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Clinical and Sociodemographic analysis, and Diagnostic Research of Undiagnosed Pediatric Patients Suspected to Have Genetic Disorders

유전 질환이 의심되는 국내 미진단 소아 환자들의
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서울대학교 대학원
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Clinical and Sociodemographic analysis, and Diagnostic Research of Undiagnosed Pediatric Patients Suspected to Have Genetic Disorders

By

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A thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medicine (Major in Translational Medicine) in the Seoul National University, Seoul, Korea

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Abstract

Background: Rare diseases (RDs) usually require convoluted assessment and life-long medical care, which cause excessive medical cost and social burden. Many countries launched a nationwide research program for RDs reflecting their characteristic medical system, based on advancement of genetic technologies. In Korea, a research program for undiagnosed RDs have been launched in 2017. This study is aimed to analyze the result of clinical workflow, and review the clinical and social characteristics of pediatric patients enrolled to the Korean Undiagnosed Disease Program (KUDP).

Methods: Undiagnosed patients under 18 years old and suspected to have genetic etiologies were screened from the KUDP cohort. Sequential diagnostic process, final diagnosis, and further validation was decided and conducted to identify molecular basis of patients. Clinical and demographic data of all patients were reviewed and analyzed. All patients were classified into 3 groups based on initial clinical assessment, to identify patients' characteristics and estimate of the value of the study. The patients who had specific clinical diagnosis which can be confirmed by targeted testing was defined as Group I. Patients diagnosed with certain disease categories, with genetic or phenotypic heterogeneity, were defined as Group II. Group III was defined as patients with an uncategorized or atypical disease thus

far.

Results: Among the 666 patients who participated in the KUDP between Jan 2017 to Dec 2021, 606 patients were finally enrolled in this study. The Group I, II, and III accounted 6.8% (41/606 patients), 74.9% (454/606) and 18.3% (111/606) respectively. The average age of symptom onset was 1.4 years old and most patients (504/606, 83.2%) started diagnostic evaluation within 6 months from the point of symptom onset. About three quarters of patients (447/606, 73.8%) complaint neurologic symptom as their main feature. Patients underwent 6.1 kinds of diagnostic tests (range, 1-14) at 1.4 tertiary hospital (range, 0-5), and spent more than 3 years before the KUDP admission on average. Enrolled patients had customized and stepwise diagnostic evaluation including multi-disciplinary consultation, chromosomal microarray, targeted test for single gene, exome sequencing (ES), RNA sequencing, and various non-genetic tests. Confirmative diagnoses were obtained in 327 patients (54.0%). Diagnoses were made by next-generation sequencing for 275 patients (84.1%) and other genetic testing for 44 patients (13.4%). Eight patients (2.4%) were finally diagnosed by nongenetic tests. Nine patients were diagnosed with reanalysis of ES data. The proportion of patients who had prior ES has increased over years because of cost reduction and easy accessibility. This group, however, showed similar diagnostic yield (50.4%) compared with overall cohort (54.0%), which suggested importance of in-depth phenotyping and trio-based data analyses. For remained patients undiagnosed,

candidate genes were screened with a collaboration of the KUDP functional core laboratories. As a result, functional validations have completed on 4 genes and continued on 6 candidates.

Conclusions: This study solved underprivileged pediatric patients with RDs and figured out overall medical environment in Korea. The favorable outcome was a result of superior clinical workflow and supporting functional core laboratories, which are quite challenging to maintain in practice. The study proved constant need for the national RD program, although its detail such as inclusion criteria or contents of diagnostic process should be revised with advancement of RD practice.

Keywords: rare disease diagnosis, undiagnosed disease program, genetic rare diseases, next generations sequencing

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List of Abbreviations

RD, Rare disease

US, United States

NGS, next-generation sequencing

UDN, Undiagnosed Diseases Network

SpainUDP, Spain Undiagnosed Diseases Program

IRUD, Initiative on Rare and Undiagnosed Diseases

KUDP, Korean Undiagnosed Diseases Program

CMA, chromosomal microarray

ES, exome sequencing

GS, genome sequencing

PCR, Polymerase chain reaction

CGH, Comparative Genomic Hybridization Microarray

CNVs, copy number variations

FISH, fluorescence in situ hybridization

qPCR, quantitative PCR

MME, matchmaking exchanger

HPO, Human Phenotype Ontology

PWS, Prader-Willi syndrome

MS-MLPA, methylation specific-multiplex ligation dependent probe amplification

MRI, magnetic resonance imaging

NF1, neurofibromatosis type 1

CK, creatinine kinase

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Introduction

Rare disease (RD) is defined as one that affects fewer than 5 per 10,000 persons in the European Union or fewer than 200,000 persons in the United States (US). In Korea, the Rare Disease Act of 2016 defined RD as affecting fewer than 20,000 patients or for which the prevalence is unknown because of its rarity. Research on RDs is rapidly expanding through the use of advanced genetic technologies and big-data management. Approximately 7,000 kinds of RDs have been genetically identified and their numbers have continued to increase to date, while there still remain numerous unidentified diseases [1-3]. Current RD studies also emphasize determining disease mechanisms and searching for therapeutic targets using various methodologies including data sharing, model organisms and supporting experiments [3-6]. However, the clinical demand for RDs still exists. There are still many genetically unidentified diseases, and many nongenetic RDs often hard to distinguish from genetic RDs in practice. Patients with RDs accounts for approximately 8-10% of the general population, and their prompt diagnosis is still challenging in many countries despite recent cost reductions and the easy accessibility of next-generation sequencing (NGS) [2]. Some patients with RDs can spend more than 5 years reaching a diagnosis, and many of them remain undiagnosed [7, 8]. These circumstances cause excessive medical costs and long-term social burdens, as well as loss of well-being among both patients and their

families. Many countries have operated their own RD projects, including the Undiagnosed Diseases Network (UDN) by the US National Institutes of Health, the Spain Undiagnosed Diseases Program (SpainUDP), the Finding of Rare Disease Genes project in Canada, and the Initiative on Rare and Undiagnosed Diseases (IRUD) project in Japan, to support clinical needs and establish a nationwide registry and infrastructures [9-13].

The Korean Undiagnosed Diseases Program (KUDP) was launched as a pilot project in 2017 with the purpose of supporting undiagnosed patients and initiating RD research. The program established clinical protocols that were suitable for the Korean insurance system and showed a fair diagnostic yield for a year [14]. The main project has been operated as yet, focusing on the advancement of the workflow and establishing a long-term research platform. The program tried to reflect some changes in the medical insurance system of Republic of Korea and applied an additional diagnostic algorithm for the remaining undiagnosed patients from the KUDP pilot project. The program initially focused on pediatric patients as large proportion of RDs affect children, although the KUDP recently expanded into separate projects for children and adults to reflect their clinical differences. Herein, we summarized RD diagnosis and practical issues of Korean pediatric patients who participated in the KUDP.

Materials and Methods

1. Project design and study approval

The KUDP project was initiated and supported by the Korea Disease Control and Prevention Agency. Seoul National University Children's Hospital functioned as the main center and supervised the entire clinical process. The expert consortium consisted of more than 20 specialists covering nearly all clinical pediatric department such as neurology, cardiology, nephrology, hematology, immunology, gastroenterology, endocrinology, ophthalmology, otology, orthopedics and clinical genetics, as well as laboratory medicine and bioinformatics across six institutes. Applying for the KUDP was made by direct referral or referral letters from regional network hospitals, as well as through primary screening of visiting patients at the center hospital. The study protocol, including the biorepositories, diagnostic procedures, clinical data collection, selective functional experiments and web-based data sharing, was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 110-110-353, 1406-081-588, 1511-099-722, and 1904-054-102).

2. Enrollment criteria and classification of patients in the study

Patients suspected to have rare genetic disorder were screened for KUDP. To participate in the program, patients were required to meet one of the following

criteria (Table 1): 1) still undiagnosed after appropriate evaluation decided by clinical experts; 2) be suspected to have medically actionable disease that presented rapid deterioration and an irreversible clinical course; or 3) had a diagnostic journey of more than 5 years despite regular check-ups and evaluation for the disease. Most patients who needed diagnostic tests that were covered by insurance systems at the time of screening were excluded and recommended to undergo routine diagnostic processes at their referring hospital. Among the entire KUDP cohort, patients initially suspected to have genetic disorder and under 18 years old at the time of KUDP admission were finally enrolled in this study. Patients who refuse to participate the program or did not provide sufficient clinical data were excluded.

The expert consortium classified enrolled patients into 3 groups according to the clinical assessment (Table 2). Group I was defined as patients with a specific diagnosis that required targeted testing for single etiology, made by clinical perception and basic medical information (e.g. Charge syndrome). Patients diagnosed with certain disease categories with typical clinical course and heterogeneous causative genes were defined as Group II (e.g., epileptic encephalopathy, common variable immunodeficiency). Group III was defined as patients who presented atypical clinical course, systemic or multi-organ involvements uncategorized thus far. The aim of the classification was to identify clinical characteristics of enrolled patients and use it as an indicator of KUDP

status.

Table 1. Inclusion and exclusion criteria for Korean Undiagnosed Disease Program

Inclusion criteria
Patients suspected to have rare genetic disorders and meet one of the following standards: 1. Patients who remained undiagnosed after appropriate examination and diagnostic tests decided by experts 2. Patients suspected to have medically actionable diseases that presented rapid deterioration and an irreversible clinical course 3. Patients who had a diagnostic journey of more than 5 years despite regular check-ups in second or tertiary hospitals
Exclusion criteria
1. Patients with insufficient clinical data 2. Patients who refuse to participate the program or provide previous medical record 3. Patients who did not underwent clinical assessment for diagnosis

Table 2. Clinical classification of enrolled patients

Group I	Patients with a specific clinical diagnosis which initially require targeted testing for single or few genetic loci
Group II	Patients with certain disease spectrum with clinical and genetic heterogeneity: Single gene tests are usually unavailable because of various causative genes, and next generation sequencing is considered as first-tier diagnostic test.
Group III	Patients who show uncategorized, multiple systemic presentations or atypical clinical course for certain assessment at the time of enrollment.

