor
gapA3_los
tas2r64p_variant
aplp2_angiopathy
aplp2
aplp2_betapeptide
aplp2_beta
alzheimer=disease_pathogenesis

Conclusion

- A method to build semantic network
- Used in PGx:
  - For curation and knowledge summarization
    @PharmGKB
  - For knowledge discovery

    e.g.Predicting Drug-Drug interaction

    =>Yael Garten's PhD thesis



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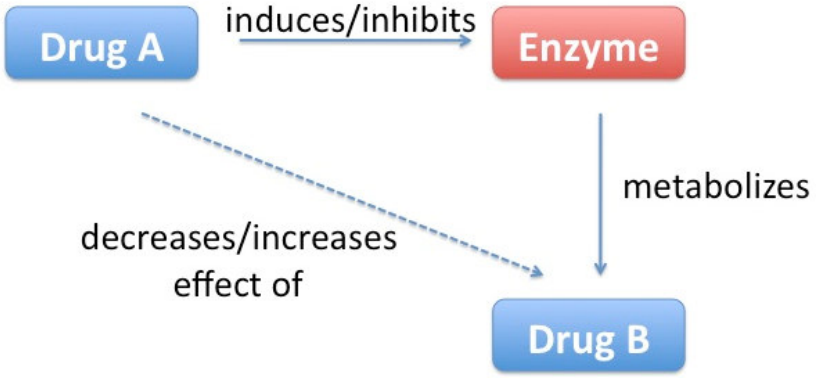


Questions?

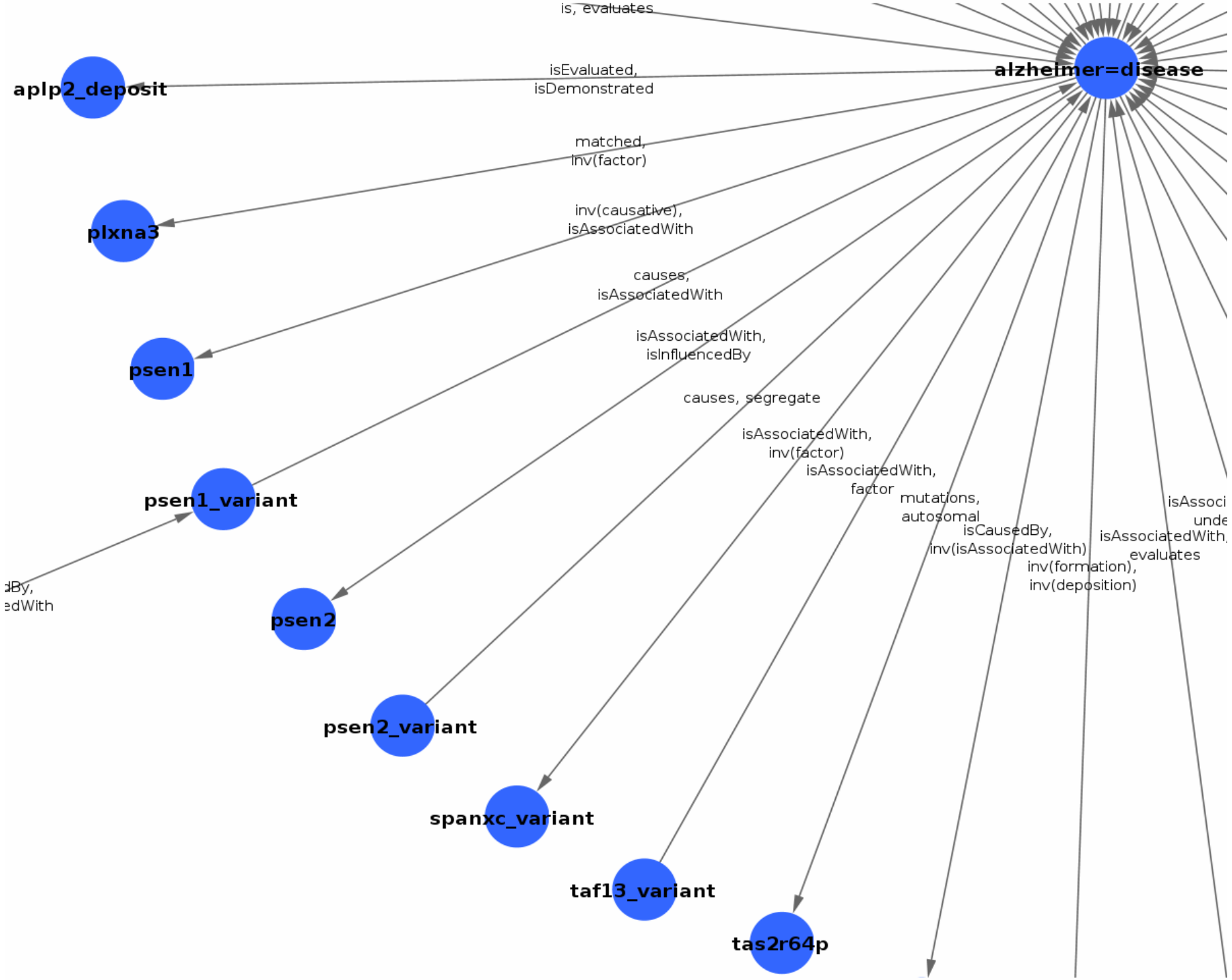
Coulet *et al. Journal of Biomedical Informatics*, In Press, 2010

