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A propositional AI system for supporting epilepsy diagnosis based on the 2017 epilepsy classification: Illustrated by Dravet syndrome

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ABSTRACT

Purpose: The 2017 epilepsy and seizure diagnosis framework emphasizes epilepsy syndromes and the etiology-based approach. We developed a propositional artificial intelligence (AI) system based on the above concepts to support physicians in the diagnosis of epilepsy.
Methods: We analyzed and built ontology knowledge for the classification of seizure patterns, epilepsy, epilepsy syndrome, and etiologies. Protégé ontology tool was applied in this study. In order to enable the system to be close to the inferential thinking of clinical experts, we classified and constructed knowledge of other epilepsy-related knowledge, including comorbidities, epilepsy imitators, epilepsy descriptors, characteristic electroencephalography (EEG) findings, treatments, etc. We used the Ontology Web Language with Description Logic (OWL-DL) and Semantic Web Rule Language (SWRL) to design rules for expressing the relationship between these ontologies.
Results: Dravet syndrome was taken as an illustration for epilepsy syndromes implementation. We designed an interface for the physician to enter the various characteristics of the patients. Clinical data of an 18-year-old boy with epilepsy was applied to the AI system. Through SWRL and reasoning engine Drool's execution, we successfully demonstrate the process of differential diagnosis.
Conclusion: We developed a propositional AI system by using the OWL-DL/SWRL approach to deal with the complexity of current epilepsy diagnosis. The experience of this system, centered on the clinical epilepsy syndromes, paves a path to construct an AI system for further complicated epilepsy diagnosis.
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1. Introduction

Epilepsy is a changeable and variable disease. With the vigorous applications of gene sequencing related to epilepsy, a considerable number of clinical issues have arisen. One gene could have many phenotypes; for example, SCN1A pathogenic variants have many phenotypes, such as Dravet syndrome, febrile seizures plus, genetic epilepsy with febrile seizures plus, etc. [1]. Another concern is syndromes with many genetic pathogenic variants; for example, although the causes of early infantile epileptic encephalopathy (EIEE) are mostly related to abnormal brain structures or brain injuries, more than 50 genetic mutations related to EIEE could be ascribed [2,3]. In addition, epilepsy is a complex disease with a high degree of heterogeneity; it is marked by multiple seizure patterns, diverse clinical manifestations, and numerous etiologies (not only genetic), leading to markedly different outcomes in patients. These problems also indicate that more complete and updated diagnostic tools and classifications should be made available for epilepsy and seizures.

The 1981 seizure classification has been widely used over the past 30 years. In response to the arrival of precision medicine, the International League Against Epilepsy (ILAE) established the 2017 classification formulas for seizure types and epilepsies, which provide a modern descriptive classification template [4–6]. The 2017 classifications emphasize the etiology-based approach, which informs

Abbreviations: EIEE, early infantile epileptic encephalopathy; ILAE, International League Against Epilepsy; AI, artificial intelligence; OWL-DL, Ontology Web Language with Description Logic; SWRL, Semantic Web Rule Language; EEG, electroencephalography.

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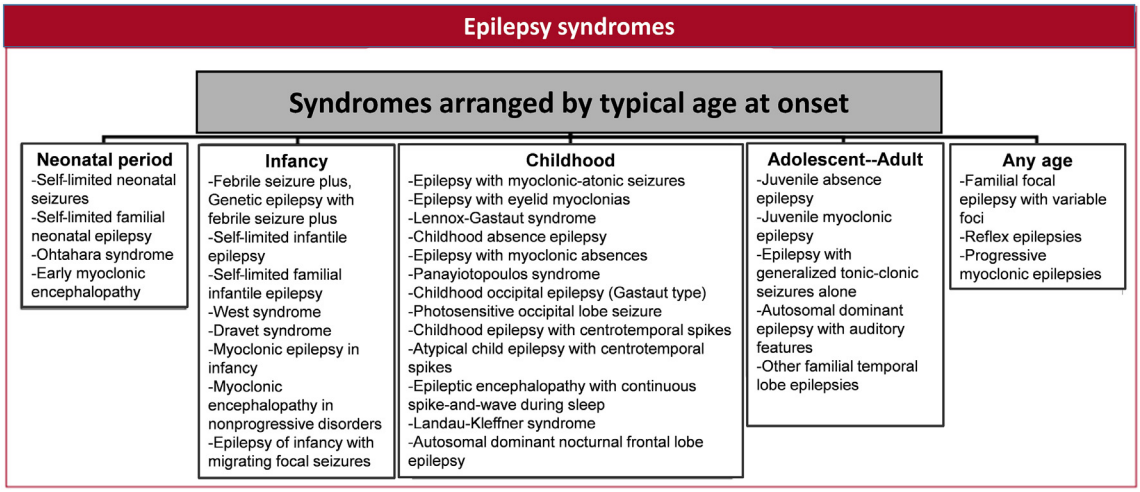

Fig. 1. Epilepsy syndrome classification arranged by typical age at onset.

the therapies and trial designs related to epilepsy [4]. The new classification includes six etiology categories (structural, genetic, infections, metabolic, immune, and unknown).

Nowadays, epilepsy syndromes are an important part of the new diagnostic framework. EpilepsyDiagnosis.org [7] organized a complete classification of syndromes based on the typical age at seizure onset. A reorganized syndrome classification is depicted in Fig. 1. In addition, the 2017 diagnosis framework emphasizes the importance of comorbidities in the diagnosis of epilepsy, especially neuropsychiatric disorders. If those comorbidities are not noticed and treated in time, even if epilepsy is well-controlled, the patient will have a poor prognosis.

With the above comprehensive, sophisticated, and progressing knowledge bases, it is necessary to utilize multidisciplinary approaches, such as artificial intelligence (AI), to reduce the burden of diagnosis for the epilepsy syndromes for nowadays urging needs of precision medicine.

Among AI systems, ontology provides a rich, visible, revisable, and expandable taxonomy to accommodate vocabularies of knowledge, compared with other expert systems. It is especially excellent in knowledge representation [8]. In addition, the associated reasoning functions can help develop decision support functions. Although there were some research applying ontology to help patients diagnoses and cares in epilepsy [9,10], the nowadays progressing knowledge in genetics, epilepsy syndromes, etiologies, and comorbidities, urges a need to develop a more comprehensive clinical supporting system of epilepsy for physicians.

2. Material and methods

This study used Protégé ontology tools to construct an expert system [11]. Attempts were made to focus on strengthening the construction of a complete knowledge base and improving the exchange of meaningful clinical information about epilepsies. It is expected that the inference engine will be used to derive recommendations for diagnosis.