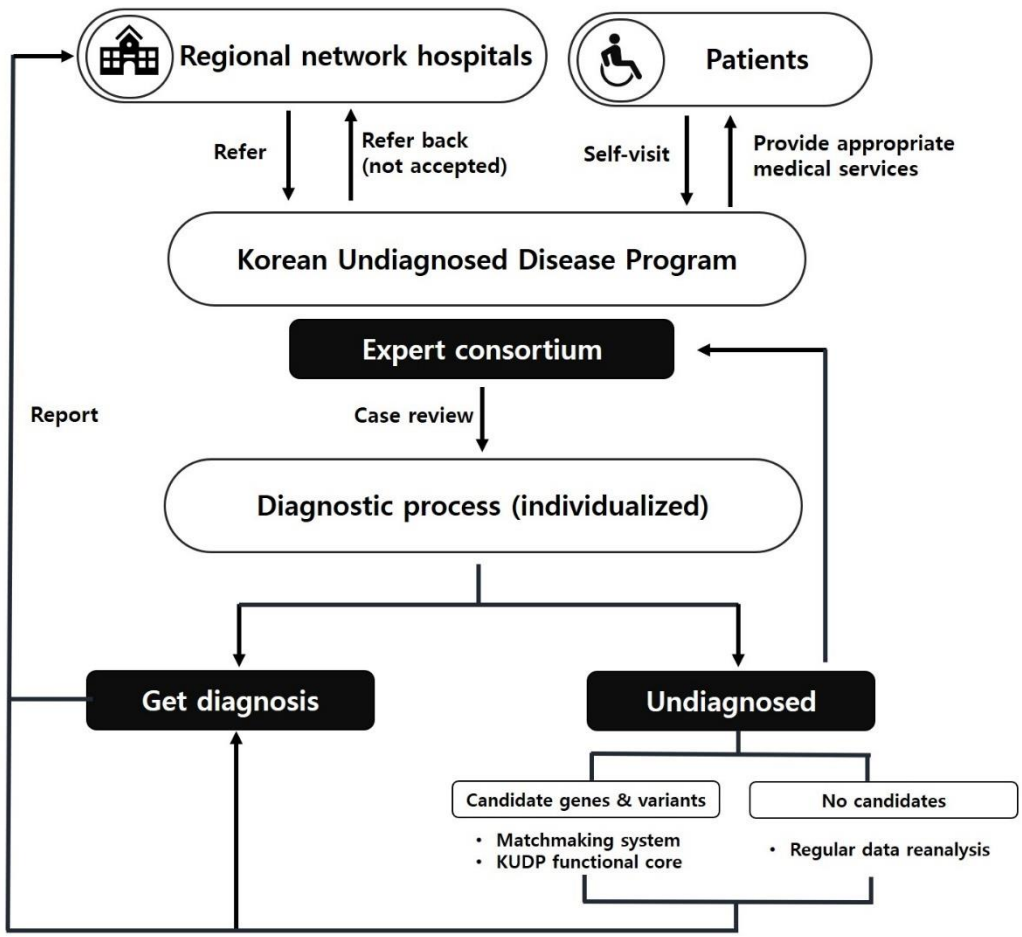
3. Diagnostic Process

Overall diagnostic workflow

Schematic workflow was described in the Figure 1. Decisions on final enrollment and following diagnostic process were made by the KUDP expert consortium. All data generation and analysis was centralized in the coordinating center, and the result was shared with the referring hospitals. All patients were discussed at an expert consortium and had sequential genetic tests, including chromosomal microarray (CMA), direct Sanger sequencing for target genes, target gene panel, exome sequencing (ES), and RNA sequencing, as well as non-genetic tests. Data was reviewed and a final diagnosis was confirmed based on the test results and patients' phenotypes. If a patient did not obtain a confirmative diagnosis after ES,

the consortium discussed the validity of further evaluation, including RNA sequencing, genome sequencing (GS) and other biochemical testing. The patients had regular checkups at center or network hospitals, and the reanalysis of NGS data was conducted for some patients based on revised phenotypes and updated analytic pipelines. Possible candidate genes or variants were discussed with the KUDP functional core laboratories followed by independent validation or international sharing by a matchmaking system. This study focused on clinical results from patients' diagnostic process.

Figure 1. Schematic diagram of workflow of the Korean Undiagnosed Diseases Program



DNA preparation

To obtain DNA for genetic testing, blood samples were taken from the patients and their biological parents using ethilen dianmin acetic acid tube at Seoul National University Hospital. In case of patients enrolled via referral letter, the referral hospital drew blood and transported through private system within 3 days from the sample acquisition. Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp® DNA Blood Midi Kit according to the manufacturer's instructions (Qiagen, Valencia, CA, USA).

Sanger sequencing

Sanger sequencing was used to confirm the causative variants identified by NGS or to figure out causative variants in highly suspicious genes. It was performed using self-designed primer pairs. Polymerase chain reaction (PCR) amplification was performed in a thermal cycler (Model 9700; Applied Biosystems, Foster City, CA, USA) and cycle sequencing was performed on an ABI Prism 3730x1 Analyzer using the BigDye Terminator Sequencing Ready Reaction Kit (Applied Biosystems).

Chromosomal microarray and its validation

Detailed protocol was same as previous report [15]. CMA was conducted using Agilent Human Genome Oligonucleotide Comparative Genomic Hybridization Microarray (CGH) 1 x 244K, 4 x 180K, or 8 x 60K (Agilent Technologies, Santa Clara, CA, USA) with 8.9kb 13kb, or 41kb overall median probe spacing, respectively. Genomic DNA was labeled and hybridized to the array, according to the manufacturer's protocol for Oligonucleotide Array-Based CGH for Genomic DNA Analysis (Version 6.2; Agilent Technologies). A DNA reference sample (male or female human genomic DNA; Promega, Madion, WI, USA) was used. The Slide was scanned on a microarray scanner (G2565CA; Agilent Technologies). Data were extracted as tiff image using Agilent Feature Extraction software (version 10.7.3.1) and analyzed with genomic Workbench software (version 7.0.4.0, Agilent Technologies). The local background was subtracted from the median intensities of the Cy3 and Cy5 channels. The log2 patient-to-reference ratio was calculated for each spot and normalized to the median of the ratios of all chromosomes. All copy number variations (CNVs) were called based on human assembly CRCh37.

Fluorescence in situ hybridization (FISH) or quantitative PCR (qPCR) was conducted to verify CNVs under 2Mb. The qPCR was performed using an ABI Prism 7500 system (Applied Biosystems, Foster City, CA, USA) with a fluorescent SYBR Premix Ex Taq (TaKaRa). Specific primer sequences and qPCR conditions

are available on request. Raw data were analyzed using the comparative delta delta (ΔΔ) threshold cycle number (Ct) method. Standard FISH analysis was performed on metaphase chromosomes using commercially available or customized BAC clones (specific information can be provided upon request). Metaphase chromosomes were collected from the blood samples of patients and their parents and were analyzed using a fluorescence microscope (Nikon, Eclipse 80i, NY, USA) equipped with a computerized chromosome analysis system, ChIPS-FISH (GenDix, Seoul, Korea). At least 20 metaphase cells were analyzed for genomic imbalances.

Next generation sequencing

Target gene panel sequencing was conducted for patients suspected to have genetic epilepsies and congenital muscle diseases. The panel was designed using SureSelect Target Enrichment System Kits (Agilent Technologies, Santa Clara, CA, USA) that included 127 genes in epilepsy panel and 434 genes in muscular disease. Library preparation was performed according to the manufacturer's instructions (Agilent Technologies). The library was paired-end sequenced on a HiSeq 2500 sequencing system (Illumina, San Diego, CA, USA). For ES, we used the SureSelect Human All Exon V5 capture kit (Agilent Technologies) for target enrichment. Sequenced reads were aligned to GRCh37 by Burrows-Wheeler alignment (v. 2.2.0) and PCR duplicates were removed

using SAMtools (v. 1.9.0). Variant calling was performed using GATK's Haplotype Caller. We employed several databases along with RefSeq using ANNOVAR for variant annotation. Variants were classified and annotated based on their rarity, impact on the encoded protein, conservation score, expression, and recent functional studies. The allele frequencies were referenced from the Exome Aggregation Consortium database. We also searched for all variants in the Human Gene Mutation Database. The pathogenicity of novel variants was evaluated according to the American College of Medical Genetics and Genomics standards and guidelines [16].

Clinical data collection

I reviewed clinical data including perinatal history, present illness, result of previous tests, family history and associated medical history. The age of symptom onset defined as the age at first symptom recognition by the patient or parents. Chief complaint, the main symptom directly relevant to the KUDP enrollment, and all of other illness which required medical examination were recorded. Previous tests performed for diagnosis and their results were also collected. Detailed demographic data was also gathered to analyze Korean medical service on RD patients: Patients' residence, number of tertiary hospitals for diagnosis, time differences between the symptom recognition and first medical assessment or KUDP admission.

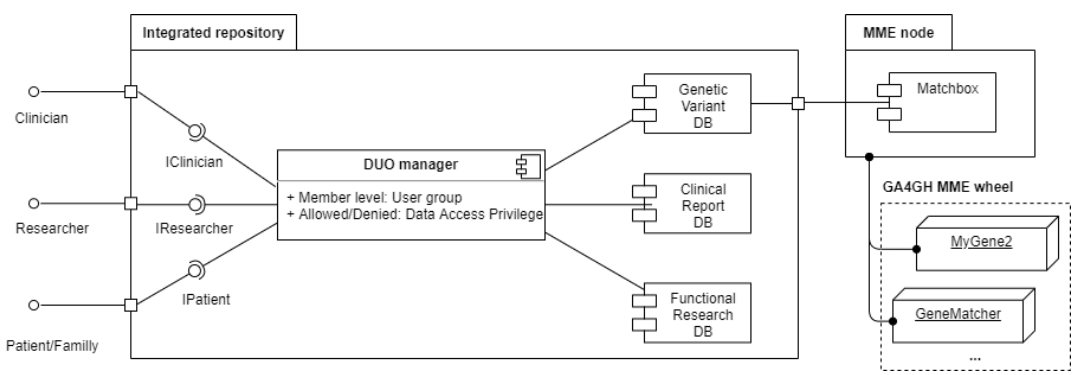
4. Functional core laboratories and database management system

In 2020, functional core laboratories have launched to screen and evaluate candidate variants or genes for undiagnosed cases. It consisted of a laboratory for protein structure and function, two model organism screening centers (zebrafish and *Drosophila*), and preclinical science laboratories for metabolomics, stem cells, neuroscience and immunology. The KUDP expert consortium and functional core laboratories discussed about candidate genes at monthly meeting, based on previously reported gene functions, tissue expression, and experimental data. Some variants were shared on the international matchmaking exchanger (MME) system, and functional experiments were performed for highly-suspicious genes.

A web-based repository system was developed to support cohort management and provide a data mediation function. For cohort management, our system provides three databases (Figure 2). In the Clinical Report Database, the clinically screened data are stored and classified into 4 categories: the basic patient information, present illness, past history, and previous study. The significant symptoms that a patient is currently experiencing are included in the “present illness” category and defined as standardized terms with the Human Phenotype Ontology (HPO) project. The system also provides the mediation function based

on a matchbox [17]. The matchbox is a standalone server to implement the MME protocol with standardized nomenclatures. We have applied this system and through its use, implemented the connecting interface with two MME nodes (GeneMatcher and MyGene2) using their application programming interfaces [18, 19]. The DUO manager designates the access control privileges about the stored data as the standardized ontology structure [20]; through this, the data owner can share and mediate their data for a designated period to designated users and groups only for a designated purpose.

Figure 2. Schematic diagram of the web-based repository system



Results

1. RD diagnosis

Patient characteristics

Total 666 patients participated in the KUDP for 5 years (from Jan 2017 to Dec 2021) and 606 were finally enrolled to this study. Demographic and clinical information for the 606 patients is described in Table 3 and Figure 3–6. More than one third of patients (219/606, 36.1%) presented their first symptom before one month of age. Infantile–onset cases accounted 68.2% (413 patients), whereas only 26 patients (4.3%) showed their symptoms after 10 years old. Diagnostic evaluation by clinical experts was started within 6 months from the symptom onset in 504 cases (83.2%). The median age at KUDP admission was 4.95 years old. The enrolled patients were classified into Group I (41 patients, 6.8%), Group II (454 patients 74.9%), or Group III (111 patients, 18.3%) based on the criteria described in the Methods section. The main complaints were neurological symptoms in about three quarters of patients (447/606, 73.8%) and simultaneous systemic or undetermined features in 65 patients (10.7%) (Figure 3). We reviewed all the presenting symptoms requiring special examination at separate clinics for diagnosis (Figure 4 and 5). Multiple organ involvement or co-existed symptoms were noted in 407 patients (67.2%). Patients visited an average of 1.4 tertiary hospitals (range, 0-5) and underwent an average of 6.1 diagnostic tests (range, 1-

14). including metabolic screening, multiple imaging, single gene testing and NGS (target gene panel or ES), before the KUDP admission. About 85% of patients (515/606) had one or more genetic tests, including karyotyping or CMA in 345 (56.9%, some patients had repeated tests), various single gene tests in 281 (46.4%), target gene panel in 117 (19.3%), and ES in 125 (20.6%) (Figure 6).

