The EuroBiotech Journal
RESEARCH ARTICLE
Bioinformatics

ClioMD: An artificial intelligence model for ciliopathies

Mahmut Çerkez Ergören[1,*],Niyazi Senturk[2], Manal Salah B. Ali[1], İlkem Özce Özcelik[1], Kübra Damla Erol[1], Sehime Gulsun Temel[3,4], Munis Dundar[5]

Abstract

Cilia are highly specialized cellular organelles that serve multiple functions in human development and health. Their central importance in the body is demonstrated by the emergence of various developmental disorders resulting from defects in cilia structure and function caused by different inherited mutations in more than 150 different genes. Genomic analysis has rapidly improved our understanding of ciliopathies' intracellular molecular biological basis over the past two decades, and new technological advances have accelerated this progress. However, most of the time, in correlation of phenotypic results with genetic variation and environmental factors, patient phenotypes do not match with the thought disease despite being a basic search in genomic medicine, candidate variants are in genes not characterized by disease, and model organisms are insufficient to explain the disease, many obstacles continue to hinder rapid and accurate diagnosis. Using advanced computing tools, artificial intelligence models can phenotypically identify overlapping disease models, such as ciliopathies, in research and diagnostic contexts. Large-scale integration of model organisms and clinical trial data can provide a wealth of knowledge unavailable in individual sources and contextualize data back to these sources. In this context, with the machine learning platform we designed, ClioMD, a program that is compatible with the HPO guideline, OMIM, GeneCards, and ClinVar databases, provides treatment and genetic counseling recommendations online in English, enabling individuals affected by ciliopathies such as Joubert syndrome, Cornelia de Lange, Bardetp Biedl syndrome, etc. to get a fast and accurate diagnosis. In conclusion, the ClioMD platform enables you to explore the relationship between phenotype and genotype for disease and as a tool to help you make an accurate diagnosis.

Keywords: Ciliopathy; machine learning; fuzzy logic, artificial intelligence

Introduction

A Over the past two decades, Artificial Intelligence (AI) has been widely used in medicine through risk assessment models and increasing diagnostic accuracy and workflow efficiency [1]. AI models are expected to be used in advanced computing tools and in identifying phenotypically overlapping disease models in research, especially in diagnostic contexts. Fuzzy logic has been applied in medicine in several areas, such as decision-support systems, developments of tools for risk assessment, and diagnostic approaches for overlapping disorders such as ciliopathy. Fuzzy logic involves defuzzification techniques, rule-based systems, and membership functions to process unclear inputs. Due to these characteristics, it's considered an ideal approach to address the diagnostic difficulties brought by complicated diseases [2]. Large-scale integration of models and clinical trial data might provide a wealth of knowledge that is not available in individual sources and contextualize this data back to these sources.

Cilia are highly specialized cellular organelles that serve multiple functions in human development and health. Their central importance in the body is demonstrated by the emergence of various developmental disorders resulting from defects in cilia structure and function caused by several inherited mutations in more than 150 different genes [3]. Ciliopathies are a class of genetic multisystemic disorders that affect ciliary structure

[1] Department of Medical Genetics, Faculty of Medicine, Near East University, Nicosia 99138, Cyprus
[2] Department of Biomedical Engineering, Faculty of Engineering, Near East University, Nicosia 99138, Cyprus
[3] Department of Medical Genetics, Faculty of Medicine, Bursa Uludag University, Bursa 16059, Turkey
[4] Department of Translational Medicine, Institute of Health Science, Bursa Uludag University, Bursa 16059, Turkey
[5] Department of Medical Genetics, Faculty of Medicine, Erciyes University, Kayseri 38000, Turkey

***Corresponding author:**
Assoc. Prof. M.C. Ergoren, PhD
Near East University, Faculty of Medicine,
Department of Medical Genetics, 99138 Nicosia, Cyprus.
E-mail address: mahmutcerkez.ergoren@neu.edu.tr

DOI: 10.2478/ebtj-2025-0011

and function [4], such as Bardet-biedl syndrome, Joubert syndrome, Meckel-Gruber syndrome, primary ciliary dyskinesia, Alstom syndrome, senior Loken syndrome, polycystic kidney disease, nephronophthisis, and orofaciodigital syndrome.

Bardet-Biedl syndrome (BBS) is characterized by obesity, retinal dystrophy, polydactyly, renal malformations, mental retardation, and hypogonadism [5]. Joubert syndrome (JS) is a combination of brain anomalies caused by abnormal developments in the "cerebellar vermis" and brain stem, called the molar tooth sign. Hypotonia causing ataxia; hyperpnea and apnea causing breathing problems; abnormal eye findings, ocular motor apraxia; general learning disability, mental retardation, and developmental delay are observed [6,7].

Meckel-Gruber syndrome (MGS) is a disease characterized by multiple cysts in the kidneys, occipital encephalocele, dandy-walker malformation, and polydactyly. The most common central nervous system anomaly associated with MGS is the occipital encephalocele. Affected children may have ocular abnormalities such as microphthalmia, optic nerve hypoplasia, or coloboma. Polycystic kidney dysplasia is the most common symptom of the MGS [8,9].

Primary ciliary dyskinesia causes inflammation and recurrent infections in the upper and lower airways. It progresses with unexplained breathing difficulties, cough, and atelectasis since birth. Complex cardiac abnormalities, recurrent respiratory tract infections with situs inversus, bronchiectasis of unknown etiology, and infertility are the main clinical symptoms. Many congenital anomalies may accompany primary ciliary dyskinesia. These include transposition of great vessels, heterotaxy, cardiac anomalies, pyloric stenosis, epispadias, pectus excavatum, and scoliosis [10,11].