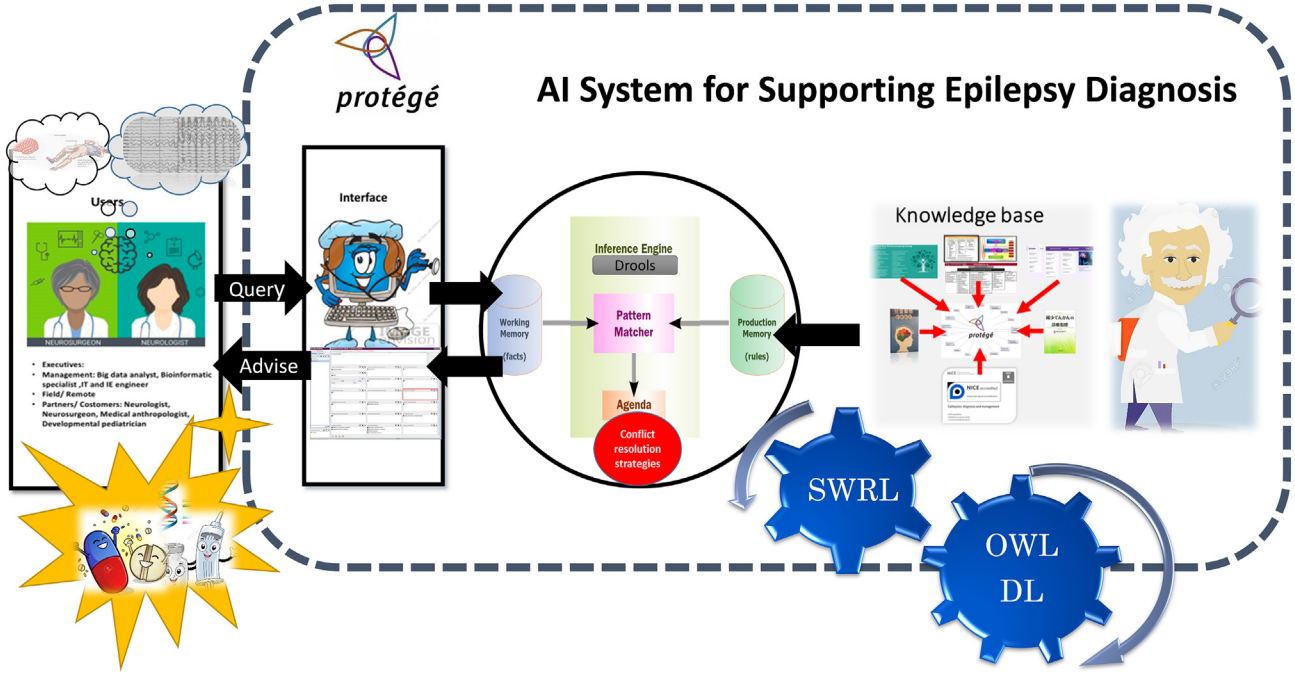

Fig. 2. System architecture diagram and derivation knowledge flow.

Table 1
OWL properties related to major components of epilepsy syndromes.

Component	Properties and the associated class with only/some
1. Age at seizure onset	1. hasOnsetAgePeriod only Age_period
2. Seizure patterns	2.1.mandatorySeizurePattern only Seizure_classification 2.2. couldHasSeizurePattern only Seizure_classification 2.3 exclusionaryOfSeizurePattern some Seizure_classification
3. Certain patterns of EEG	3. hasCharacteristicEEG only EEG
4. Comorbidities (especially mental or cognitive problems)	4.1. highRatioOfMentalOrLearningOrCognitionProblem only Boolean 4.2. hasComorbiditiyOrSequela some Comorbidities and hasComorbiditiyOrSequela some Epilepsy_syndrome
5. Etiologies	5. hasEtiologyOf only Epilepsy_etiologies
6. Genetic information	6.1. hasMostImportantGeneticProblem only Genetic_etiologyClass 6.2. hasOtherGeneticProblems only Genetic_etiologyClass
7. Past or family history	7.1. hasPastHxSyndrome some Epilepsy_syndrome 7.2. highPastHxOfFebrileSeizure only Boolean 7.3. highFamilyHxOfFebrileSeizure only Boolean 7.4. highFamilyHxOfSeizureOrEpilepsy only Boolean
8. Severity and frequency	8.1 highRatioOfIntractableSeizure only Boolean 8.2. highFrequencyOfSeizure only Boolean 8.3. hasSeizureMeasuresOrDiseaseCharacteristics some Seizure_measurements_Disease_Conditions
9. Imaging findings	9.1. highRatioOfBrainImageAbnormality only Boolean 9.2. hasAbnormalBrainImage only Images
10. Provoking factors/Diurnal variation	10. hasProvokingFactorsOrDiurinalEffects only Activation_trigger_or_diurinal_effect
11. Prognosis	11.1. highRatioOfSeizureSelfLimited only Boolean 11.2. hasPossibleEvolvingSyndrome some Epilepsy_syndrome
12. Sex difference	12. sexEffect only Sex_equaltiy_measurement
13. Other diagnosis methods	13. otherAssistedDiagnosisMethods some Other_assisted_diagnosis_methods
14. Differential diagnosis	14.1. differentialDiagnosis some Epilepsy_imitators and differentialDiagnosis some Epilepsy_syndrome 14.2. differentialDiagnosisSyndrome some Epilepsy_etiologies and differentialDiagnosisSyndrome some Epilepsy_syndrome 14.3. differentialDiagnosisImitator only Epilepsy_imitators
15. Treatments	15.1. hasMostRecommendedTreatments some Treatments 15.2. otherRecommandedTreatments some Treatments 15.3. notRecommandedTreatemnts some AEDs and notRecommandedTreatemnts some Other_treatments

2.1. The OWL/SWRL approach as a solution for supporting epilepsy diagnosis

Ontologies are knowledge representation formalism in any area of interest, in which their properties, relations, and restrictions are formally established. Ontologies have widely been used for knowledge representation for healthcare [8]. Ontologies provide a secure and stable tool for integrative disease modeling to achieve the goal of precision medicine [12].

The Ontology Web Language (OWL), as a standard language of ontology, is a semantic descriptive framework, with a meaning that allows expressing machine-understandable content, automatic interpretation and processing by machines [8,13]. Ontology Web Language with Description Logic (OWL-DL) is the most widespread sublanguage of OWL in medical knowledge ontologies [14]. The OWL-DL is designed to support existing description logic units and has computational attributes required by the inference system. However, ontology has expressivity limitations on representing general rules. To conquer the limitations, Semantic Web Rule Language (SWRL) [15,16] in this research is applied in two areas: (1) to expand the capability of knowledge classification and representation of ontology (addressed in Section 2.4) and (2) to allow complex decision rule modeling (addressed in Section 4.3).

2.2. Knowledge bases for epilepsy

The knowledge base information included in our AI system includes the following:

(1) The 2017 seizure and epilepsy classification formula [4–6],
(2) Epileptic online diagnostics website, "EpilepsyDiagnosis.org", and
(3) Enhanced knowledge of etiologies and treatments from the following:
(3.1) The Epilepsy Foundation's website [17],
(3.2) "The guidelines for childhood epilepsy", compiled by the Taiwan Epilepsy Society [18],
(3.3) "The diagnosis and management of epilepsy in children: NICE epilepsy guidelines" [19],
(3.4) "Medical Index of Rare Epilepsy" compiled by the Japan Epilepsy Society [20],
(3.5) Rare Epilepsy Network's (REN's) publications [21,22], and
(3.6) other related papers in recent years [23–29].

2.3. System

The system architecture diagram and derivation knowledge flow are shown in Fig. 2. A physician can apply the AI system by entering the clinical information of the patient, e.g., onset age of seizure, seizure clinical presentations, biomedical characteristics, and characteristics of electroencephalography (EEG). The knowledge base system then infers the possible epilepsy syndrome or etiological diagnoses based on the established aforementioned knowledge bases coded by OWL-DL and SWRL.

In this research, epilepsy syndrome knowledge consists of 15 components (Table 1). As illustrated in Table 1, we defined that each component is described by and/or connected properties, and each property has its associated classes with only/some descriptor. "Only" is meant that every other class can only associate with the class by the property. "Some" is meant that every other class can associate with multiple classes through the property.