Table 3. Demographic profile of the enrolled patients.

	Number of patients (n=606)
Sex (male : female)	335 : 271
Age of the symptom onset	
< 1 month	219 (36.1%)
1-6 months	107 (17.7%)
6-12 months	87 (14.4%)
1-3 years	117 (19.3%)
3-5 years	21 (3.5%)
5-10 years	29 (4.8%)
> 10 years	26 (4.3%)
Age at KUDP admission	
< 1 month	9 (1.5%)
1-6 months	33 (5.4%)
6-12 months	60 (9.9%)
1-3 years	173 (28.5%)
3-5 years	101 (16.7%)
5-10 years	131 (21.6%)
> 10 years	99 (16.3%)
Classification	

Group I	41 (6.8%)
Group II	454 (74.9%)
Group III	111 (18.3%)
Number of previously visiting hospital before KUDP admission	
0	47 (7.8%)
1	365 (60.2%)
2	144 (2.4%)
3	36 (5.9%)
> 4	14 (2.3%)
Number of total diagnostic tests before KUDP admission	
<5	133 (21.9%)
5-10	436 (71.9%)
≥ 10	37 (6.1%)

KUDP, Korean Undiagnosed Diseases Program

Figure 3. Distribution of main presenting symptoms (according to clinical divisions)

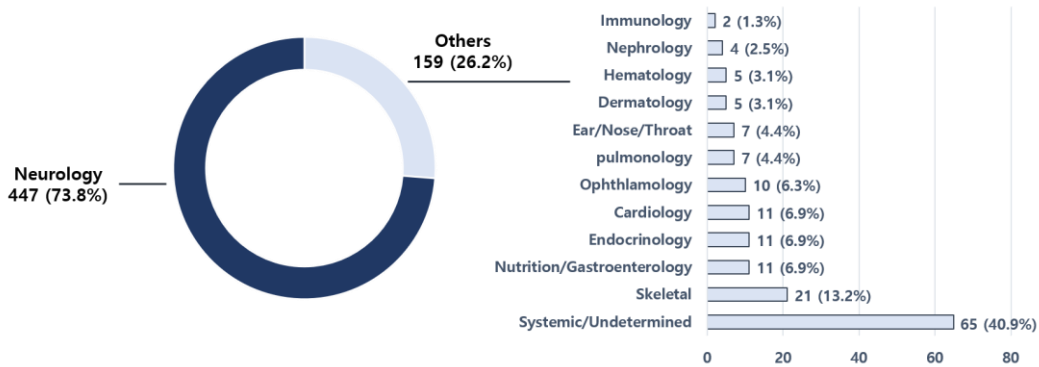


Figure 4. Distribution of all presenting symptoms (according to clinical divisions)

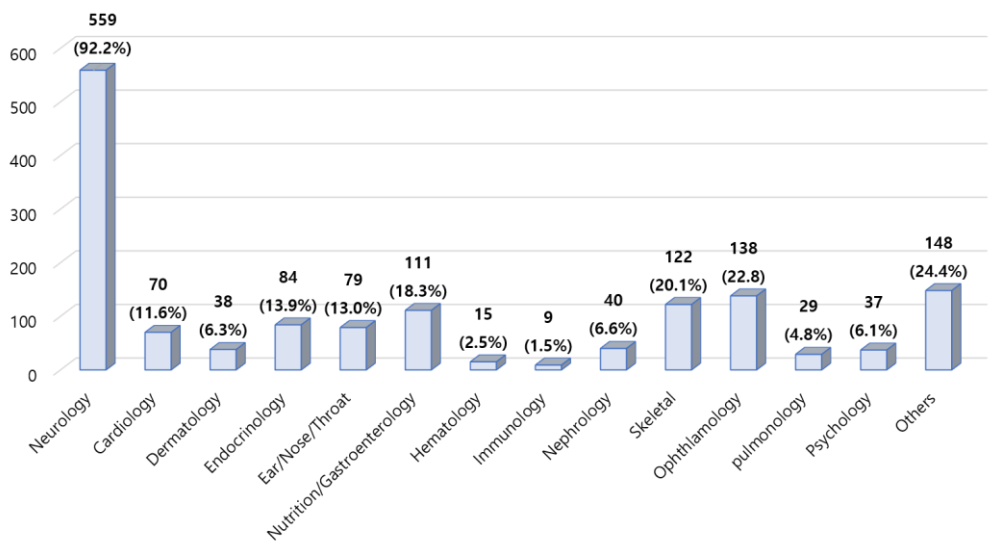


Figure 5. Number of presenting symptoms (according to clinical divisions) in each patient

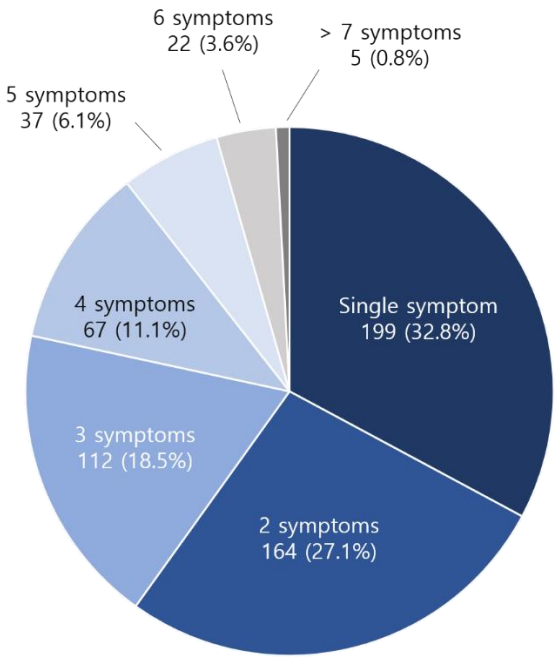
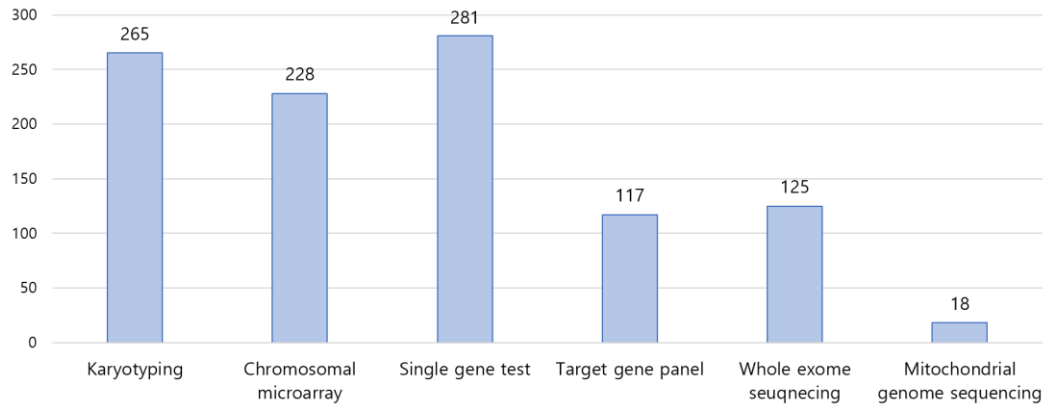


Figure 6. performed tests before the study enrollment



Diagnostic process and its outcome

Enrolled patients underwent individualized tests by stage (Table 4). The total numbers of performed tests were as follows: CMA (73 tests), single gene testing (48 tests), target gene panel sequencing (56 tests), ES for patient only (287 tests), ES for family (patients, parents or other affected family (363 tests)), and other evaluation (15 cases). Reanalysis of ES data was conducted in 55 patients enrolled before 2020. Among the 363 patients who finally underwent trio or duo ES, 104 families were sequenced by stages (proband ES first and additional sequencing for parents due to inconclusive result).

Final diagnosis was made based on the test results and its clinical relevance. The overall final diagnostic rate was 54.0% (327 of 606 patients, Figure 7)). Detailed information on the diagnosed patients is presented in Supplementary

Table 1. Pathogenic or likely pathogenic variants in 186 genes were detected in 299 patients. Forty-seven genes (*ARID1B, ASLX3, ATL1, ATP1A3, CACNA1A, CASK, COL6A1, CTNNB1, CUL7, CYFIP2, DMD, DNM1L, FOXG1, GLB1, GNAO1, GRIN1, IARS2, KAT6A, KCNQ2, KIAA1109, MN1, NALCN, NIPBL, PDHA1, PIGT, PLP1, PMM2, PPP2R5D, PTEN, RYR1, SETBP1, SGSH, SLC16A2, SLC2A1, SLC35A2, SMARCB1, SMN1, SON, SPTAN, SRCAP, SYNGAP1, TCF4, TUBB4A, UBE3A, USP9X,* m.G3697A. m.A8344G) were found in 2 or more patients. Somatic variants in *PIK3CA* and *MTOR* were identified as genetic etiologies based on phenotypes. Causative CNVs were identified in 22 patients, by ES as well as CMA. A patient suspected to have Prader-Willi syndrome (PWS) was enrolled because he had shown negative result of methylation specific-multiplex ligation dependent probe amplification (MS-MLPA) test for PWS and CMA, but the patient confirmed as PWS by repeated test in the study. Five patients had variants identified by mitochondrial genome sequencing. Among the 327 diagnosed cases, 80.1% of diagnoses (262/327) were made by ES, 4.0% (13/327) by target gene panel, 1.5% (5/327) by mitochondrial DNA testing, and 11.9% (39/327) by conventional genetic testing (CMA and various single gene tests). Nine cases from ES-positive group were made by additional reanalysis of data. Eight patients (2.4%) including 6 with non-Mendelian disorders got their final diagnoses by other evaluation such as including specific biochemical assay, antibody panel testing, and experts' examination. The diagnostic yield was different for each

group: 81.3% (33/41) for Group I, 54.0% (245/454) for Group II, and 44.1% (49/111) for Group III in accordance with accuracy and specificity of clinical assessment (Figure 8).

At the time of writing, 11 patients had started active treatment based on their final diagnoses: nusinersen for 3 spinal muscular atrophy patients, a ketogenic diet for 2 GLUT1 deficiency syndrome cases, L-dopa for a patient with Segawa disease, acetylcholinesterase inhibitors for a congenital myasthenic syndrome case, immunotherapy for 2 patients with autoinflammatory myositis and dermatomyositis, mexiletine therapy for a paramyotonia congenita patient, enzyme replacement therapy for a patient with Pompe disease. Some patients changed long term plans. Three patients with *PTEN* variants started annual tumor surveillance. Two families decided to withdraw life-sustaining treatment based on the diagnoses and 6 patients (including 2 myositis cases) ceased further genetic testing after the confirmation of non-genetic etiologies. Genetic counselling was given to all diagnosed patients and 16 families planned for next baby.

Before the initiation of KUDP functional core laboratories at 2020, candidate genes were shared throughout international MME. Among them, functional validations on 4 genes (*MN1, ACOX1, SIAH1, GEMIN5*) were completed with international collaboration [21-24].