The clinical presentation of Alström syndrome (AS) varies and might be patient-specific. During its clinical course, defects in cone and rod cell growth and various eye diseases, such as cataracts, photophobia, nystagmus, limited visual field, bilateral sensorineural hearing loss, along with chronic otitis media, dilated cardiomyopathy, and congestive heart failure, may occur. Hyperinsulinemia, hyperlipidemia, liver fat accumulation, short stature, advanced bone age, kyphosis, scoliosis, acanthosis nigricans, hypogonadism, and gynecomastia can also be present in affected individuals [12].

Although polycystic kidney disease (PKD) involves multiple organ systems, it primarily affects the kidneys and liver. Common complications of PKD include hypertension, hematuria, and recurrent urinary tract infections. PKD increases the risk of aneurysm in the aorta. Although the severity of the disease varies among individuals, it can result in death. Some affected children develop end-stage renal disease within the first decade of life, while others may remain asymptomatic until puberty or adulthood [13].

Nephronophthisis is a clinical condition caused by autosomal recessive cystic kidney disease. Patients may have polyuria, polydipsia, nephritis, and chronic renal failure. In some cases, patients may also exhibit extrarenal defects, such as visual impairment due to retinitis pigmentosa, scoliosis, polydactyly, cerebral ataxia, hypotonia, severe developmental delay, hepatosplenomegaly, and situs inversus can be seen [14]. Senior Loken syndrome (SKS) represents a combination of retinitis pigmentosa and nephronophthisis [15]. Oral-facial-digital syndrome (OFDS) manifests clinically with an abnormality in the development of the jaw, teeth, face, fingers, and toes. Abnormalities in the fingers include syndactyly, brachydactyly, clinodactyly, polydactyly, or a combination of these. The most well-known type of OFDS is associated with OFD-I and polycystic kidney disease. Other types of OFDS may also present with neurological problems, specific structural changes in the brain, bone abnormalities, vision loss, and heart conditions [16].

Materials and Methods

2.1 Data Collection

One hundred and sixty-five subgroups of nine major ciliopathies have been classified in this study including twenty-two subgroups of Bardet-Biedl syndrome, thirty-nine of Joubert syndrome, eight of Senior Loken's syndrome, six of polycystic kidney disease, thirteen of Meckel-Gruber syndrome, fourteen of nephronophthisis syndrome, forty-six of primary ciliary dyskinesia, sixteen subgroups of orofaciodigital syndrome and Alstrom syndrome. Syndromes were segregated by name, OMIM number, and phenotype series, the inheritance patterns on a molecular basis derived from the human phenotype ontology. On a molecular basis, chromosomal location and related gene information from OMIM, GeneCards, and ClinVar databases were used to ensure comprehensive coverage of gene-related information. The Human Phenotype Ontology nomenclature was used to determine the clinical symptoms such as the abdomen, blood and blood-forming tissue, breast, cardiovascular system, connective tissue, ear, endocrine system, eye, growth, genitourinary system, immune system, integument, head, limbs, metabolism and homeostasis, musculature, neck, nervous system, prenatal development or birth, respiratory system, skeletal system, thoracic cavity, voice, and neoplasm all documented. All these data were tabulated in Excel for each disease and used to develop MATLAB and fuzzy logic system.

2.2 MATLAB and Fuzzy Logic System

MATLAB is a multiple-paradigm digital computing software (R2018a) and a fourth-generation programming language. In this study, fuzzy logic-based artificial intelligence models were developed on this platform using Mamdani's fuzzy inference [17] and Sugeno's inference methods [18].

Five main steps were used to develop models. First, the fuzzification of inputs. Then, rule values were determined by using fuzzy logic operations. Third, the implementation of fuzzy cluster logical processors as "and/or." Fourth, the collection of results. In this step, the combination of fuzzy clusters was represented as the output of each rule. Lastly, defuzzification, where the system clarified the total fuzzy cluster results and converted them into a single number.