Based on Table 1, for example, the epilepsy syndrome class can "only" associate the EEG class through the property hasCharacteristicEEG (Certain patterns of EEG, Component 3). The epilepsy syndrome class can associate with "some" classes of Epilepsy_imitators "and" Epilepsy_syndrome by property differentialDiagnosis (Differential diagnosis, Component 14). Nevertheless, EpilepsyDiagnosis.org specified that the relationship between epilepsy syndrome and seizure patterns is various like "mandatory", "may have", and "exclusionary" [7]. The associations were also defined in Component 2 (Seizure patterns) in Table 1.

Table 2
SWRL rule groups used in the current system.

Items	Rule groups
Age period rules	Rule 1. Patients(?p) ∧ onestAgeYear(?p, ?y) ∧ swrlb:greaterThan(?y, 12) ∧ swrlb:lessThanOrEqual(?y, 100) →belongOnsetAgePeriod(?p, Adolescent_and_adulthood)
	Rule 2. Patients(?p) ∧ onestAgeYear(?p, ?y) ∧ swrlb:greaterThan(?y, 2) ∧ swrlb:lessThanOrEqual(?y, 12) → belongOnsetAgePeriod(?p, Childhood)
	Rule 3. Patients(?p) ∧ onestAgeYear(?p, ?y) ∧ swrlb:greaterThan(?y, 0.083) ∧ swrlb:lessThanOrEqual(?y, 2) → belongOnsetAgePeriod(?p, Infancy)
	Rule 4. Patients(?p) ∧ onestAgeYear(?p, ?y) ∧ swrlb:lessThanOrEqual(?y, 0.083) → belongOnsetAgePeriod(?p, Neonate)
Classified epileptic encephalopathy (narrow definition)	Rule 1. Epilepsy_syndrome(?s) ∧ highRatioOfIntractableSeizure (?s,T) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧ hasCharacteristicEEG (?s,Suppression-burst_pattern_1) →Epileptic_encephalopathy (?s)
	Rule 2. Epilepsy_syndrome(?s) ∧ highRatioOfIntractableSeizure(?s,T) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧ hasCharacteristicEEG (?s,Suppression-burst_pattern_2) →Epileptic_encephalopathy (?s)
	Rule 3. Epilepsy_syndrome(?s) ∧ highRatioOfIntractableSeizure(?s,T) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧hasCharacteristicEEG(?s, Slow_spike-and-wave_lass_than_2.5_Hz) → Epileptic_encephalopathy (?s)
	Rule 4. Epilepsy_syndrome(?s) ∧ highRatioOfIntractableSeizure(?s,T) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧ hasCharacteristicEEG(?s, Generalized_spike-and-wave) →Epileptic_encephalopathy(?s)
	Rule 5. Epilepsy_syndrome(?s) ∧ highRatioOfIntractableSeizure (?s,T)∧highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧ hasCharacteristicEEG (?s, Hypsarrhythmia) → Epileptic_encephalopathy (?s)
Classified epileptic encephalopathy (broad definition)	Rule 1. Epilepsy_syndrome(?s) ∧ highRatioOfIntractableSeizure(?s, T) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧ hasCharacteristicEEG(?s, ?string) → Epileptic_encephalopathy(?s)

With Table 1, we can easily specify "childhood absence epilepsy", for example, to associate with the following characteristics: **hasOnsetAgePeriod** as childhood onset, **mondatorySeizurePattern** as absence seizures, hasCharacteristicEEG as generalized 3-Hz spike-and-wave discharges, and **hasProvokingFactorsOrDiurinalEffects** as hyperventilation. Those relationships are the core for OWL-DL and SWRL to reason/infer the possible diagnosis for the patient.

In Fig. 2, the task of the inference engine is to match facts to rules and make choices. The rules engine conducts tasks such as pattern matching, conflict resolution, and execution. Drools based on Rete algorithm is adopted in this research [30]. Drools was used as the inference engine for SWRL rules to infer the possible epilepsy syndromes and/or etiologies [16,30].

2.4. Use of SWRL in the auxiliary semantic description of the system

However, OWL-DL has limitations in describing the complexity of epilepsy ontology. The SWRL rules are defined and applied to process the aforementioned ontology, so they can infer the outcomes (e.g., possible syndrome) of a specific patient. Table 2 shows some examples of SWRL rules. Patients(?p) ∧ onestAgeYear(?p, ?y) ∧ swrlb:greaterThan(?y, 12) ∧ swrlb:lessThanOrEqual(?y, 100) → belongOnsetAgePeriod(?p, Adolescent_and_adulthood) indicates that the Patient (p) is with onsetAgeYear (y) and y is greater than 12 and y is less than 100. Then, the property belongOnsetAgePeriod will assign the class individuals (i.e., instance of the class) of Patient (p) as an individual of adolescent or adult to class Adolescent_and_adulthood. Note, ∧ is a symbol of "and", → is a symbol of "then", and ? is used to denote a variable. In addition, individual is a term in ontology for specifying an instance of a class.

Another example, Epilepsy syndrome(?s) ∧ highRatioOfIntractableSeizure (?s, T) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s, T) ∧ hasCharacteristicEEG(?s, ?string) → Epileptic_encephalopathy(?s) indicates that epilepsy syndrome(s) with high ratio of intractable seizure and high ratio of mental or learning or cognition problems and EEG with any characteristic is specified as epileptic encephalopathy.

3. System deployment

With the help of Protégé for building the knowledge bases, Fig. 3 shows the tree-like system architecture, which includes *epilepsy classifications*, *seizure classifications*, *epilepsy syndromes*, *epilepsy etiologies*, and *comorbidities*, etc. Specific descriptions of the system are as follows:

1. Detailed ontological classifications of epilepsy and seizure were summarized in Fig. 4.
2. For epilepsy syndromes, four groups classified by age at onset are as follows: neonatal/infantile epilepsy syndromes, childhood epilepsy syndromes, adolescent/adult epilepsy syndromes, and epilepsy syndromes with any age at onset (Fig. 5). Meanwhile, distinctive constellations for surgical syndromes were also included in Fig. 5.
3. For epilepsy etiologies, six subcategories, namely genetic, immune system-related, metabolism-related, infection-related, structural, and unknown factors were specified (Fig. 6; detailed subitems were included in Fig. S1 of the Supplementary materials).

Fig. 3. Main and detailed subclasses of epilepsy knowledge ontology. In the main classification section, classifications with red bottoms are crucial items proposed by the 2017 epilepsy diagnosis system.