Table 4. Types and numbers of performed tests at each diagnostic stage

	1st stage	2nd stage	3rd stage	Total
Chromosomal microarray	70	3	0	73
Mitochondrial DNA testing*	10	6	0	16
Single gene testing	46	2	0	48
Target gene panel	52	4	0	56
Exome sequencing				
Proband	212	74	1	287
Duo	4	3	1	8
Trio**	204	130	21	355
Others***	8	4	3	15
Data reanalysis of ES	0	24	31	55
Total	606	250	57	913

* includes mitochondrial DNA sequencing and deletion/duplication test using long PCR

** some of trio exome sequencing were additionally performed on family members after the proband ES whose result was inconclusive (double-counted)

*** includes nongenetic tests (rare biochemical studies or antibody panel tests), clinical rounds, RNA sequencing, and functional studies for validating candidate genes or variants

Figure 7. Total diagnostic yield and proportion of performed tests for positive cases

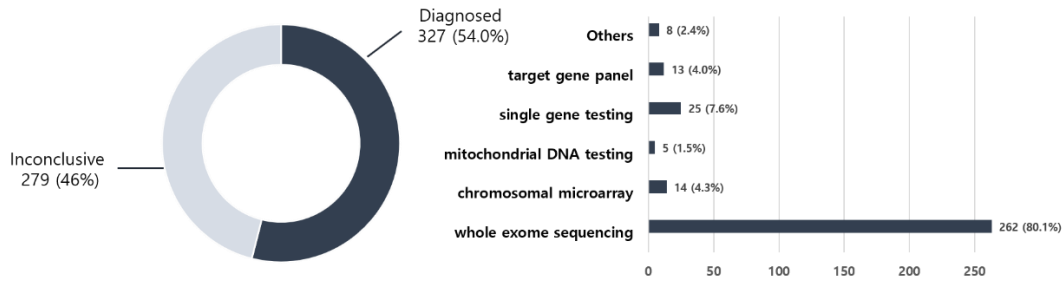
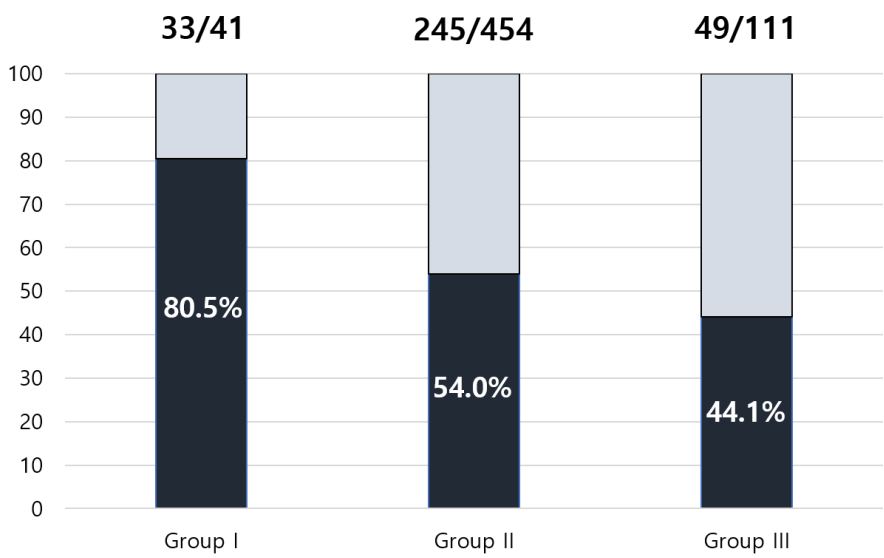


Figure 8. The diagnostic yield according to the patients' classification



2. Analysis of nationwide medical services and contribution of KUDP

Current status of medical practice for pediatric rare disease in Korea

The average time required to assess initial medical service after the first symptom recognition was 5.2 months (range, 0-16 years). About three quarters of patients (450/606, 74.3%) visited tertiary hospital via primary care provider within 3 months from symptom onset, while only 78 patients (12.9%) took more than a year (Figure 9). In detail, patients who showed initial symptoms in infancy tended to get diagnostic evaluation with minimal time gap (Figure 10). Most patients whose symptom started at birth (congenital onset) or before 1 month of age were able to be admitted to the neonatal intensive care unit immediately, except few patients with relatively non-emergent manifestations (e.g. early onset ichthyosis). Patients with late–onset manifestations tended to start evaluation with some delay. The average time spent for diagnosis before the participation was 3.24 years (range, 0-16.6 years). More than half of patients participated in the study within a year from the time of first diagnostic evaluation in 2017. The number of patients who had diagnostic journey over 5 years have increased every year, and more than 20% of patients had more than 5 years of history for diagnostic evaluation since 2018 (Figure 11). A hundred patients aged 10 years and over spent 7.3 years for their diagnostic evaluation, significantly longer than whole average.

This study included patients with suspected rare genetic disorders, and

performed genetic tests and its results of all patients were reviewed. Types and number of standard diagnostic evaluation have been changed over years in line with advancement in techniques (Figure 12). Chromosome studies and single gene tests were performed in similar rate, whereas the proportion of patients who had NGS have rapidly increased over years. A CMA have replaced conventional karyotyping and the proportion of patients who underwent target gene panel have also increased over years, as both were officially approved in 2019 (Figure 13). Among the 345 patients who had one or more chromosome study, 148 (42.9%) had a CMA after the conventional karyotyping and 6 (1.7%) repeated the same study at different hospitals.

Figure 9. The time gap between symptom onset to first diagnostic evaluation

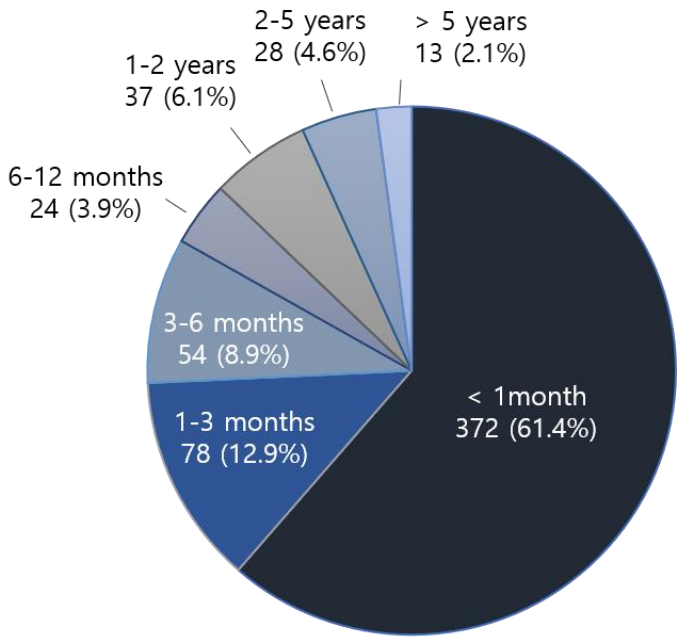


Figure 10. The time gap between symptom onset to first diagnostic evaluation according to various symptom onset age

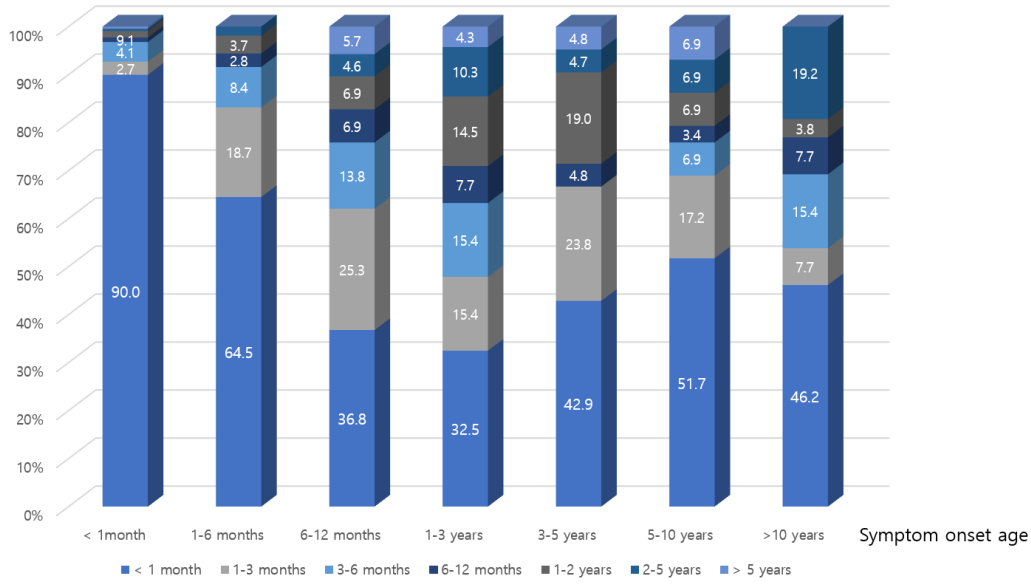


Figure 11. The duration of undiagnosed state before the KUDP admission

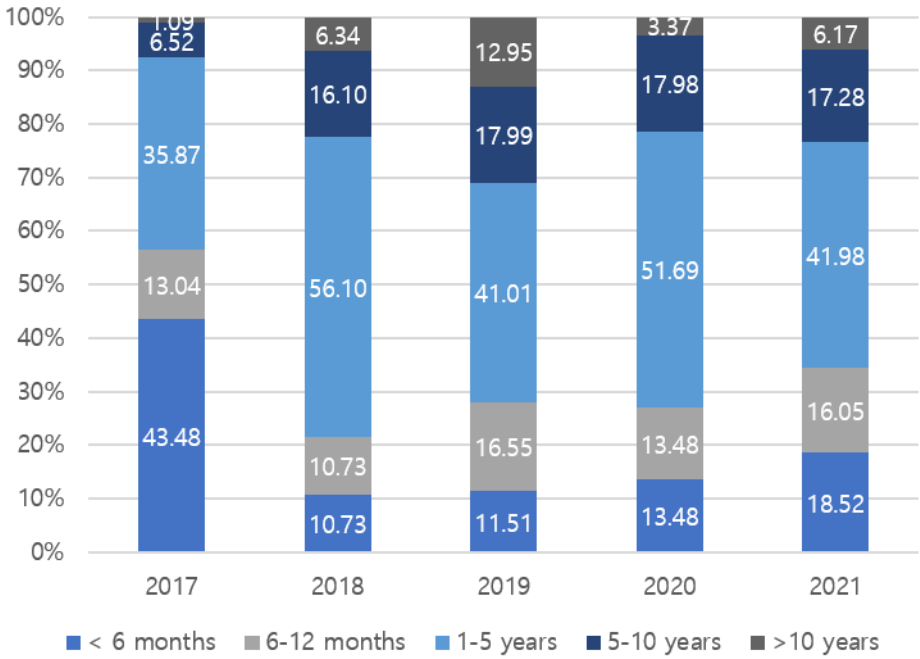


Figure 12. Changes of the proportion of diagnostic tests performed before the KUDP admission