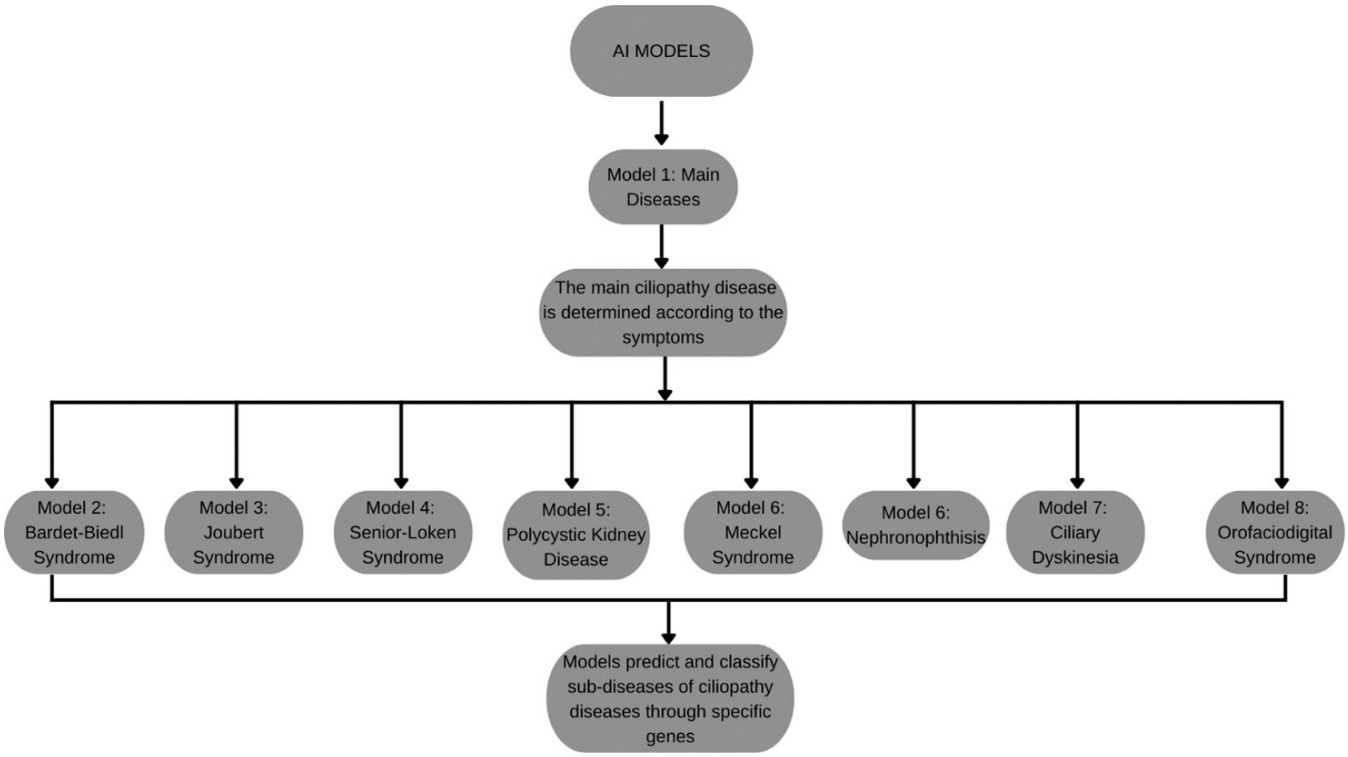

Figure 1. Flowchart of AI models based on Fuzzy Logic System on MATLAB.

2.3 Mamdani's Fuzzy Inference Method

The basis of the fuzzy logic system is the creation of a model that can think and make decisions by using data in input clusters. A total of nine fuzzy logic models were developed. The first model was designed to predict nine different ciliopathy diseases using symptom regions as an input cluster. Our system was developed with 22 input values from the dataset of nine main Chiliopathy-associated genetic diseases. We defined 22 different body areas where symptoms occur as input clusters, which include the abdomen, Blood and blood-forming tissues, breast, cardiovascular system, ear, endocrine system, eye, growth, genitourinary system, immune system, integument, head, limbs, metabolism, musculature, neck, nervous system, prenatal development, respiratory system, skeletal, thoracic cavity, and neoplasm. One output attribute with nine features: Bardet-Biedl syndrome, Joubert syndrome, Senior-Loken syndrome, Polycystic Kidney Disease, Meckel syndrome, Nephronophthisis, Ciliary dyskinesia, and Orofaciodigital syndrome. Fuzzification was structured in triangular and trapezoidal membership functions. A Membership Function (MF) is a continuous curve that defines the degree of any numerical variable. The degree of membership ranges between 0 and 1. Implementation of the Mamdani inference system was made with a rule-based system of nine rules using if-then statements. The system was characterized by these statements using logical combinations of inputs with an 'AND' operator [19]. The Centroid technique was used for defuzzification and yielded a 99.9% accuracy.

2.4 Sugeno's Fuzzy Inference Method

In the remaining eight models, specific genes were used as the input cluster to predict the sub-diseases of the main ciliopathy diseases identified in the first model. These main diseases are Bardet-Biedl syndrome, Joubert syndrome, Senior-Loken syndrome, Polycystic Kidney Disease, Meckel syndrome, Nephronophthisis, Ciliary dyskinesia, and Orofaciodigital syndrome, were identified as outputs in the first model (Figure 1). Fuzzifications were structured in triangular membership functions. Implementation of the Sugeno inference system was made with a rule-based system using if-then statements. The systems were characterized by these statements using logical combinations of inputs with an AND operator. The Centroid technique was used for defuzzification and yielded a 99.9% accuracy from all AI models.

Results and Discussion

3.1 Generating Fuzzy Logic Systems on the MATLAB

In AI model one, twenty-two different symptom regions were determined for each main ciliopathy disease. Each region was divided into sub-groups known as membership functions. Membership functions of each symptom region for a fuzzy logic model are shown in (Table 1).

As it is crucial to train the complete data to all models, fuzzy logic, which includes input, rules, and output sections, was generated on MATLAB.

A total of 23 different membership functions were generated from 23 different input clusters for each specific gene associat-

Table 1. The values of the membership functions for each input cluster (Regions) in AI model one.

Input Clusters (Regions)	Membership Functions	Values [0,1]
Abdomen	No	0
	Yes	1
Blood and Blood-Forming Tissues	No	0
	Yes	1
Breast	No	0
	Yes	1
Cardiovascular System	No	0
	Yes	1
Ear	No	0
	Yes	1
Endocrine System	No	0
	Yes	1
Eye	No	0
	Yes	1
Growth	No	0
	Yes	1
Genitourinary System	No	0
	Yes	1
Immune System	No	0
	Yes	1
Integument	No	0
	Yes	1
Head	No	0
	Yes	1
Limbs	No	0
	Yes	1
Metabolism	No	0
	Yes	1
Musculature	No	0
	Yes	1
Neck	No	0
	Yes	1
Nervous System	No	0
	Yes	1
Prenatal Develop	No	0
	Yes	1
Respiratory System	No	0
	Yes	1
Skeletal	No	0
	Yes	1
Thoracic Cavity	No	0
	Yes	1
Neoplasm	No	0
	Yes	1

ed with the related sub-ciliopathy disease, moreover, Specific genes associated with sub-diseases within nine different main ciliopathy diseases identified were defined for each model with the various number of input clusters (Table 2).