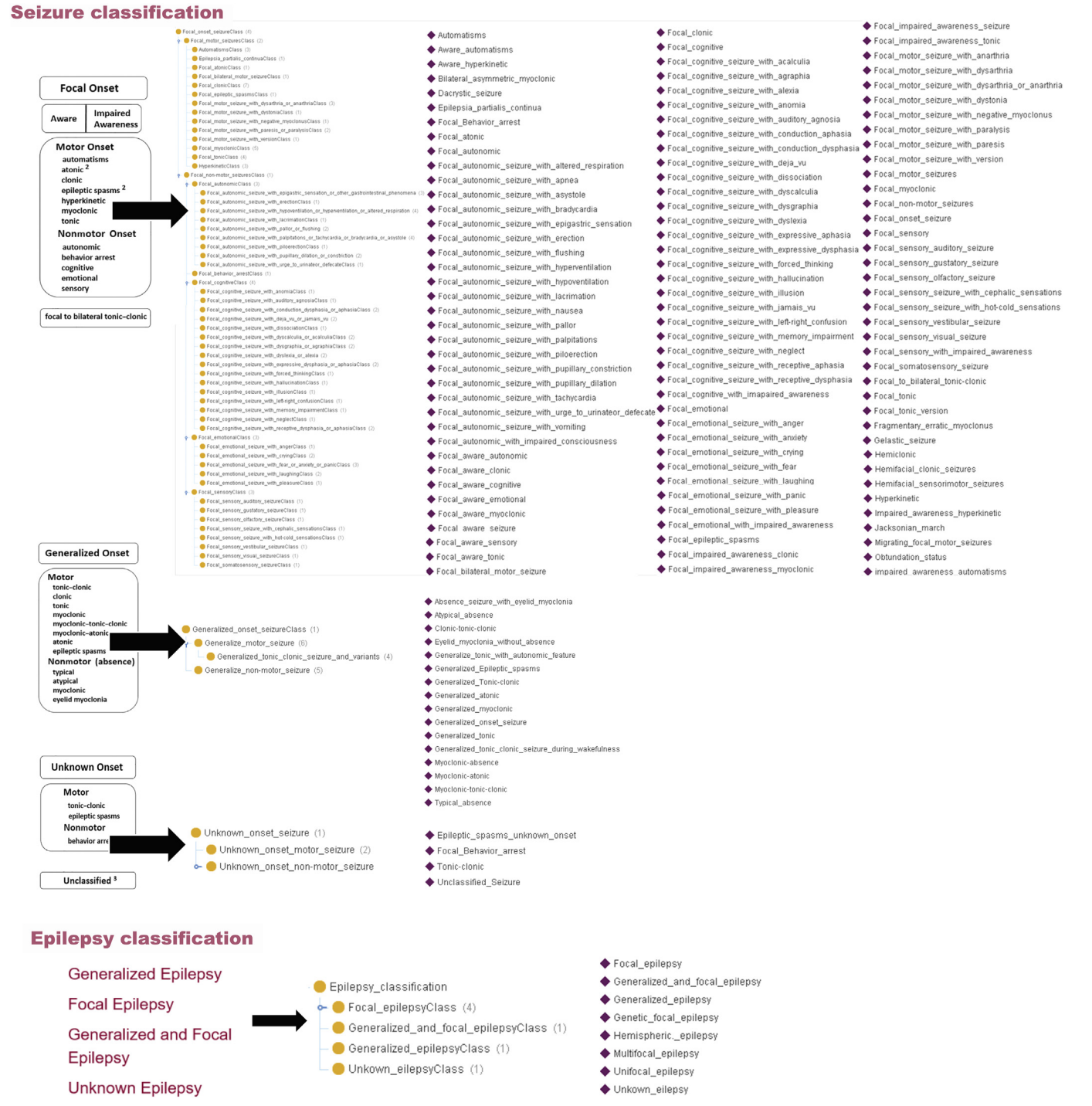

Fig. 4. Subclasses and individuals related to seizure and epilepsy classifications.

4. Comorbidities, EEG descriptors, and others can be referred to the Supplementary materials of this paper (Figs. S2–S9 of the Supplementary materials).

The complete epilepsy ontology built in this study contain 35,720 axioms (assertions of relationships for classes, individuals, and properties), 397 classes, 1744 individuals, 80 object properties, and 8368 subclass axioms. The screenshot of the axioms (arcs) and the most top classes (round rectangles) of the ontology is shown in Fig. 7.

An *individual* specifies a designated type of class, e.g., a focal aware tonic is an individual of the class of focal motor seizure. An *object property* specifies the associations between classes, e.g., a syndrome class uses **couldHasSeizurePattern** (object property) to associate itself with the potential seizure pattern classes. Our idea was to demonstrate the power of the OWL/SWRL approach in such a domain knowledge of healthcare by coding all necessary design rules to enable the system to deduce epilepsy syndrome or infer the etiologies.

4. Results (applications of the AI system)

4.1. Implementing epilepsy syndromes (illustrated by Dravet syndrome)

It is necessary to specify each syndrome by its associations with the class individuals of the 15 components in Table 1. Dravet syndrome was

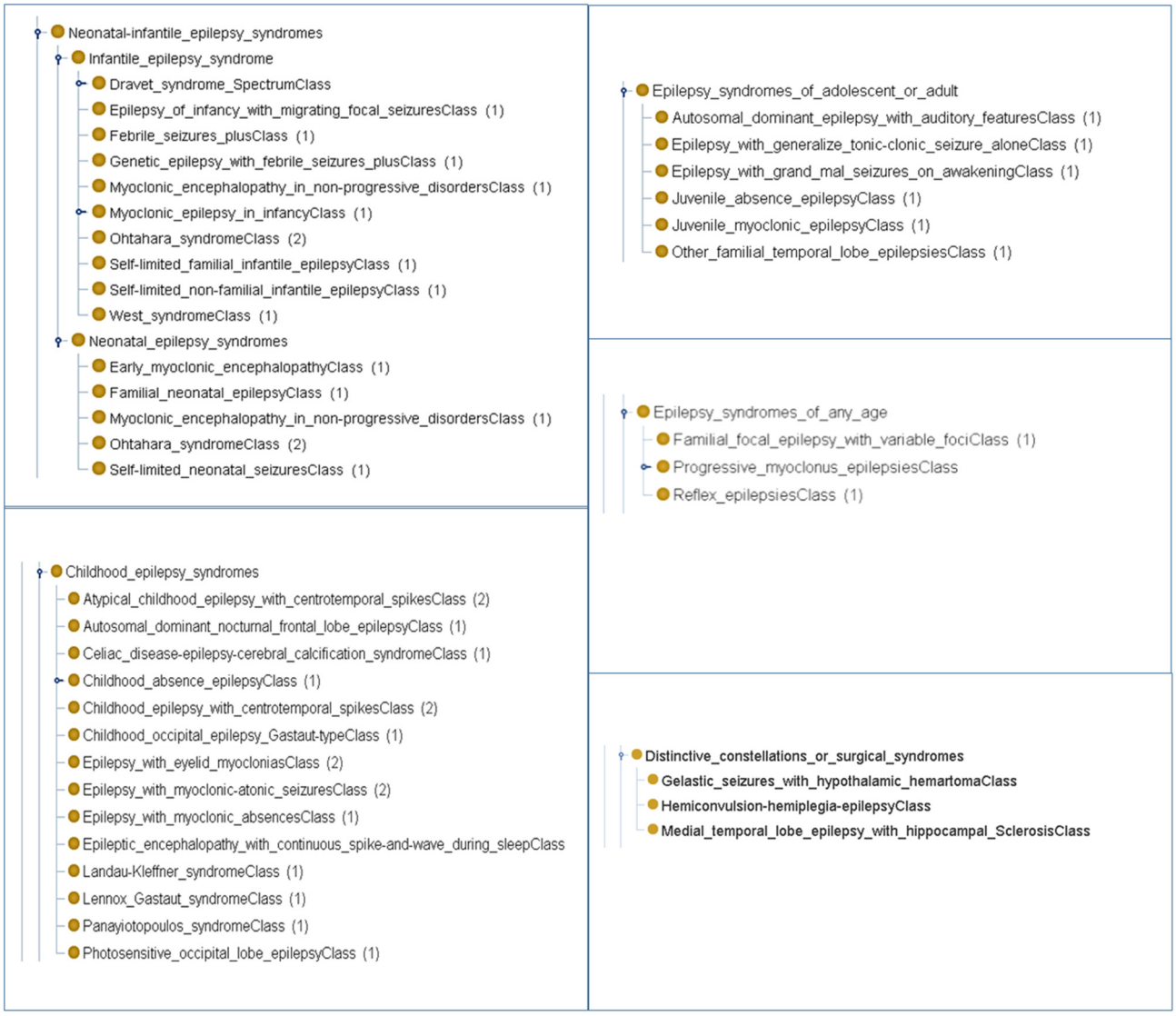

Fig. 5. Classification of epilepsy syndrome in this study.