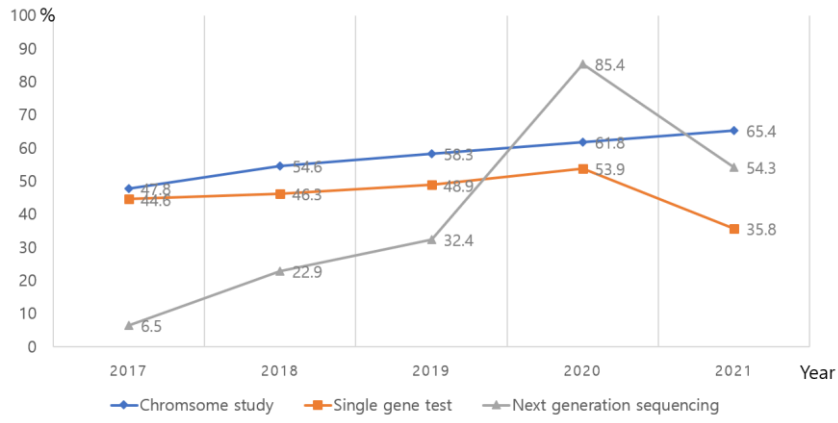
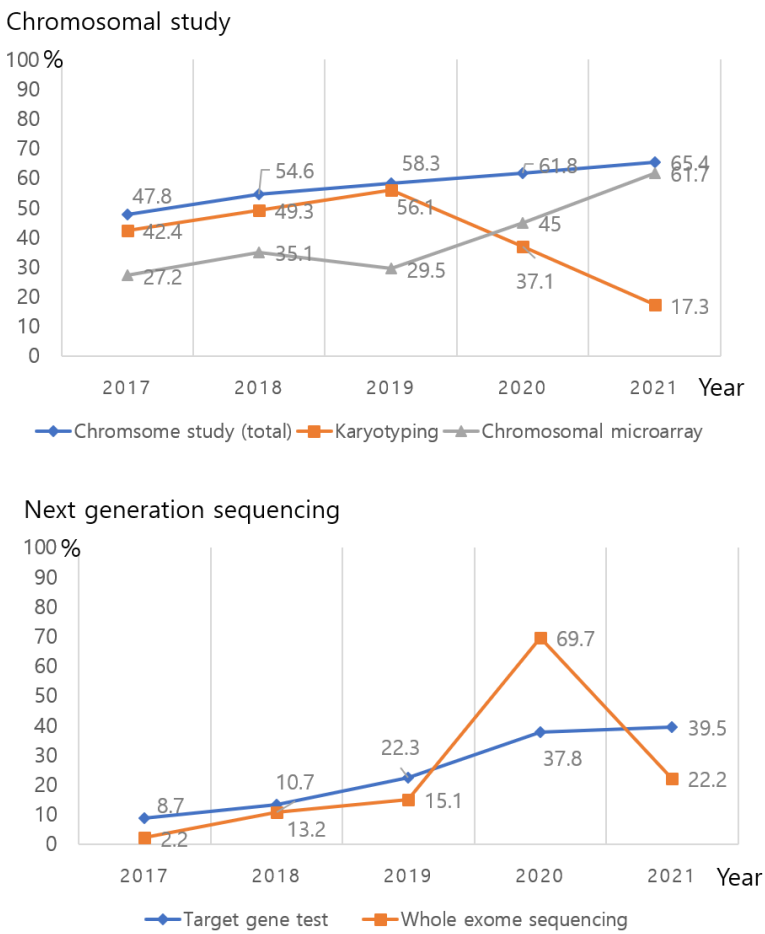


Figure 13. Changes of the proportion of the chromosome study and next generation sequencing before performed the KUDP admission



Social indicators: geographic distribution and changes in referral system

One of the main goals of the KUDP is to cover the entire nation. Enrolled patients were scattered throughout the nation according to their legal residences (Figure 14) [25]. The distribution was similar with the general population, although the proportion of patients was slightly higher than general population in

metropolitan area, reflecting the high proportion of youth. Sixteen of 250 patients (6.4%) who did not live in metropolitan area chose the hospital in the capital city despite of available regional hospital near the residence.

The application to the study was made by 2 different ways: 1) refer from other clinician, 2) direct screening of patients who visited Seoul National University Hospital. The majority of patients participated in the study through the latter way in 2017, but the proportion of patients referred from other clinician have increased over year, from 0% in 2017 to 24.7% in 2021 (Figure 15). The study protocol included regular check-ups for patients at center or regional hospitals regardless of final diagnosis, as undated phenotypes were essential for deciding next step or reverse phenotyping. Forty-eight patients (48/606, 7.9%), however, lost to follow-up or refuse to next evaluation.

Figure 14. The geographical distribution of patients compared to general population

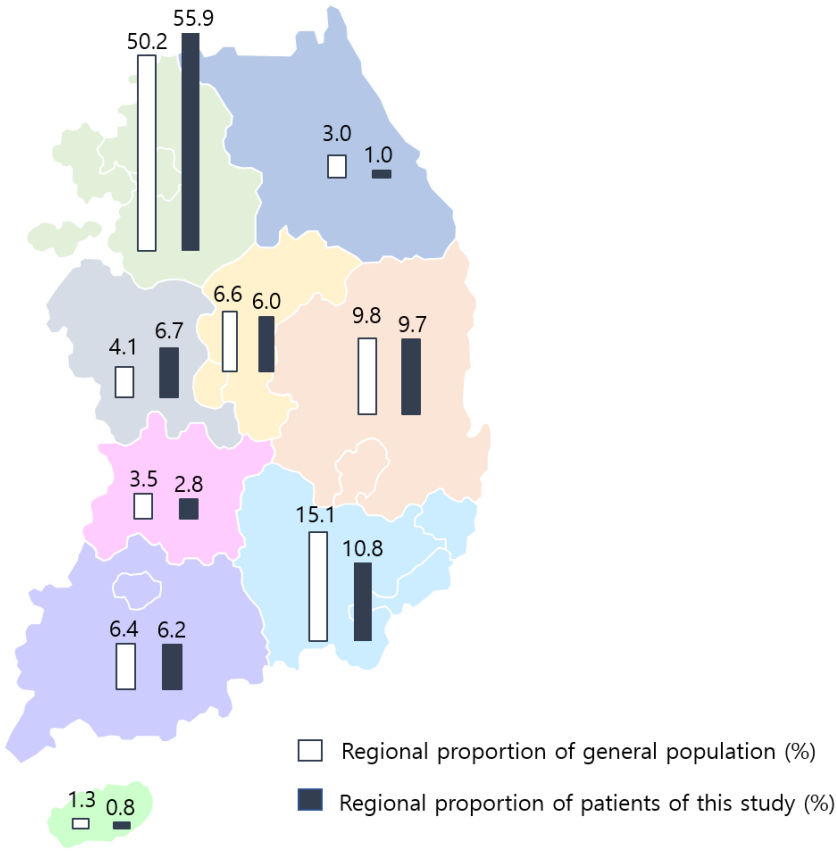
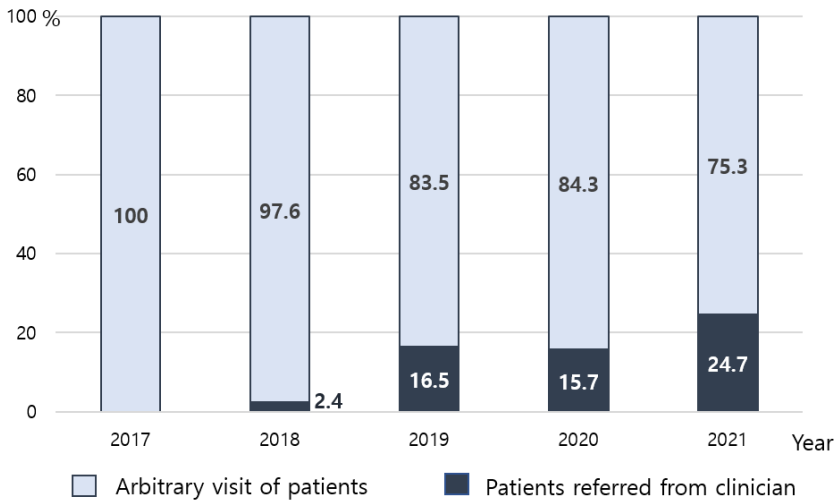


Figure 15. The change in the way of application over years



3. Illustrative cases

Ending the diagnostic odyssey

A 10-month-old girl admitted to KUDP initially presented with developmental delay from the age of five months. She had been seen at two different tertiary care neurology clinics and had undergone extensive testing, including repeat brain magnetic resonance imaging (MRI), metabolic screening, and diagnostic ES. These comprehensive evaluations failed to identify genetic defects, although she was identified as having developmental delay with brain malformation. After KUDP admission followed by reevaluation at an expert clinic, additional findings such as myopathic face and elevated serum creatinine kinase (CK) level (6275 IU/L, normal range 20–270 IU/L) were identified. The expert consortium suspected alpha-dystroglycan-related congenital muscular dystrophy (especially Fukuyama type), and fukutin gene analysis was performed. Compound heterozygous mutations in *FKTN*, c.165+835T>G (deep intronic mutation, founder mutation in Korean population) and c.49A>C, were identified as a confirmative diagnosis [26].

In another case, a 12-month-old girl had been evaluated for developmental delay at two other tertiary hospitals. Brain MRI had revealed mild brain atrophy and delayed myelination, and laboratory tests including metabolic screening were unremarkable except for slightly elevated liver enzymes. She was admitted to KUDP and reevaluated by the expert consortium, which recognized her

developmental arrest as being followed by regression and noticed diffuse hypomyelination on her brain MRI. We then performed a skeletal survey, which indicated dysostosis multiplex including inferior beaking of the lumbar spine. Suspecting GM1-gangliosidosis, enzyme assay for β-galactosidase was ordered, which revealed markedly decreased activity (1.0 nmol/hr/mg protein, normal range 80–140 nmol/hr/mg protein). We also performed Sanger sequencing for *GLB1* and identified compound heterozygous mutations, c.517_519delCTC and c.1343A>T.

Nongenetic rare disease

The patient was a 6-year-old boy who presented progressive muscle weakness. He started his diagnostic journey at 4 years old for a motor delay and elevated CK levels (5245 IU/L, reference 20-270 IU/L). Subsequent genetic study, a MLPA test and sequencing for *DMD*, a targeted gene panel for muscular dystrophy, and ES were conducted for diagnosis, but none of these tests could make a correct diagnosis. A muscle biopsy indicated many degenerating and regenerating fibers with endomysial fibrosis, consistent with muscular dystrophy, but normal expression of dystrophin was seen on immunohistochemical study. After KUDP admission, clinicians reviewed the patient's entire medical history and noticed rapid deterioration and weakness in the lower extremities within a year, followed by progression to the upper extremities after flu infection. He became wheel-chair bound and could not elevate his arms within 2 years from symptom recognition.

We suspected a rare form of inflammatory myositis and checked for multiple myositis-specific autoantibodies. As a result, he was diagnosed with anti-signal recognition particle antibody-related inflammatory myositis. He was treated with corticosteroids, immunoglobulin and rituximab after diagnosis and showed improvement in muscle power.

Identification of a case of double-trouble

The third patient was 35 months old when he was admitted to the KUDP. He was born at a gestational age of 40 weeks after an uneventful pregnancy. He had multiple café-au-lait spots that spread over time. His developmental milestones were slightly delayed, and he showed tiptoeing followed by left ankle contracture since the age of 30 months. He visited the tertiary center, and underwent brain MRI and ES. The brain MRI indicated high signal intensity lesions on the bilateral basal ganglia. The ophthalmological examination demonstrated bilateral Lisch nodules. A pathogenic variant, c.344C>T, from *NF1* was identified by ES. The patient was diagnosed with neurofibromatosis type 1 (NF1) with atypical NF1 stigmata on brain imaging and rehabilitation was recommended for abnormal walking. His parents voluntarily visited the KUDP center for further evaluation due to his sustained gait abnormality. The patient showed increased muscle tone and definite upper motor neuron signs on lower legs, and a review of the MRI suggested a metabolic disorder such as Leigh disease other than NF1 stigmata, although NF1

was also consistent with the phenotype. We enrolled the patient and performed additional mitochondrial genome sequencing, which revealed the m.3697G>A homoplasmy variant, known as the causative variant for Leigh syndrome [27].