Each specific related gene was defined as a different rule, which yielded a system with different perspectives and possibilities by evaluating various numbers of different data to give more accurate and sensitive results in each model. For example, the fuzzy logic rules of Bardet-Biedl Syndrome are shown in (Figure 2).

Twenty-three membership functions, the values of which were given for each membership, were defined in the output section. The values in Table 2 were determined by their specific gene classification. Results were evaluated at the test phase according to given classification values, which were created for the output cluster. A fuzzy logic interface for (Model 2: Bardet-Biedl syndrome) on MATLAB was shown in (Figure 3).

Twenty-three membership functions, the values of which were given for each membership, were defined in the output section. The values in Table 2 were determined by their specific gene classification. Results were evaluated at the test phase according to given classification values, which were created for the output cluster. A fuzzy logic interface for (Model 2: Bardet-Biedl syndrome) on MATLAB was shown in (Figure 3).

The designed software systems were tested using an operation test. Twenty-three different tests were conducted for Bardet-Biedl syndrome to check the accuracy and success rates in model 2. Thirty-three different tests were conducted for Joubert syndrome, seven for Senior-Loken syndrome, six for Polycystic Kidney Disease, 13 for Meckel syndrome, 15 for Nephronophthisis, 44 for Ciliary dyskinesia, and nine different tests for Orofaciodigital syndrome, respectively. These sub-ciliopathy diseases were grouped according to their specific gene results. It is important to note that these subjects had not previously been introduced to the system. After the AI models were trained, tests were run for each specific gene. When the related genes were introduced into the system, it was tested to determine whether they predicted the correct sub-disease. As a result, all artificial intelligence models achieved a success rate of 99.9% (Error rate = 0.01%), as shown in (Figure 4).

Ciliopathies have many common signs and symptoms, such as mental retardation, kidney and urinary system problems, brain anomalies, facial anomalies, eye and visual tract problems, chronic infections, liver diseases, endocrine problems, skeletal anomalies, respiratory system diseases, cardiac diseases, microgenitalia, and infertility. Although the findings seem specific at first glance for each patient in the clinic, some signs and symptoms overlap with many other systemic diseases as well as with each other. The correlation of phenotypic results with genetic variations and environmental factors, patient phe-

Table 2. Input clusters for sub-ciliopathy diseases (AI Models 2-9)

Disease Name	Specific Genes (Input Cluster)	Disease Name	Specific Genes (Input Cluster)
Bardet-Biedl syndrome 1	CCDC28B, ARL6, BSS1	Joubert syndrome 22	PDE6D
Bardet-Biedl syndrome 2	BBS2	Joubert syndrome 23	TALPID3
Bardet-Biedl syndrome 3	ARL6	Joubert syndrome 24	TCTN2
Bardet-Biedl syndrome 4	BBS4	Joubert syndrome 25	CEP104
Bardet-Biedl syndrome 5	BBS5	Joubert syndrome 26	KATNIP
Bardet-Biedl syndrome 6	MKKS	Joubert syndrome 27	B9D1
Bardet-Biedl syndrome 7	BBS7	Joubert syndrome 28	MKS1
Bardet-Biedl syndrome 8	TTC8	Joubert syndrome 29	TMEM107
Bardet-Biedl syndrome 9	PTHB1	Joubert syndrome 30	ARMC9
Bardet-Biedl syndrome 10	BBS10	Joubert syndrome 31	CEP120
Bardet-Biedl syndrome 11	TRIM32	Joubert syndrome 32	SUFU
Bardet-Biedl syndrome 12	BBS12	Joubert syndrome 33	PIBF1
Bardet-Biedl syndrome 13	MKS1	Joubert syndrome 34	B9D2
Bardet-Biedl syndrome 14	TMEM67	Joubert syndrome 35	ARL3
Bardet-Biedl syndrome 14	CEP290	Joubert syndrome 36	FAM149B1
Bardet-Biedl syndrome 15	WDPCP	Joubert syndrome 37	TOGARAM1
Bardet-Biedl syndrome 16	SSDCCAG8	Joubert syndrome 38	KIAA0753
Bardet-Biedl syndrome 17	LZTFL1	Joubert syndrome 39	TMEM218
Bardet-Biedl syndrome 18	BBIP1	Joubert syndrome 40	IFT74
Bardet-Biedl syndrome 19	IFT27	Senior-Loken syndrome 1	NPHP1
Bardet-Biedl syndrome 20	IFT172	Senior-Loken syndrome 4	NPHP4
Bardet-Biedl syndrome 21	CFAP418	Senior-Loken syndrome 5	IQCB1
Bardet-Biedl syndrome 22	IFT74	Senior-Loken syndrome 6	CEP290
Joubert syndrome 1	INPP5E	Senior-Loken syndrome 7	SDCCAG8
Joubert syndrome 2	TMEM216	Senior-Loken syndrome 8	WDR19
Joubert syndrome 3	AHI1	Senior-Loken syndrome 9	TRAF3IP1
Joubert syndrome 4	NPHP1	Polycystic Kidney Disease 1	PKD1
Joubert syndrome 5	CEP290	Polycystic Kidney Disease 2	PKD2
Joubert syndrome 6	TMEM67	Polycystic Kidney Disease 3	GANAB
Joubert syndrome 7	RPGRIP1L	Polycystic kidney disease 4	PKHD1
Joubert syndrome 8	ARL13B	Polycystic Kidney Disease 5	DZIP1L
Joubert syndrome 9	CC2D2A	Polycystic kidney disease 6	DNAJB11
Joubert syndrome 10	OFD1	Meckel syndrome 1	MKS1
Joubert syndrome 12	KIF7	Meckel syndrome 2	TMEM216
Joubert syndrome 13	TCTN1	Meckel syndrome 3	TMEM67
Joubert syndrome 14	TMEM237	Meckel syndrome 4	CEP290
Joubert syndrome 15	CEP41	Meckel syndrome 5	RPGRIP1L
Joubert syndrome 16	TMEM138	Meckel syndrome 6	CC2D2A
Joubert syndrome 17	CPLANE1	Meckel syndrome 7	NPHP3
Joubert syndrome 18	TCTN3	Meckel syndrome 8	TCTN2
Joubert syndrome 19	ZNF423	Meckel syndrome 9	B9D1
Joubert syndrome 20	TMEM231	Meckel syndrome 10	B9D2
Joubert syndrome 21	CSPP1	Meckel syndrome 11	TMEM231