taken as an example to show the implementation. Fig. 8 shows the interface for entering the components of Dravet syndrome. The following clinical information is included and specified in the figure:

(1) The seizure onset is usually in infancy.
(2) The etiology is related to genetic problems (especially SCN1A).
(3) Mandatory seizure types include hemiclonic seizure, focal impaired awareness seizure, clonic–tonic–clonic seizures, and generalized tonic–clonic seizures. Typical "may have" seizure types include obtundation status, complex febrile seizure, Non-Convulsive Status Epilepticus (NCSE), and myoclonic seizures in childhood. Dravet syndrome's exclusionary seizure type is epileptic spasms. In addition, within less than 12 months of initial onset, status epilepticus or prolonged seizures are important features of Dravet syndrome.
(4) In epilepsy class, it is specified as "focal and generalized epilepsy".
(5) Common comorbidities are cognitive problems, cognitive deterioration, speech impairment, photosensitivity, ataxia, tremor, and crouch gait afterwards.
(6) Electroencephalographic characteristics may reveal multiple focal discharges and generalized spikes and waves.
(7) The brain image is generally normal initially, though some patients exhibit bilateral hippocampus atrophy later.
(8) Provoking factors include infection, fever, photosensitivity, an increase in body temperature, and gross motor activity or exertion.
(9) Patients of this syndrome have high frequency and long duration of seizures.
(10) In terms of seizure measurement and disease condition, it is intractable and is not self-limited.
(11) Family history of the patients sometimes reveals epilepsy and/or febrile seizures.

4.2. A case study example

In order for readers to understand the inference process, we take the data of a Dravet syndrome case as an illustration. This was an 18-year-old boy. He started his first complex febrile seizure at the age of 7 months. Since then, he had had seizures several times, most of which were provoked by fever or infection. His seizure frequency gradually increased after one year old. At its worst, he was hospitalized 2–3 times a month. At that time, the seizure patterns included focal clonic seizure, hemiclonic seizure, complex febrile seizure, generalized tonic–clonic seizure, and focal to bilateral tonic–clonic seizure. Many of these seizures are prolonged seizures. After two years of age, he began to develop other seizure patterns, including myoclonic seizures, atonic seizure, and atypical absence. The EEG taken before age of one

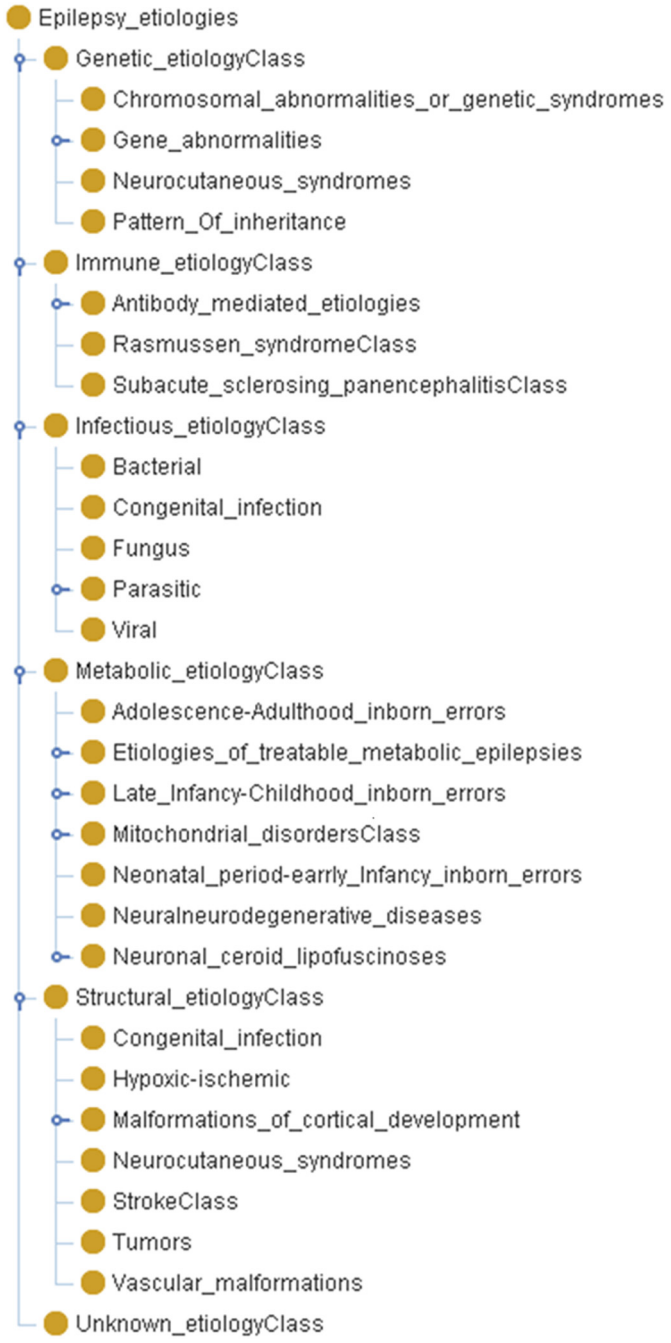

Fig. 6. Etiological classification of epilepsy in this study.

year showed no obvious epileptiform discharge except discontinuous symmetrical background. However, when focal clonic seizures or hemiclonic seizures were developed, focal or multifocal sharp or spike slow wave activities had appeared in his later EEGs. Additionally, when myoclonic seizures, atonic, and atypical absence were developed, there were interictal generalized spike–wave discharges or multiple spike–wave discharges, intermittently appearing in the diffuse slow background activity. Although the frequency of seizures has decreased, since the age of 5, he has experienced significant psychomotor retardation, including cognitive delay, mild mental retardation, articulation problems, ataxia, and tremor. Later, crouch gait was developed after puberty. The initial brain magnetic resonance (MR) images showed no obvious abnormality. However, it revealed significant right hippocampal atrophy in his late childhood. Tracing his family history, one of his uncle and an older female cousin of father side had febrile seizure history, and his uncle developed epilepsy later but not severe. He was arranged a genetic study at the age of 10. The whole exon sequencing proved he was a case of SCN1A missense mutation, c.2807A > T (p.Asp936Val).

4.3. System interface of the AI system for physicians

Most epilepsy experts agree that the most crucial factors in the diagnosis of epilepsy syndromes are age at seizure onset, seizure types, and EEG characteristics. Other related attributes include family history of epilepsy, history of febrile seizure, frequency of seizures, factors of provoking, whether the epilepsy is intractable, whether cognitive and learning problems are present, whether brain images are abnormal, and whether special comorbidities are present. We designed an interface for the epileptologists to enter the various characteristics of the patient. The design of the interface and the input data of the case example in Section 4.2 is showed in Fig. 9.