Emergent process for an early medical decision

A 2-month-old girl who showed intractable seizures, hyperreflexia, and hypertonia since her first day of life was referred to the KUDP. She was administered multiple antiepileptic drugs and muscle relaxants, including continuous intravenous midazolam, and was fully dependent on a mechanical ventilator. Serial brain MRI revealed rapidly progressive brain atrophy. The expert consortium classified her as an emergent case that needed rapid diagnosis and clinical decisions. Rapid ES for the family was conducted, and compound heterozygous variants, c.1276C>T and c.1313_1314delAG, from *BRAT1* were identified within 2 weeks. She was confirmed to have rigidity and multifocal seizure syndrome (MIM#614498). The parents withdrew life-sustaining treatment for the patient after diagnosis and comprehensive genetic counseling. Two years later, the couple had a healthy baby by in vitro fertilization with preimplantation genetic diagnosis.

Discovery of a new disease via international collaboration

A 4-year-old boy was admitted to KUDP with developmental delay and bilateral sensorineural hearing loss. Hypertelorism and high arched palate was

noted at initial examination. His brain MRI was unremarkable except anterior convex appearance of posterior fossa and obliteration of CSF space at foramen magnum. The patient could walk independently at 3 years old but could not speak a word at the time of last follow-ups. Sanger sequencing for *CHD7* and ES for a patient did not figure out the genetic etiology. As there was no definite clinical diagnosis, trio ES was performed, revealing a de novo variant, p.His1284fs in *MN1*. Because *MN1* had never been reported in a human as a disease-causing gene, we shared the phenotype and genomic data with other international groups through the online matchmaking service and thereby confirmed that the genetic defect of *MN1* plays a critical role in human brain development [21].

Discussion

This study included pediatric patients suspected to have rare genetic disorders and focused on identifying molecular basis of patients from the KUDP program. The KUDP is a national project launched by Korean government, with primary goals of solving the unmet needs of patients with undiagnosed RDs and establishing nationwide infrastructures for long-term research. In detail, the program aimed to cover whole country throughout organizing nationwide network and develop research system, as well as clearing the undiagnosed cases. According to the inclusion criteria considering social requirement, patients' enrollment was made by diagnostic status at the time of application. Target diseases were not limited to certain organs or categories, and medical urgency or time spent to diagnosis was important factors for deciding final enrollment. To evaluate the study, therefore, comprehensive analysis in many different ways is required. Here I reviewed the study result in clinical and social aspects, and suggested the future direction of the KUDP.

The present study indicated 54% of diagnostic yield (327/606). There are many different national RD research program, and their diagnostic yields are different, from 28% in UDN to 67% in Spain UDP [9, 28, 29]. There are some similarities and differences in programs (Table 5). The SpainUDP and Singapore undiagnosed disease program focused on genetic diagnosis using ES or GS for undiagnosed patients [9, 10]. Neurologic problems and/or multiple anomalies were

major chief complaint, accounting over 70% [10, 29]. The IRUD project reported 43% of positive result (1,808 of 4,205 patients) [28]. This project used only ES and GS for diagnosis, but functional core laboratories also supported the project and some new diseases were identified [28]. The UDN showed the lowest diagnostic yield, which suggested inclusion of patients with ultra-rare diseases. Although the UDN is known to utilize RNA sequencing or metabolomic experiments, conventional tests or clinical round have conducted important role. Both the KUDP and UDN showed similar proportion of conventional tests for diagnosis, which suggested important role of deep phenotyping and targeted testing (Table 6).

The relatively high diagnostic rate of the KUDP resulted from patients with medically actionable genetic diseases or long diagnostic journey to satisfy social unmet need. Enrollment of these patients is still necessary, but it is also clear that the patients with ultra-rare disease undiagnosed after ES should be the majority of the program. We classified patients to evaluate whether the program goes in the right direction or not, although the criteria were not objective and depend on clinicians' experiences especially in Group II and III. The proportion of Group I have yearly decreased, whereas that of Group III increased (Figure 16). The proportion of Group III was relatively high in 2017 (19.6%), probably because of relatively short experiences in the pilot study and completion of some functional studies. The proportion of Group III was similar in 2020 and 2021 (36.0% and 33.3%), but the diagnostic yield was significantly lower in 2021 than 2020 (50.0%

vs. 29.6%, Table 7). We expect higher proportion of Group III decided by fully experienced expert consortium.

Detailed enrollment criteria was reviewed every year, and the standard of the “appropriate test” changed as permitted diagnostic tests were changed by the government insurance policy. We tried to reflect diagnostic tests previously performed in participants screening, and patients who already underwent NGS had priority in the KUDP admission. The diagnostic yield was quite similar in patients or prior NGS group. Sixty-three of 125 patients (50.4%) who already underwent ES before enrollment had final diagnosis on the strength of trio-based ES, data reanalysis, and updated knowledge. It was also clear that most solved cases had causative genes that would be detected by previous analysis, although we could not compare the exact data because of its unavailability. In detail, 2 patients were diagnosed as non-genetic disorder and 4 cases were cleared by CMA or single gene testing. Four cases carried somatic variants detected by individualized analysis based on phenotypes. These are direct examples of importance of comprehensive clinical assessment. Others were cleared by ES and it suggested the importance of expertized and comprehensive analysis of data. We also performed RNA sequencing and multiple biochemical assays, which are still unavailable in Korea. All of the abovementioned findings indicated an unchanged, unmet need for rare disease patients.

The program planned regular clinical follow-ups for the patients and

reanalyzed ES data every 6 months to 1 year. I screened and selected patients with the following criteria: 1) patients who were highly suspected to have a certain genetic disease with characteristic features; 2) patients with a pathogenic or likely pathogenic variant of one allele in the autosomal recessive pattern gene and the matched phenotypes; and 3) patients with a rapidly deteriorating course without acquired cause. Reanalysis made additional diagnoses in 9 of 55 patients (16.4%). Three cases had variants of low-coverage. They were identified on the strength of concentrating on clinically interesting region. Others had variants of recently documented disease-causing genes. Large number of ES was conducted and relative in-house RD database have been established. In summary, we made a fair clinical result both in quantitative and qualitative terms.

Establishing infrastructures for RD research is another goal of KUDP. The web-based system included electronic cohort management based on the HPO and searching or selective data sharing functionalities for open electronic case reports, MME, and functional research. This is in the final adjustment period, and we expect this system to help sharing clinical data among clinicians, avoiding unnecessary data generation and activating international collaboration. The functional core laboratories for validating candidate genes or variants also performed essential role in RD diagnosis. The data management system and functional core laboratories will be essential infrastructure for sustainable RD research in Korea.

This study showed characteristics of medical delivery and insurance system

in Korea. Korean government provides universal medical insurance that prioritizes easy accessibility to above-average medical services and determines the affordable cost and indication of all medical practices. This centralized system makes patients choose tertiary hospitals for their first medical service and voluntarily visit another hospital in a short time, disregarding the stepwise medical delivery system. Patients often had same tests repeatedly at different hospitals, significant resource wasting in social perspectives. It assures patient rights and certain level of medical services to the general population, but it also reveals a serious problem with the current medical system. Applications for the KUDP were made in two ways reflecting this point: referral from a clinician or a voluntary visit to the coordinating central hospital. The latter accounted for the majority of the total enrollment since the KUDP pilot project [14]. The KUDP tried to establish a nationwide network throughout the country and improve the medical delivery system. We introduced the KUDP in various nationwide academic societies and regional rare disease network centers, requesting early referrals followed by referrals back with exact diagnosis and therapeutic guidelines within the medical network so that patients do not need to go from hospital to hospital. The Korea Disease Control and Prevention Agency also designated regional rare disease centers in each province and established a nationwide rare disease network in 2019. We also made various channels for patient referrals, such by phone, electronic mail, and the internet. As a result, the program recruited patients throughout the country, and the proportion

of referrals from regional network hospitals dramatically increased.

Our study also verified radical changes in medical environment and demonstrated social need for national RD program. Despite of easy accessibility to special clinics, enrolled patients remained undiagnosed for approximately over 3 years on average. Patients enrolled in 2017 spent the shortest amount of time, whereas more than 20% of patients have long diagnostic journey over 5 years. It suggested the positive effect of constant public relation and necessity of maintenance of the study. Another interesting point is the rise in NGS study in practice. As only target gene panels consisting of a limited number of genes are permitted in the Korean insurance system to date, further approaches such as ES are only performed by research platforms. Such data, however, seemed hard to qualify and manage consistently. As noted earlier, more and more patients were enrolled despite of prior target gene panel or ES and about half of them were newly diagnosed. It supported the need of reforming of medical policy in Korea. The KUDP is performing important role for clinical unmet need, but further focusing on Group III and function validation is next goal for competitive research. Separation between clinical support program for patients and research program for patients with truly unidentified disease can be an option. Systematic regulation of genome data and specific plans for data sharing for data reanalysis was also required.

Table 5. Comparison of RD programs in other countries

Program (country)	Period	Process	Enrolled patients	Diagnostic yield	Inclusions	Ref
UDN (United States)	2015-2022 (ongoing)	ES, GS, multi-omics, functional team	2,246	28%	● Decided by UDN clinical sites	29
SpainUDP (Spain)	Oct 2015-May 2018 (ongoing)	ES	147	67%	● Show clinical signs and symptoms but not clearly identifiable to a known disease, despite of extensive evaluation	9
Singapore UDP (Singapore)	2014-2019 (ongoing)	ES, GS	196	33.3% (ES) 37.8% (GS)	● Undiagnosed patients who had undergone previous genetic testing	10
IRUD (Japan)	2017-2020 (ongoing)	ES, GS functional team	4,205	42.9%	● Remained undiagnosed period > 6 months ● Multiorgan-involvement or positive family history	25

UDN, Undiagnosed Disease Network; ES, exome sequencing; GS, genome sequencing; SpainUDP, spina undiagnosed diseases program; IRUD, Initiative on Rare and Undiagnosed Disease

Table 6. The proportion of diagnostic tests for positive cases in the KUDP and UDN

	UDN (572 patients diagnosed)	**KUDP** (327 patients diagnosed)
NGS	81%	84%
Clinical grounds	6%	2.4%
Direct testing	9%	9.2%
Chromosomal microarray/transcriptome	4%	4.3%

UDN, Undiagnosed Disease Network; KUDP, Korean Undiagnosed Diseases Program; NGS, next generation sequencing

Figure 16. Yearly changes of proportion of patients' classification

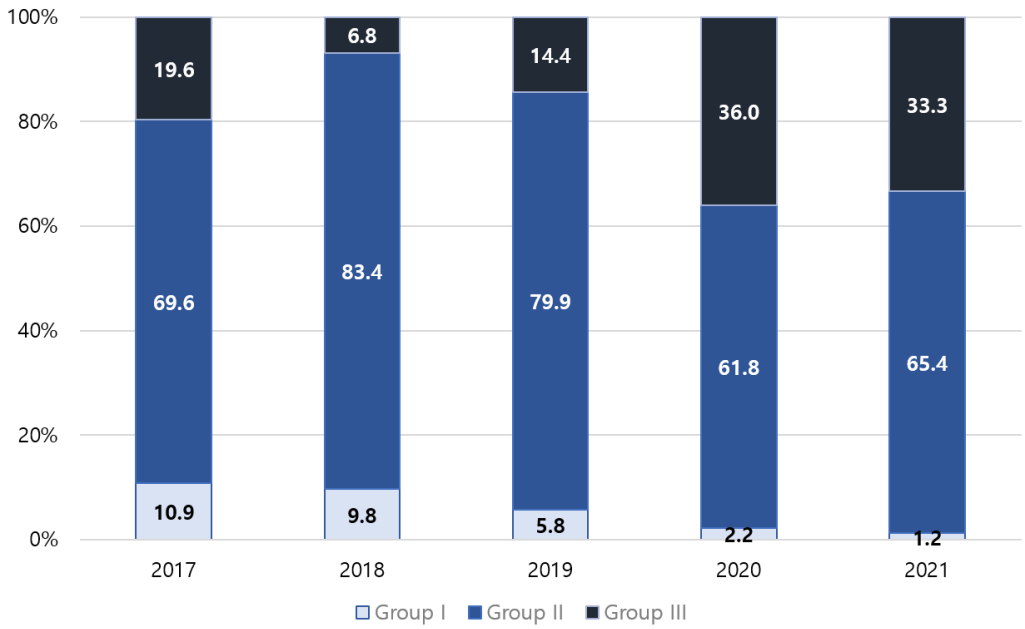


Table 7. detailed diagnostic yield according to the clinical classification in each year