Disease Name	Specific Genes (Input Cluster)	Disease Name	Specific Genes (Input Cluster)
Meckel syndrome 12	KIF14	Ciliary dyskinesia, primary, 33	GAS8
Meckel syndrome 13	TMEM107	Ciliary dyskinesia, primary, 34	DNAJB13
Nephronophthisis 1	NPHP1	Ciliary dyskinesia, primary, 35	TTC25
Nephronophthisis 2	INVS	Ciliary dyskinesia, primary, 36	PIH1D3
Nephronophthisis 3	NPHP3	Ciliary dyskinesia, primary, 37	DNAH1
Nephronophthisis 4	NPHP4	Ciliary dyskinesia, primary, 38	CFAP300
Nephronophthisis 7	GLIS2	Ciliary dyskinesia, primary, 39	LRRC56
Nephronophthisis 9	NEK8	Ciliary dyskinesia, primary, 40	DNAH9
Nephronophthisis 11	TMEM67	Ciliary dyskinesia, primary, 41	GAS2L2
Nephronophthisis 12	TTC21B	Ciliary dyskinesia, primary, 42	MCIDAS
Nephronophthisis 13	WDR19	Ciliary dyskinesia, primary, 43	FOXJ1
Nephronophthisis 15	CEP164	Ciliary dyskinesia, primary, 44	NEK10
Nephronophthisis 16	ANKS6	Ciliary dyskinesia, primary, 45	TTC12
Nephronophthisis 18	CEP83	Ciliary dyskinesia, primary, 46	STK36
Nephronophthisis 19	DCDC2	Ciliary dyskinesia, primary, 47	TP73
Nephronophthisis 20	MAPKBP1	Ciliary dyskinesia, primary, 5	HYDIN
Nephronophthisis-like nephropathy 1	XPNPEP3	Ciliary dyskinesia, primary, 6	NME8
Ciliary dyskinesia, primary, 1	DNAI1	Ciliary dyskinesia, primary, 7	DNAH11
Ciliary dyskinesia, primary, 10	DNAAF2	Ciliary dyskinesia, primary, 9	DNAI2
Ciliary dyskinesia, primary, 11	RSPH4A	Orofaciodigital syndrome I	OFD1
Ciliary dyskinesia, primary, 12	RSPH9	Orofaciodigital syndrome IV	TCTN3
Ciliary dyskinesia, primary, 13	DNAAF1	Orofaciodigital syndrome V	DDX59
Ciliary dyskinesia, primary, 14	CCDC39	Orofaciodigital syndrome VI	CPLANE1
Ciliary dyskinesia, primary, 15	CCDC40	Orofaciodigital syndrome XIV	C2CD3
Ciliary dyskinesia, primary, 16	DNAL1	Orofaciodigital syndrome XV	KIAA0753
Ciliary dyskinesia, primary, 17	CCDC103	Orofaciodigital syndrome XVI	TMEM107
Ciliary dyskinesia, primary, 18	DNAAF5	Orofaciodigital syndrome XVII	INTU
Ciliary dyskinesia, primary, 19	LRRC6	Orofaciodigital syndrome XVIII	IFT57
Ciliary dyskinesia, primary, 2	DNAAF3		
Ciliary dyskinesia, primary, 20	ODAD1		
Ciliary dyskinesia, primary, 21	DRC1		
Ciliary dyskinesia, primary, 22	ZMYND10		
Ciliary dyskinesia, primary, 23	ODAD2		
Ciliary dyskinesia, primary, 24	RSPH1		
Ciliary dyskinesia, primary, 25	DNAAF4		
Ciliary dyskinesia, primary, 26	CFAP298		
Ciliary dyskinesia, primary, 27	CCDC65		
Ciliary dyskinesia, primary, 28	SPAG1		
Ciliary dyskinesia, primary, 29	CCNO		
Ciliary dyskinesia, primary, 3	DNAH5		
Ciliary dyskinesia, primary, 30	ODAD3		
Ciliary dyskinesia, primary, 32	RSPH3		