We set SWRL rules for the system to automatically infer logic of certain epilepsy syndromes and took simulated patient data as an example to reveal the inference logic and process. A complete version of the SWRL rules for deducing epilepsy syndromes was developed in supplemental Table 1 of the Supplementary materials. A SWRL rule collects the required attributes and make a reason to deduce the syndrome. The following rule is an example that considers 21 attributes simultaneously to deduce the syndrome:

Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ mondatorySeizurePattern(?s, ?sp) ∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs) ∧ highFrequencyOfSeizure (?p, ?fz) ∧ highFrequencyOfSeizure (?s,?fz) ∧ intractableSeizure (?p, ?iz) ∧ highRatioOfIntractableSeizure (?s,?iz) ∧ hasMentalOrLearningOrCognitionProblem(?p, ?mc) ∧ highRatioOfMentalOrLearningOrCognitionProblem(?s,?mc) ∧ hasComorbidityOrOtherDisease (?p, ?cb) ∧ hasComorbiditiyOrSequela (?s,?cb) ∧ asAbnormalEEG(?p, ?e) ∧ hasCharacteristicEEG(?s, ?e) ∧ abnormalBrainImage (?p, ?im) ∧ highRatioOfBrainImageAbnormality (?s,?im) ∧ provokedOrDiurnalTendency (?p, ?pd) ∧ hasProvokingFactorsOrDiurinalEffects (?s, ?pd) ∧ Epilepsy_syndrome(?s)epossibleDiagnosis(?p, ?s)

Table 3 shows how the 18-year-old patient was gradually deduced to a case of Dravet syndrome. Starting from “Onset age period”, a large number of syndromes was suggested on the Result column of the table. When the physician continued inputting the attributes of the simulated patient (Seizure Pattern, Family History, etc.), the number of the differential diagnosis of epilepsy syndromes is decreasing. In Table 3, it indicated when intractable seizure was identified; the AI system suggested the patient has a high possibility to be a case of Dravet syndrome. As long as the physician entered more characteristics, such as having cognitive problem or not, characteristics of EEG, and others, the conclusion will be more ascertained. It is noted that the sequence for the physicians to enter the attributes into the AI system is not limited. The recommendations from the AI system are based on the given characteristics each time.

Based on the characteristics of the 18-year-old boy in Section 4.2, the AI system deduced a conclusion of Dravet syndrome for the patient with epilepsy afterwards. Note that the lower right four red windows in Fig. 9 (empty before reasoning) will show the inferencing results of possible diagnosis, accompanying with optimized treatments, possible genetic problem, and possible etiology.

5. Discussion

The common ontological field applications include AI, semantic web, software engineering, biomedical informatics, healthcare and

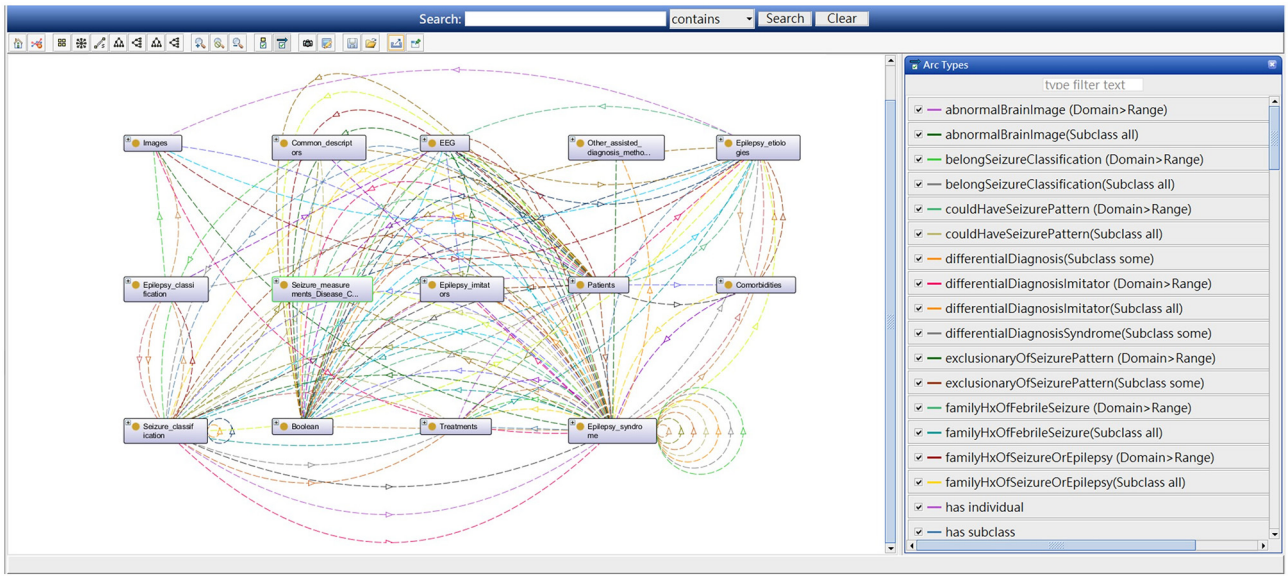

Fig. 7. A screenshot of the axioms (arcs) and the most top classes (round rectangles) of the ontology.

administration, library science, and information architecture [8,31,32]. Nowadays, enormous genetic and clinical data are considered for epilepsy diagnosis. However, because the data are far beyond the cognitive load of humans, it is becoming more difficult to perform accurate determination of complex compositions of epilepsy diagnoses. Ontology can simulate the concept of classification of human knowledge by realizing fast semantic search with high-precision reasoning and excellent scalability. Therefore, the numbers of ontology- and precision-based medical studies are increasing [12,33–35].

In addition, the flexibility of the knowledge base and the reusable nature of ontology allow different decision support systems to share knowledge of specific domains through ontological exchanges. García-Crespo et al. [36] proposed an ontology-driven medical diagnostic expert system, termed ODDIN, which uses ontology to represent specific structural messages, calculate the probability of various factors, and logically consider patients' signs and symptoms. ODDIN has also been applied as a decision-making tool for medical staff and student training [36].

Sahoo et al. [10,37] proposed an appreciated ontology-driven infrastructure for epilepsy and seizures based on the 2010 ILAE version. However, the recent development of the 2017 ILAE version, which referred epilepsy syndromes with clinical characteristics and electrical features, and informs etiology categories, urged the development of this research.

The diagnosis of epilepsy is based on the estimation of different parameters to deduce the most likely cause or syndrome. The advantage of SWRL applying in the epilepsy diagnosis is that it allows us to build not only for reasoning syndromes with complicated indications, but also for syndromes with fewer features. For example, if the only type of seizure is epileptic spasm and the first seizure occurs when the patient is younger than 1.5 years old, we will consider the possibility of the patient having West syndrome. For another example, an early childhood onset seizure with myoclonic–atonic seizure should be considered Doose syndrome. Those syndromes with few features can be implemented with SWRL with little effort.