	2017	2018	2019	2020	2021
Group I	8/10 (80.0%)	15/20 (75.0%)	7/8 (87.5%)	2/2 (100%)	1/1 (100.0%)
Group II	31/64 (48.4%)	99/171 (57.9%)	55/111 (49.5%)	33/55 (60.0%)	27/53 (50.9%)
Group III	10/18 (55.6%)	6/14 (42.9%)	9/20 (45.0%)	16/32 (50.0%)	8/27 (29.6%)
Total	49/92 (53.4%)	120/205 (58.5%)	71/139 (51.1%)	51/89 (57.3%)	36/81 (44.4%)

5. Conclusions

This study summarized the result of KUDP and figured out the present practice for pediatric patients with undiagnosed genetic RDs in Korea. To date, patients in medically or socially underprivileged were well screened, and about half of them were diagnosed. The favorable diagnostic yield was made based on detailed phenotyping and appropriate diagnostic tests with superior analytic pipeline. The present study also proved remained or constant need for the national RD program, although its details such as inclusion criteria or contents of diagnostic process should be revised in tandem with national policy and advancement of RD practice. Overall, the program should keep fulfilling the clinical unmet need, and also making improvements on unidentified disease using functional research and data sharing.

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국문 초록

연구 배경: 희귀질환은 일반적으로 진단 과정이 지난하고 평생에 걸친 관리가 필요한 경우가 많아, 과도한 의료 비용 및 사회적 부담을 야기한다. 유전학적 기법의 발전에 힘입어, 여러 나라에서는 각국의 의료제도를 반영한 국가 차원의 희귀질환 연구 프로그램을 운영하기 시작하였다. 대한민국의 경우 2017년에 미진단 희귀질환자에 대한 연구 프로그램을 시작하여 현재까지 운영 중에 있다. 본 연구는 현재까지 한국 미진단 프로그램에 등록된 소아 환자들을 대상으로 환자들의 임상적, 사회인구학적 특성을 확인하고 프로그램 운영 결과를 분석하여 국내 소아 희귀질환자 진료 현황 및 한국 미진단 프로그램운영의 의의에 대해 고찰하고자 한다

연구 방법: 한국 미진단 프로그램에 등록된 18세 미만의 유전적 원인이 의심되는 희귀질환자를 대상으로 하였다. 환자들의 분자 진단을 위한 단계적 검사, 검사 결과의 확인 및 최종 진단, 추가 검증 등을 개별적으로 진행하고, 동시에 임상적, 사회학적 정보를 수집하여 진단 검사 결과와 함께 분석하였다. 환자의 특성 파악과 미진단 프로그램의 효과 분석을 위해 모든 환자는 초기 임상 진단에 따라 세 그룹으로 분류하였다. 단일 검사로 확인 가능한 특징적인 질환으로 판단되는 환자는 그룹 1, 임상적, 유전학적 다양성을 보여 비교적 광범위한 검사가 필요한 질환군이 의심되는 경우 그룹 2, 현재까지의 의학 정보로는 진단 추정이 어렵거나 기존의 임상상과 다른 비전형적 특성을 보이는

경우 그룹 3으로 정의하였다.

연구 결과: 2017년 1월부터 2021년 12월까지 한국 미진단 프로그램에 등록된 666명의 환자 가운데 606명이 본 연구에 최종적으로 포함되었다. 이 중 41명(6.8%)의 환자는 그룹 1, 454명(74.9%)은 그룹 2, 그리고 111명(18.3%)은 그룹 3으로 분류되었다. 환자들의 평균 증상 발현 나이는 1.4세였으며 504명(83.2%)의 환자는 증상 발현시점으로부터 6개월 이내 진단을 위한 첫 진료를 받았다. 전체 환자의 73.8% (447명)는 신경학적 증상을 주요 증상으로 보고하였다. 환자들은 본 연구 참여 전 약 3년에 걸쳐 평균 1.4군데의 병원에서 6.1가지의 진단 검사를 시행한 것으로 확인되었다. 본 연구에서 환자들은 서로 다른 진단 검사를 단계적으로 시행받았고, 이 검사에는 염색체마이크로어레이, 단일 유전자 검사, 전장엑솜검사, RNA 염기서열분석검사, 특수 생화학 검사, 면역항체 검사 등이 포함되었다. 606명 중 327명이 최종적으로 진단받았고 (진단율 54.0%) 이 중 84.1% (275례)는 차세대염기서열검사를 통해 확인되었다. 그 외 44명(13.4%)은 다른 종류의 유전자검사로, 8명(2.4%)는 비유전자검사등을 통해 비유전성 희귀질환으로 최종 진단되었다. 전장엑솜검사로 진단된 환자 중 9명은 초기 결과 분석에서는 결론을 내리지 못하였으나, 데이터 재분석을 통해 추가로 진단되었다. 지속적인 검사 비용 감소등을 통해 본 연구 등록 전 이미 진단 검사의 일환으로 전장엑솜검사를 시행했던 환자의 비율이 지속적으로 높아지고 있으며 기존 전장엑솜검사 후에도 진단을 받지 못하여 연구에 등록한 환자 그룹에서도 전체와 비슷한 50%의 진단율을 보여 진단 검사 자체보다

환자에 대한 다각적이고 전문적인 접근이 중요함을 시사하였다. 임상 진단 검사를 수행한 후에도 진단받지 못한 환자군의 경우 한국미진단프로그램 기능연구팀과 협력하여 지금까지 알려지지 않은 후보 유전자를 선정하고 이 중 4례에 대해 기능연구를 완료하여 환자에 대한 추가 진단이 가능하였고 6례에 대해서도 연구 중에 있다.

결론: 본 연구를 통하여 현재까지 진단받지 못한 희귀유전질환이 의심되는 소아 환자를 대상으로 반 수 이상의 환자에서 질환 원인을 규명하였고 한편으로 국내 소아 희귀질환자의 진료 환경을 확인하였다. 국내 상급의료기관 접근성은 매우 높고 여러 종류의 유전자 검사도 폭넓게 시행되고 있으나, 일반 진료 환경에서는 지속적인 진단 검사 진행 및 연구 수행이 어렵다. 이러한 문제의 해결을 위해서는 우수한 진단역량을 갖춘 희귀질환 전문진료팀 및 기능연구팀의 뒷받침이 필요하다. 따라서 소아희귀질환의 지속 가능한 연구를 위한 국가차원의 지원이 필요하며, 여기에는 진료 환경의 변화와 발전에 따라 세부 내용의 변경이 수반되어야 하겠다.

주요어: 희귀질환진단, 미진단프로그램, 유전성 희귀질환, 차세대염기서열분석

학번: 2019 – 35326

Supplementary Table 1. Detailed information on the diagnosed patients

No.	Sex/Age	clinical group	Initial assessment	Final diagnosis (#OMIM)	Gene
1	M/3.3	3	Syndromic short stature and failure to thrive	Bainbridge-Ropers syndrome (#615485)	*ASXL3*
2	M/0.5	3	Neonatal hypotonia with sensorineural hearing loss	Intellectual developmental disorder, X-linked, syndromic, Wu type (#300699)	*GRIA3*
3	M/0.5	3	Neurodevelopmental disorder	Martsolf syndrome 2 (#619420)	*RAB3GAP1*
4	M/1.7	3	Neurometabolic disorder (R/O nonketotic hyperglycinemia)	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant (#614254)	*GRIN1*
5	F/0.5	3	Neurodevelopmental disorder with macrocephaly	Shashi-Pena syndrome (#617190)	*ASXL2*
6	M/1.3	3	Neurodevelopmental disorder	Intellectual developmental disorder, X-linked 21 (#300143)	*IL1RAPL1*
7	M/0.2	3	Developmental and epileptic encephalopathy	developmental and epileptic encephalopathy 7 (#613720)	*KCNQ2*
8	M/0	2	Congenital muscular dystrophy	Myopathy, centronuclear, X-linked (#310400)	*MTM1*
9	M/0.6	2	Congenital muscular dystrophy	Muscular dystrophy-dystroglycanopathy, type A (#253280)	*POMGNT1*
10	F/0.7	3	Neurodevelopmental disorder with multiple anomalies	17p13 deletion (1Mb)	
11	M/1.1	3	Developmental and epileptic encephalopathy, early-onset	Epilepsy, pyridoxine-dependent (#266100)	*ALDH7A1*

12	F/1.8	4	Uncategorized interstitial lung disease, early-onset, progressive	Surfactant metabolism dysfunction, pulmonary, 2 (#610913)	*SFTPC*
13	M/1.8	3	Syndromic short stature	Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis (#614813)	*POC1A*
14	F/0	4	Multiple anomalies and unknown multiple endocrine dysfunction	Even-plus syndrome (#616854)	*HSPA9*
15	F/0.6	2	CHARGE syndrome	CHARGE syndrome (#214800)	*CHD7*
16	M/16.5	3	Neurodevelopmental disorder with multiple anomalies	Cornelia de Lange syndrome (#122470)	*NIPBL*
17	F/7.8	3	Developmental and epileptic encephalopathy	Intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia (#300749)	*CASK*
18	M/0.8	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 6B, non-Dravet (#619317)	*SCN1A*
19	M/4.8	3	Profound neurodevelopmental disorder with dysmorphic facies	Cortical dysplasia, complex, with other brain malformations 4 (#615412)	*TUBG1*
20	M/11.9	3	Congenital myopathy	Nemaline myopathy 6, autosomal dominant (#609273)	*KBTBD13*
21	M/1.5	3	Neurodevelopmental disorder with sensorineural hearing loss	1q43q44 duplication (7Mb) 18q21q23 deletion (22Mb)	
22	M/3.0	3	Neurodevelopmental disorder with multiple anomalies	Coffin-Siris syndrome 1 (#135900)	*ARID1B*
23	M/2.6	3	Neurodevelopmental disorder with multiple anomalies	Baraister-Winter syndrome (#614583)	*ACTG1*
24	M/4.0	3	Neurodevelopmental disorder with dysmorphic facies	Bainbridge-Ropers syndrome (#615485)	*ASXL3*