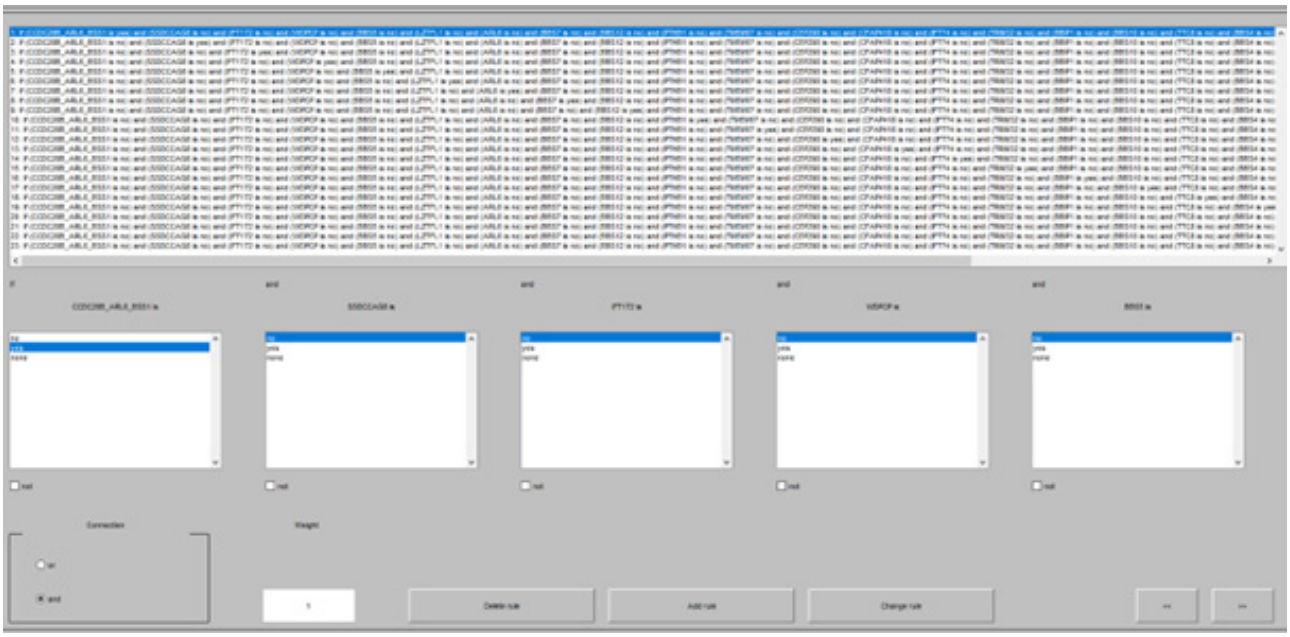

Figure 2. The figure illustrates the generated rules section within the Fuzzy Logic system. The upper rectangle box presents an example of the data from sub ciliopathy diseases of Bardet-Biedl syndrome used that used to train the system. Lower small square boxes show examples of the parameters (related specific genes), which were defined as input and membership functions within the rule section.

notypes do not match with the considered disease, candidate variants are in genes that are not characterized by the disease, model organisms are insufficient to explain the disease, and

Previous efforts and research have been conducted to integrate machine learning into medicine to deduce phenotypes in rare diseases and to create and classify databases for patient and

Figure 3. The generated appearance of the output cluster using the fuzzy logic interface (Model 2) on MATLAB. Small-merged yellow boxes illustrate twenty-three parameters that were introduced as inputs. The blue box shows the output part and determines twenty-three different gene classifications as membership functions. The Y-axis presents membership functions of output, which can be determined according to the output score. The X-axis presents values of the membership function between 0–1.

clinical symptoms of diseases are susceptible to confusion with each other, and with other diseases, these are complexities that make the diagnosis of ciliopathies difficult.

patient diagnosis [20]. However, there has not been an artificial intelligence system that has been conducted so comprehensively on ciliopathies before. In this study, we developed a

Table 3. Obtained results from testing the AI Model 1.

	Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Test 7	Test 8	Test 9
	Bar-det-Biedl Syndrome	Joubert Syndrome	Alstrom Syndrome	Sen-ior-Loken Syndrome	Polycystic Kidney Disease	Meckel Syndrome	Nephronophthisis	Ciliary Dyskinesia	Orofaciodigital Syndrome
Abdomen	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blood and Blood-Forming Tissues	No	No	No	Yes	No	No	Yes	No	No
Breast	No	Yes	Yes	No	No	No	No	No	No
Cardiovascular System	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ear	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Endocrine System	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
Eye	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Growth	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Genitourinary System	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immune System	Yes	Yes	Yes	No	No	No	No	Yes	No
Intergument	Yes	Yes	Yes	No	No	Yes	No	No	Yes
Head	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Limbs	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Metabolism	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Musculature	No	Yes	No	No	No	No	No	No	Yes
Neck	No	No	No	No	No	No	No	No	Yes
Nervous System	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Prenatal Develop	No	No	No	No	No	Yes	Yes	No	No
Respiratory System	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Skeletal	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Thoracic Cavity	No	Yes	No	No	No	No	No	No	No
Neoplasm	No	Yes	No	No	No	No	No	No	No
Accuracy Rate	99.9%	99.9%	99.9%	99.9%	99.9%	99.9%	99.9%	99.9%	99.9%
Error Rate	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%