Ontology is an enhanced expert system developed according to the expert thinking inference method. The purpose of the AI system is to

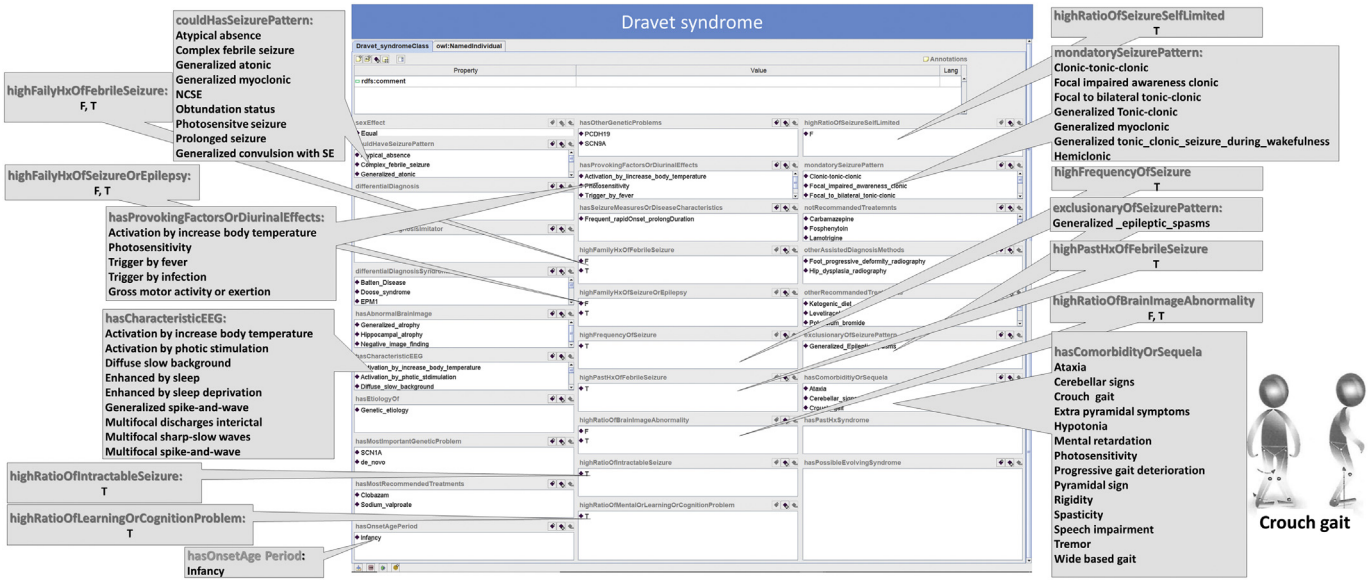

Fig. 8. Visual interface of all necessary information for Dravet syndrome.

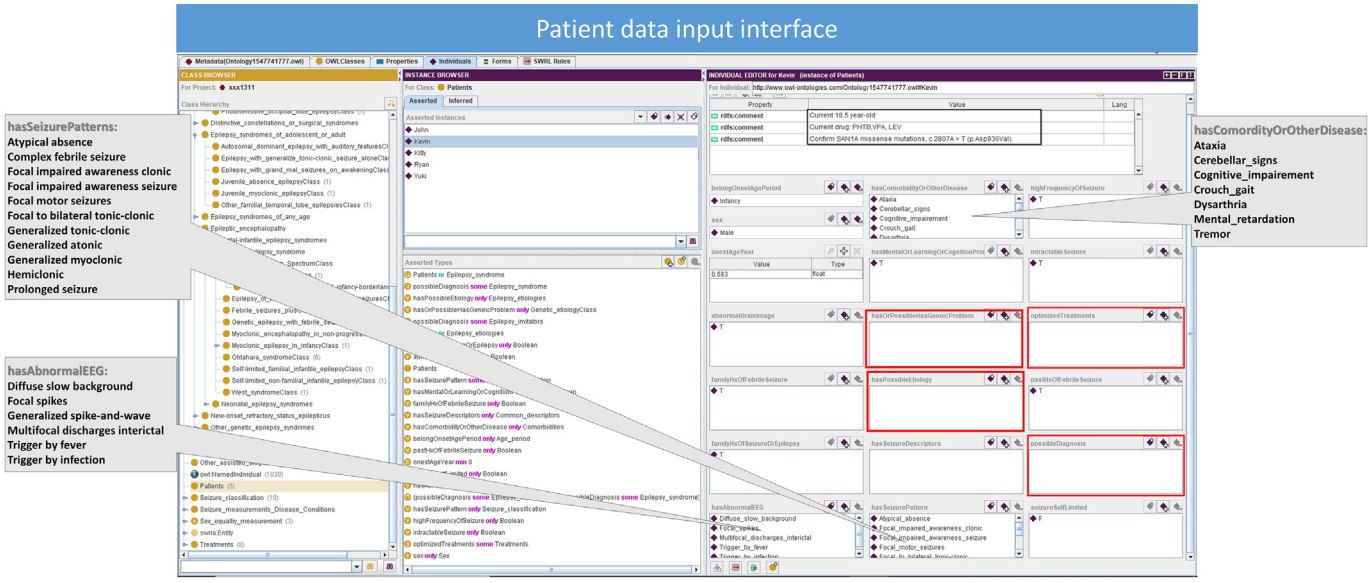

Fig. 9. Interface for inputting the patient data of the 18-year-old case example. The lower right four red windows (empty before reasoning) will show the reasoning results of possible diagnosis, accompanying with optimized treatments, possible genetic problem, and possible etiology.

mimic the expert physicians' diagnosis process. Drools is the inference engine that plays the role of brain reasoning in our AI system. Therefore, the available patient characteristics as inputs to the AI system should produce the results of a diagnosis similar to what the expert physicians could produce.

Most epileptologists would think that their sufficient experience and efforts, coupled with the Google search engine, seem to be sufficient to meet clinical needs, and they doubt whether it is necessary to build an expert diagnosis system for epilepsy. However, as epilepsy classification is increasingly difficult for physicians to remember, and new genes associated with various syndromes arise frequently, the AI system supporting the physicians in diagnosis is clinically valuable. Besides, the AI system is not a static system; it allows epileptologists to expand the knowledge base based on their clinical and professional experiences.

Taking Dravet syndrome as an example, at least 80% of the patients are considered to be related to SCN1A gene mutations [38]. Most of the mutations are nonsense mutations, frameshift mutations, deletions, amplifications, or duplications [38,39]. Since most of the SCN1A mutation cases are de novo mutations, if we follow the cases of SCN1A mutations with different genetic mutation statuses for a long period of time to track their severity of epilepsy, EEG features, utilization of antiepileptic drugs, quality of life, outcomes, and comorbidities, we speculate that there may be significant differences in the above characteristics among the patients. Research by de Lange et al. [40] also addressed the issue in their findings.

The literature reports that cases with negative SCN1A mutation gene tests may have mutations in genes such as SCN2A, SCN8A, SCN9A, SCN1B, PCDH19, GABRA1, GABRG2, STXBP1, HCN1, CHD2, and KCNA2 [41]. With the widespread use of next-generation gene sequencing, the clinical and EEG features of these non-SCN1A mutation Dravet syndrome-like phenotypes should be redescribed. If the data of these patients can be compiled based on the current propositional system, we will be able to develop a more precise classification system for Dravet syndrome and its mimics.

The purpose of the illustrated case is to show the whole picture on disease progress of the patient with typical Dravet syndrome. The child was clinically suspected of Dravet syndrome at age 5 and confirmed diagnosis at age 10. However, for each new case of Dravet syndrome, we believe that with the recommendation of the AI system, a doctor can make an earlier diagnosis by reliably narrowing down the differential diagnosis, when the patient developed typical seizure types, EEG patterns, speech delay, and psychomotor retardation.

Electroencephalography is an important basis for the diagnosis of epilepsy syndromes, but EEG descriptors have not yet been completely unified. Even if epileptologists judge the results to be the same, they may choose different descriptors. Our ontological system provides a vehicle to unify the expert consensus on the EEG descriptors.