or

adrien.coulet@loria.fr

Thanks

And thanks to Yael Garten for many slides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alzheimer=disease
aplp2_deposit
isEvaluated,
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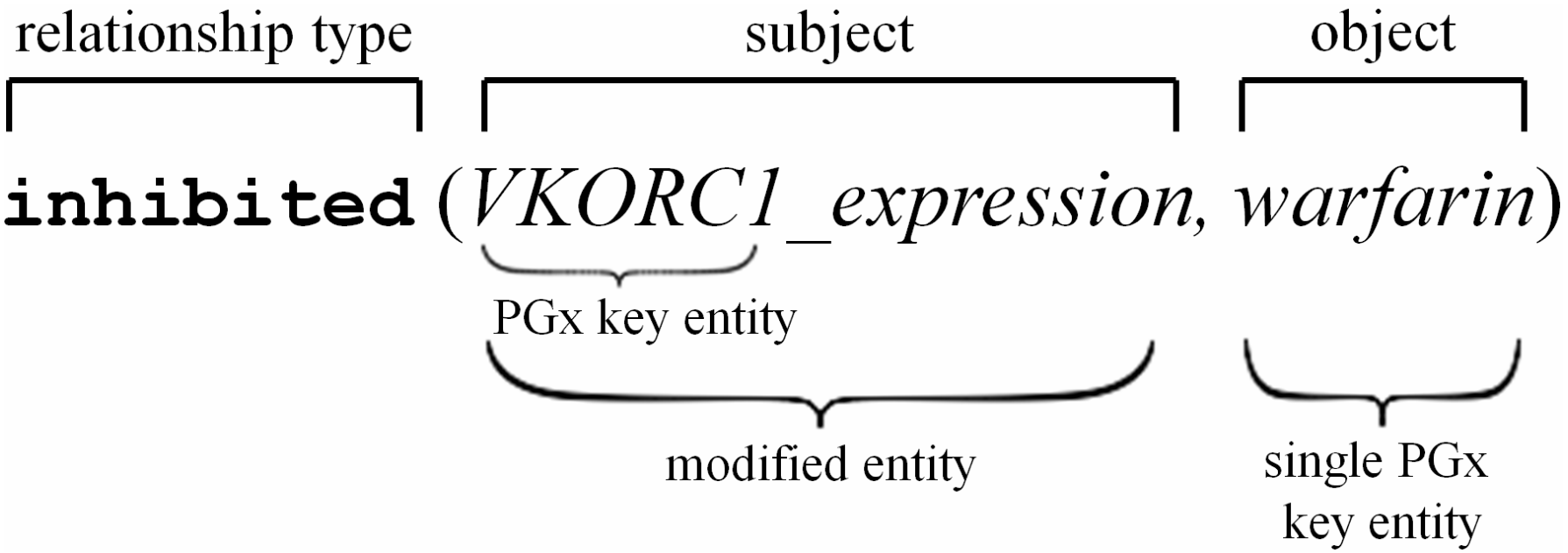
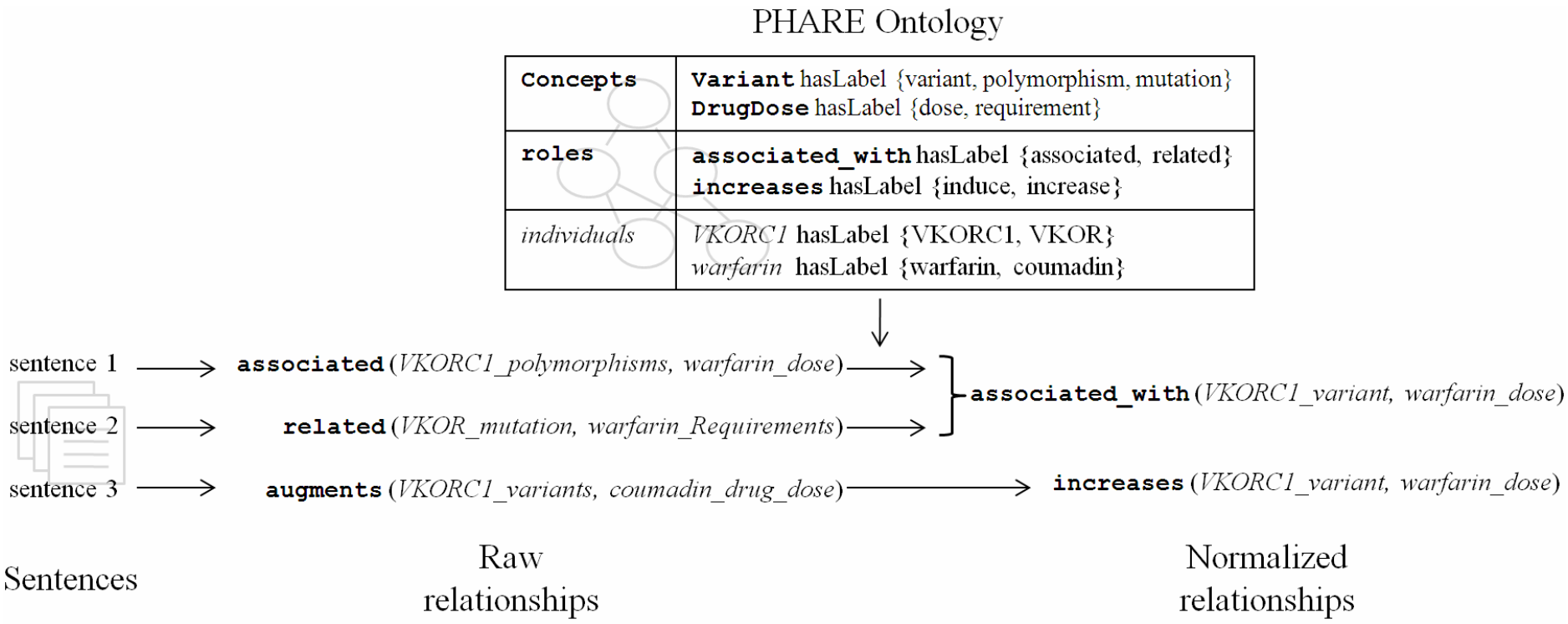
matched,
inv(factor)
plxna3
inv(causative),
isAssociatedWith
causes,
isAssociatedWith
psen1
isAssociatedWith,
isInfluencedBy
causes, segregate
isAssociatedWith,
inv(factor)
isAssociatedWith,
factor
psen1_variant
mutations,
autosomal
isCausedBy,
inv(isAssociatedWith)
isAssociatedWith,
evaluates
inv(formation),
inv(deposition)
psen2
psen2_variant
spanxc_variant
taf13_variant
tas2r64p


relationship type
subject
object
inhibited (VKORC1_expression, warfarin)
PGx key entity
modified entity
single PGx key entity


PHARE Ontology
Concepts
Variant hasLabel {variant, polymorphism, mutation}
DrugDose hasLabel {dose, requirement}
roles
associated_with hasLabel {associated, related}
increases hasLabel {induce, increase}
individuals
VKORC1 hasLabel {VKORC1, VKOR}
warfarin hasLabel {warfarin, coumadin}
sentence 1
associated(VKORC1_polymorphisms, warfarin_dose)
sentence 2
related(VKOR_mutation, warfarin_Requirements)
associated_with(VKORC1_variant, warfarin_dose)
sentence 3
augments(VKORC1_variants, coumadin_drug_dose)
increases(VKORC1_variant, warfarin_dose)
Sentences
Raw relationships
Normalized relationships