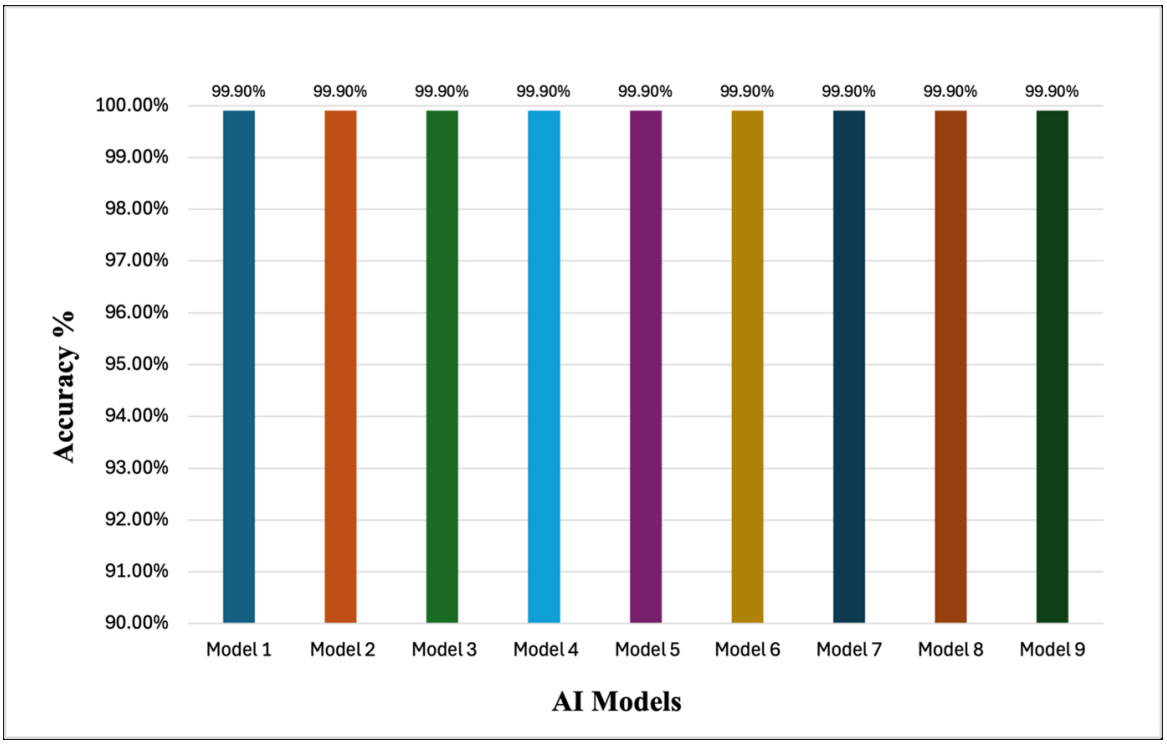

Figure 4. The accuracy percentages of the Fuzzy Logic models. All artificial intelligence models for ciliopathy subgroups achieved an accuracy rate of 99.9%, with only 0.01% error rate.

machine learning platform that will help ciliopathy patients obtain a faster and more accurate diagnosis, start the treatment process earlier, and help doctors in managing ciliopathy cases. All artificial intelligence models for ciliopathy subgroups in our fuzzy logic system achieved an accuracy rate of 99.9%, with only 0.01% error rate. In contrast, many studies report different accuracy rate regarding the use of fuzzy logic and predicting diseases. A fuzzy rule-based model for predicting swine flu was developed by Kakulapati et al. (2022) and achieved an accuracy of 99%. While it is true that their model is highly accurate, in some measures, it was slightly lower than our models. The variance may be because we addressed multiple symptom areas and many specific genes, which enhanced the accuracy of our diagnosis system [21]. Additionally, Ali et al. (2019) developed a system for diagnosing cardiac disorders using fuzzy logic; their model had a 90% accuracy rate, which demonstrates how effectively physiologic works in medical diagnosis [22]. Another study conducted recently by Jain, V., & Raheja, S. (2015) used a fuzzy expert system to predict diabetes. Compared to conventional techniques, their study showed an improvement in prediction rates [23]. This supports our results that methods based on fuzzy logic could greatly improve the accuracy of diagnosis. Our high accuracy, however, may be because our models notably benefit from the tailored membership functions and the large data set of ciliopathy-associated genetic diseases that we used.

Conclusion

Difficulty in the diagnosis of rare diseases, especially in ciliopathies, brings along the wrong treatment. Unfortunately, ciliopathies are a group of diseases that are difficult to diagnose and treat due to their genetic heterogeneity and overlapping symptoms.

Human intelligence has solved many problems until now and continues to solve them. However, we are entering an era where there may be problems that cannot be solved by human intelligence or artificial intelligence alone. The ClioMD platform will be the perfect blend of human intelligence and artificial intelligence, which we spent days developing. It is an idea that will give us a much faster and much more accurate diagnosis. Rapid and accurate diagnosis is the most important step for correct, effective treatment. The ClioMD platform gives an accuracy rate of close to one hundred percent and can be an important tool in referencing patients to a geneticist.

While conducting this study, we have been faithful to the principle that 'there is no disease, there are patients', and we believe ClioMD will help every ciliopathy patient and doctor. Although it is currently developed for rare diseases, we believe that it can be a step towards the integration of artificial intelligence into medical science and can be developed for many other diseases in the future.

Conflict of Interest

The authors do not have any conflict of interest to declare.

Funding
There is no funding for this study.

Data Availability Statement
The data is available upon request.