There are several limitations in our propositional AI system. First, any system like this would need to be properly updated and maintained, with any data stored for AI learning properly de-identified for the patient's privacy. Second, many more sample test cases would need to be run, particularly in difficult-to-diagnose cases such as more borderline cases of Dravet syndrome, Lennox–Gastaut syndrome, and idiopathic epilepsies, which remain the most difficult for physicians to confidently diagnose. Third, the AI system does not consider how incorrect information affects the accuracy of the AI system.

However, for ambiguous characteristics, Protégé has a tolerance. It allows us to build the epilepsy syndromes with multiple similar or even opposite characteristics. For example, an MR image of Dravet syndrome could exist simultaneously with “normal” and “unilateral hippocampal atrophy”. Another example is that we designed the inference of Dravet syndrome that could result from patients with or without a family history of epilepsy and/or febrile seizures, because only around 30–50% of patients with Dravet syndrome have a family history of epilepsy and/or febrile seizures [7]. Table S1 of the Supplementary materials is a complete version of the process of deducing epilepsy syndrome for the example case. In contrast, Table S2 is the result under the assumption that the example case does not have a family history of epilepsy or febrile seizures. They both deduced a Dravet diagnosis.

Future studies might consider combining the use of natural language programs to alleviate the amount of work hours spent on building the knowledge base and to make it easier to use the system [10,42–45]. Moreover, this system can be combined with other AI technologies such as a cyber-physical system, neural network, and deep learning network [9] to perform epilepsy-related cross-domain information integration and collaboration. Besides, to gain empirical evidences from applying the ontological expert system, we also expect that the system will accommodate more findings on the epilepsy diagnosis and treatments in the future.

Table 3
SWRL rules for inferring possible epilepsy diagnoses and the excerpted diagnostic inference process of the case example (the complete inference process is shown in Table S1).

Attributes	SWRL rule	Results
Onset age period	1. Patients(?p) **∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s)	Batten disease, Dravet syndrome, EIEE1, EIEE7, EIEE8, EIEE29, early infantile epileptic encephalopathy, epilepsy in infancy with migrating focal seizures, febrile seizures plus, genetic epilepsy with febrile seizures plus, herpes simplex encephalitis, myoclonic encephalopathy in nonprogressive disorders, myoclonic epilepsy in infancy, myoclonic epilepsy in infancy with GTCS after adolescence, myoclonic epilepsy with neuronal ceroid lipofuscinosis, Ohtahara syndrome, progressive myoclonus epilepsy, SMEB, self-limited familial infantile epilepsy, self-limited nonfamilial infantile epilepsy, and West syndrome
Seizure types	2.1. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) **∧ hasSeizurePattern(?p, ?sp) ∧ mondatorySeizurePattern(?s, ?sp)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s) 2.2. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) **∧ hasSeizurePattern(?p, ?sp) ∧ couldHaveSeizurePattern(?s, ?sp)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s)	Batten disease, Dravet syndrome, infant epilepsy with migrating focal seizures, febrile seizures plus, genetic epilepsy with febrile seizures plus, herpes simplex encephalitis, myoclonic encephalopathy in nonprogressive disorders, myoclonic epilepsy in infancy, myoclonic epilepsy in infancy with GTCS after adolescence, myoclonic epilepsy with neuronal ceroid lipofuscinosis, progressive myoclonus epilepsy, and SMEB
Family history of febrile seizure	3.1. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ mondatorySeizurePattern(?s, ?sp) **∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s) 3.2. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ CouldHaveSeizurePattern(?s, ?sp) **∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s)	Dravet syndrome, genetic epilepsy with febrile seizures plus, myoclonic epilepsy in infancy, myoclonic epilepsy in infancy with GTCS after adolescence, and SMEB
High frequency of seizure	4.1. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ mondatorySeizurePattern(?s, ?sp) ∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs) **∧ highFrequencyOfSeizure (?p, ?fz) ∧ highFrequencyOfSeizure (?s,?fz)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s) 4.2. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ couldHaveSeizurePattern(?s, ?sp) ∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs) **∧ highFrequencyOfSeizure (?p, ?fz) ∧ highFrequencyOfSeizure (?s,?fz)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s)	Dravet syndrome, genetic epilepsy with febrile seizures plus, and SMEB
Intractable seizure	5.1. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ mondatorySeizurePattern(?s, ?sp) ∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs) ∧ highFrequencyOfSeizure (?p, ?fz) ∧ highFrequencyOfSeizure (?s,?fz) **∧ intractableSeizure (?p, ?iz) ∧ highRatioOfIntractableSeizure (?s,?iz)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s) 5.2. Patients(?p) ∧ belongOnsetAgePeriod(?p, ?q) ∧ hasOnsetAgePeriod(?s, ?q) ∧ hasSeizurePattern(?p, ?sp) ∧ couldHaveSeizurePattern(?s, ?sp) ∧ familyHxOfFebrileSeizure(?p, ?fs) ∧ highFamilyHxOfFebrileSeizure(?s, ?fs) ∧ highFrequencyOfSeizure (?p, ?fz) ∧ highFrequencyOfSeizure (?s,?fz) **∧ intractableSeizure (?p, ?iz) ∧ highRatioOfIntractableSeizure (?s,?iz)** ∧ Epilepsy_syndrome(?s) → possibleDiagnosis(?p, ?s)	Dravet syndrome

Note: 1. SMEB: severe myoclonic epilepsy of infancy-borderland, 2. GTCS: generalized tonic–clonic seizure

6. Conclusions

We constructed a propositional AI system based on the new ILAE epilepsy diagnostic framework and the most updated epilepsy-related etiology data. We also built complete information on each epilepsy syndrome. The OWL-DL and SWRL can help reorganize and ascertain possible epilepsy syndromes. Through the current system and inference engine application, diagnoses of epilepsy syndromes were inferred from relevant information and parameters of patients with epilepsy.

The current system version was completed in about six months since the system framework was determined by our interdisciplinary team (epileptologists and engineers). Fig. 7 showed the most top level of the system framework. The framework guided the construction of the following tasks for six months: knowledge base construction, the connection between classes and attributes, each epilepsy syndrome implementation, and the inference rules. Based on our developing experiences, to develop an AI system for supporting medical diagnosis, it must include team members with medical and knowledge engineering professions to complete the aforementioned system framework and tasks. As soon as the system was constructed completely, a physician can input each patient's information into the AI system within 2 h by himself/herself. As for the future research, a further improved user-friendly interface for physicians is needed and presumably will largely reduce the time to input the patient's information.

Finally, the AI system can become an excellent teaching tool for the diagnosis of epilepsy and a platform that is suitable for guiding stakeholders on the integration of resources related to the diagnosis and treatment of epilepsy. The developing experience of this system provides a good illustration for the development of AI healthcare systems for other diseases.

Author contributions

Kuo-Liang Chiang conceived, designed, and constructed this expert system and database, established rules related to diagnostic inference, prepared figures and tables, and authored the initial draft.

Chin-Yin Huang assisted in the design of this expert system and database, revised the rules related to diagnostic reasoning, and reviewed and approved the final draft.

Liang-Po Hsieh, as an expert consultant, he guided the design of the knowledge base construction, the connection between categories and attributes, and the inference rules.

Kai-Ping Chang, as an expert consultant, he guided the design of the knowledge base construction, the connection between categories and attributes, and the inference rules.

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Declaration of competing interest

The author has no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107021.

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