References
1. Kaul, V., Enslin, S., & Gross, S. A. (2020). History of artificial intelligence in medicine. Gastrointestinal endoscopy, 92(4), 807-812.
2. Gupta, N., Singh, H., & Singla, J. (2022, August). Fuzzy logic-based systems for medical diagnosis–A review. In 2022 3rd International Conference on Electronics and Sustainable Communication Systems (ICESC) (pp. 1058-1062). IEEE.
3. Wheway, G., Mitchison, H. M., & Genomics England Research Consortium (2019). Opportunities and Challenges for Molecular Understanding of Ciliopathies-The 100,000 Genomes Project. Frontiers in genetics, 10, 127. https://doi.org/10.3389/fgene.2019.00127
4. Focşa, I. O., Budişteanu, M., & Bălgrădean, M. (2021). Clinical and genetic heterogeneity of primary ciliopathies. International Journal of Molecular Medicine, 48(3), 176.
5. Elawad, O. A. M. A., Dafallah, M. A., Ahmed, M. M. M., Albashir, A. A. D., Abdalla, S. M. A., Yousif, H. H. M., ... & Abu Shama, E. A. E. (2022). Bardet–Biedl syndrome: a case series. Journal of Medical Case Reports, 16(1), 1-9.
6. Spahiu, L., Behluli, E., Grajçevci-Uka, V., Liehr, T., & Temaj, G. (2022). Joubert syndrome: molecular basis and treatment. Journal of Mother and Child, 26(1), 118-123.
7. Bachmann-Gagescu, R., Dempsey, J. C., Bulgheroni, S., Chen, M. L., D'Arrigo, S., Glass, I. A., ... & Doherty, D. (2020). Healthcare recommendations for Joubert syndrome. American journal of medical genetics Part A, 182(1), 229-249.
8. Valentini, G., Saia, M., Farello, G., Salpietro, V., Mancuso, A., Ceravolo, I., ... & Cucinotta, F. (2023). Meckel Syndrome: A Clinical and Molecular Overview. Journal of Pediatric Neurology, 21(01), 062-067.
9. Turkyilmaz, A., Geckinli, B. B., Alavanda, C., Arslan Ates, E., Buyukbayrak, E. E., Eren, S. F., & Arman, A. (2021). Meckel-Gruber syndrome: clinical and molecular genetic profiles in two fetuses and review of the current literature. Genetic testing and molecular biomarkers, 25(6), 445-451.
10. O'Connor, M. G., Mosquera, R., Metjian, H., Marmor, M., Olivier, K. N., & Shapiro, A. J. (2023). Primary ciliary dyskinesia. Chest Pulmonary, 1(1), 100004.
11. Shoemark, A., & Harman, K. (2021, August). Primary ciliary dyskinesia. In Seminars in respiratory and critical care medicine (Vol. 42, No. 04, pp. 537-548). Thieme Medical Publishers, Inc..
12. Tahani, N., Maffei, P., Dollfus, H., Paisey, R., Valverde, D., Milan, G., ... & Geberhiwot, T. (2020). Consensus clinical management guidelines for Alström syndrome. Orphanet journal of rare diseases, 15, 1-22.
13. Wexler, D., & Ms, M. D. (2023). Patient education: Preventing complications from diabetes (Beyond the Basics).
14. Wolf, M. T., Bonsib, S. M., Larsen, C. P., & Hildebrandt, F. (2024). Nephronophthisis: a pathological and genetic perspective. Pediatric Nephrology, 39(7), 1977-2000.
15. Yahalom, C., Volovelsky, O., Macarov, M., Altalbishi, A., Alsweiti, Y., Schneider, N., ... & Khateb, S. (2021). SENIOR–LØKEN SYNDROME: A Case Series and Review of the Renoretinal Phenotype and Advances of Molecular Diagnosis. Retina, 41(10), 2179-2187
16. Franco, B., & Thauvin-Robinet, C. (2016). Update on oral-facial-digital syndromes (OFDS). Cilia, 5, 1-11.
17. Elfaladonna, F., & Isa, I. G. T. (2022). UJI EFEKTIFITAS METODE FUZZY LOGIC MAMDANI PADA PENERIMAAN BEASISWA BANTUAN MENGGUNAKAN MATLAB. SINTECH (Science and Information Technology) Journal, 5(1), 75-86.
18. Ab Talib, M. H., Mat Darus, I. Z., Mohd Yatim, H., Hadi, M. S., Mohd Saufi, M. S. R., & Ngadiman, N. H. A. (2022). Gain Scaling Tuning of Fuzzy Logic Sugeno Controller Type for Ride Comfort Suspension System Using Firefly Algorithm. In Enabling Industry 4.0 through Advances in Mechatronics (pp. 335-344). Springer, Singapore.
19. Senturk, N., Tuncel, G., Dogan, B., Aliyeva, L., Dundar, M. S., Ozemri Sag, S., ... & Ergoren, M. C. (2021). BRCA Variations Risk Assessment in Breast Cancers Using Different Artificial Intelligence Models. Genes, 12(11), 1774.
20. Decherchi, S., Pedrini, E., Mordenti, M., Cavalli, A., & Sangiorgi, L. (2021). Opportunities and Challenges for Machine Learning in Rare Diseases. Frontiers in medicine, 8, 747612. https://doi.org/10.3389/fmed.2021.747612
21. Kakulapati, V., Sai Sandeep, R., Kranthi kumar, V., & Ramanjinailu, R. (2021). Fuzzy-based predictive analytics for early detection of disease—A machine learning approach. In ICT Systems and Sustainability: Proceedings of ICT4SD 2020, Volume 1 (pp. 89-99). Springer Singapore.
22. Ali, M. L., Sadi, M. S., & Goni, M. O. (2024). Diagnosis of heart diseases: A fuzzy-logic-based approach. Plos one, 19(2), e0293112.
23. Jain, V., & Raheja, S. (2015). Improving the prediction rate of diabetes using fuzzy expert system. IJ Information Technology and Computer Science, 7(10), 84-91.