25	M/5.2	3	Neurodevelopmental disorder with dysmorphic facies	Ardoleda-Tham syndrome (#616268)	*KAT6A*
26	F/3.8	3	Congenital muscular dystrophy	Bethlem myopathy (#158810)	*COL6A1*
27	M/2.3	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, X-linked 99 (#300919)	*USP9X*
28	M/5.5	3	Neurodevelopmental disorder	Allan-Herndon-Dudley syndrome (#300523)	*SLC16A2*
29	M/2.0	3	Neurodevelopmental disorder with dysmorphic facies	Bohring-Opitz syndrome (#605039)	*ASXL1*
30	M/3.0	3	Neurodevelopmental disorder with dysmorphic facies	Buratti-Harel syndrome (#619314)	*SIAH1*
31	F/8.5	2	Smith-Lemli-Opitz syndrome	Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (#617755)	*BPTF*
32	F/2.4	2	Alagille syndrome	Alagille syndrome 1 (#118450)	*JAG1*
33	M/6.2	3	Neurodevelopmental disorder with dysmorphic facies	CEBALID syndrome (#618774)	*MN1*
34	F/2.4	3	Syndromic short stature	Cornelia de Lange syndrome 5 (#300882)	*HDAC8*
35	M/6.2	3	Congenital myopathy	Nemaline myopathy 2 (#256030)	*NEB*
36	F/1.2	3	Neuromuscular disorder	Spinal muscular atrophy, lower extremity-predominant 1, AD (#158600)	*DYNC1H1*
37	F/1.3	2	Costello syndrome	Costello syndrome (#218040)	*HRAS*

38	F/0.8	3	Neurodevelopmental disorder with multiple anomalies	2q37 deletion (6.4mb)	
39	M/2.3	3	Noonan syndrome	Coffin-Siris syndrome 6 (#617808)	*ARID2*
40	M/1.5	3	Peters plus syndrome	Micropthalmia, syndromic 12 (#615524)	*RARB*
41	F/11.8	3	Hereditary spastic paraplegia	Dystonia 4, torsion, autosomal dominant (#128101)	*TUBB4A*
42	M/10.7	4	Multiple anomalies and congenital-onset fetal micromelia	3-M syndrome 1 (#273750)	*CUL7*
43	M/3.3	3	Neurometabolic disorder	Malonyl-CoA decarboxylase deficiency (#248360)	*MLYCD*
44	M/0.3	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 5 (#613477)	*SPTAN1*
45	F/1.3	3	Neurodevelopmental disorder with microcephaly	combined oxidative phosphorylation deficiency 24 (#616239)	*NARS2*
46	F/4.4	3	Neurodevelopmental disorder with Dandy-Walker variant	Intellectual developmental disorder, X-linked 99 (#300919)	*USP9X*
47	M/1.9	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, X-linked 98 (#300912)	*NEXMIF*
48	M/1.4	3	Arthrogryposis multiplex congenita	Neurodevelopmental disorder with involuntary movements (#617493)	*GNAO1*
49	M/1.1	4	Recurrent intracranial hemorrhage and congenital cataract	brain small vessel disease with or without ocular anomalies (#175780)	*COL4A1*
50	F4/2.0	3	Microcephalic osteodysplastic primordial dwarfism spectrum	Cockayne syndrome, type B (#133540)	*ERCC6*

51	M/0.8	2	Pelizaeus-Merzbacher syndrome	Pelizaeus-Merzbacher disease (#312080)	*PLP1*
52	F/2.4	3	Developmental and epileptic encephalopathy	Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities (#618089)	*FBXO11*
53	M/6.3	3	Profound neurodevelopmental disorder with dysmorphic facies	developmental and epileptic encephalopathy 7 (#613720)	*KCNQ2*
54	F/0.2	4	Neurodegenerative disorder, early-onset	Rigidity and multifocal seizure syndrome, lethal neonatal (#614498)	*BRAT1*
55	F/3.5	3	Neurodevelopmental disorder with dysmorphic facies	Impaired intellectual development and distinctive facial features with or without cardiac defects	*MED13L*
56	F/0.8	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 47 (#617166)	*FGF12*
57	M/4.8	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, autosomal dominant 63, with macrocephaly (#618825)	*TRIO*
58	M/0.8	2	Schinzel-Giedion syndrome	Schinzel-Giedion midface retraction syndrome (#269150)	*SETBP1*
59	F/1.6	3	Multiple anomalies with congenital ichthyosis	Sjogren-Larsson syndrome (#270200)	*ALDH3A2*
60	M/0.9	3	Neurodevelopmental disorder with dysmorphic facies	22q11 duplication (2Mb)	
61	M/7.8	3	Congenital myopathy	Bethlem myopathy 2 (#616471)	*COL12A1*
62	M/16.1	4	Neonatal hypotonia, early-onset progressive skeletal problems and dysmorphic face	Klippe-Feil syndrome 4, autosomal recessive, with myopathy and facial dysmorphism (#616549)	*MYO18B*
63	M/4.7	3	Neurodevelopmental disorder (central hypotonia)	Spinocerebellar ataxia, autosomal recessive 4 (#607317)	*VPS13D*

64	F/2.5	3	Arthrogryposis multiplex congenita	Baller-Gerold syndrome (#218600)	*RECQL4*
65	F/2.2	3	Congenital myopathy	Central core disease (#117000)	*RYR1*
66	F/10.6	3	Developmental and epileptic encephalopathy	Spastic paraplegia 11, autosomal recessive (#604360)	*SPG11*
67	M/0.5	4	Early-onset progressive multiorgan failure and brain atrophy	Rajab interstitial lung disease with brain calcifications 2 (#619013)	*FARSA*
68	M/10.1	3	Syndromic short stature	3-M syndrome 1 (#273750)	*CUL7*
69	F/0.9	2	Prader-Willi syndrome	15q11 maternal	
70	F/4.8	3	Developmental and epileptic encephalopathy	Neurodevelopmental disorder with microcephaly, hypotonia, and variable brain anomalies (#617481)	*PRUNE1*
71	M/1.1	3	Developmental and epileptic encephalopathy	developmental and epileptic encephalopathy 1 (#308350)	*ARX*
72	M/1.8	3	Neurodevelopmental disorder with macrocephaly and congenital neutropenia	Alkuraya-Kucinskas syndrome (#617822)	*KIAA1109*
73	M/0.1	4	Unknown neurodegenerative disease, early-onset progressive, with	Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1 (#614388)	*DNM1L*
74	M/1.5	3	Neurodevelopmental disorder with multiple anomalies	Cornelia de Lange syndrome 1 (#122470)	*NIPBL*
75	F/4.0	3	Neurodevelopmental disorder with multiple anomalies	6p25 deletion	
76	M/0.8	3	Neurodevelopmental disorder with multiple anomalies	Coffin-Siris syndrome 3 (#614608)	*SMARCB1*

77	F/0.5	3	Neurodevelopmental disorder with dysmorphic facies	Non-genetic (preterm birth and hypoxic damage)	
78	F/9.0	3	Cornelia de Lange syndrome	10q23 deletion	
79	F/7.7	3	Neurodevelopmental disorder with dysmorphic facies	Xq28 duplication	
80	M/3.1	3	Neurodevelopmental disorder with dysmorphic facies	Neurodevelopmental disorder with hypotonia and variable intellectual and behavioral abnormalities	*POLR2A*
81	M/3.3	3	Neurodevelopmental disorder with cerebellar atrophy	Wilson-Turner syndrome (#309585)	*LAS1L*
82	M/6.3	3	Leigh disease	Beta-ureidopropionase deficiency (#613161)	*UPB1*
83	F/0	2	Trichorhinophalangeal syndrome	Trichorhinophalangeal syndrome 1 (#190350)	*TRPS1*
84	F/2.0	3	Hereditary spastic paraplegia	Non-genetic (idiopathic toe walker)	
85	M/5.8	3	Ectodermal dysplasia, early-onset	Xeroderma pigmentosum, group D (#278730)	*ERCC2*
86	F/0.3	3	Neonatal hypotonia	Myasthenic syndrome, congenital, 2A, slow-channel (#616313)	*CHRNB1*
87	F/0.2	4	Profound developmental delay and regression with multiple anomalies	Developmental and epileptic encephalopathy (#300607)	*ARHGEF9*
88	M/2.1	3	Profound developmental delay with early-onset involuntary movements	Rett syndrome, congenital variant (#613454)	*FOXG1*
89	F/8.3	3	Neurodevelopmental disorder with microcephaly	Pyruvate dehydrogenase E1-alpha deficiency (#312170)	*PDHA1*

90	M/1.6	3	Neurodevelopmental disorder with dysmorphic facies	Neurodevelopmental disorder with visual defect and brain anomalies (#618547)	*HK1*
91	M/2.5	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 18 (#615476)	*SZT2*
92	F/2.1	3	Neurodevelopmental disorder with Rett-like phenotype (MECP2 negative)	Visser-Bodmer syndrome (#619033)	*CNOT1*
93	F/0.9	3	Neurodevelopmental disorder with progressive rigidity	Krabbe syndrome (#245200)	*GALC*
94	M/5.1	3	Neurodevelopmental disorder with dysmorphic facies	Neurodevelopmental disorder with seizures and nonepileptic hyperkinetic movements (#618497)	*CACNA1B*
95	M/2.1	3	Neurodevelopmental disorder with multiple anomalies	Adams-Oliver syndrome 2 (#614219)	*DOCK6*
96	F/2.7	3	Neurodevelopmental disorder with dysmorphic facies	Neurodevelopmental disorder with brain anomalies and with or without vertebral or cardiac	*DHX37*
97	M/1.8	3	Mitochondrial disorder	Intellectual developmental disorder, X-linked, syndromic, Cavezas type (#300354)	*CUL4B*
98	M/0.6	3	Neurodevelopmental disorder with multiple anomalies	Coffin-Siris syndrome 4 (#614609)	*SMARCA4*
99	F/1.4	4	Unknown metabolic disorder	Imagawa-Matumoto syndrome (#618786)	*SUZ12*
100	M/1.3	4	Unknown severe failure to thrive, hypotonia, multiorgan involvement	Wiedemann-Rautenstrauch syndrome (#264090)	*POLR3A*
101	F/10.7	3	Overgrowth-intellectual disability	19p13 deletion	
102	M/0.3	3	Neurodevelopmental disorder with Dandy-Walker variant	Global developmental delay, absent or hypoplastic corpus callosum, and dysmorphic facies (#617260)	*ZNF148*

103	F/3.5	4	Familial short stature and skeletal anomalies	Osteoarthritis with mild chondrodysplasia (#604864)	*COL2A1*
104	M/3.3	3	Neurodevelopmental disorder with dysmorphic facies	Neurodevelopmental disorder with hypotonia and dysmorphic facies (#619503)	*GNB2*
105	M/0.1	3	Developmental and epileptic encephalopathy, early-onset	2q24 deletion	
106	M/4.9	3	Multiple anomalies	Acrofacial dysostosis 1, Nager type (#154400)	*SF3B4*
107	M/6.4	3	Neurodevelopmental disorder with macrocephaly	Intellectual developmental disorder, autosomal dominant 35 (#616355)	*PPP2R5D*
108	M/9.7	3	Disorders of fatty acid metabolism	Lipid storage myopathy due to flavin adenine dinucleotide synthetase deficiency (#255100)	*FLAD1*
109	M/2.9	4	Profound failure to thrive, multiple anomalies, generalized hypertrichosis and microcephaly	ZTTK syndrome (#617140)	*SON*
110	M/6.1	3	Neurodevelopmental disorder with dysmorphic facies	16p11 deletion	
111	M/0.1	3	Arthrogryposis multiplex congenita	Ullrich congenital muscular dystrophy 1 (#254090)	*COL6A3*
112	F/0.8	3	Malformation of cortical development and microcephaly	Lissencephaly 3 (#611603)	*TUBA1A*
113	M/12.3	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 4 (#612164)	*STXBP1*
114	M/0.7	3	Neurodevelopmental disorder with multiple anomalies	Structural brain anomalies with impaired intellectual development and craniosynostosis (#618736)	*ZIC1*
115	M/1.3	3	Neurodevelopmental disorder with cerebellar dysplasia	Intellectual disability syndrome, X-linked	*PLXNA3*

116	F/7.0	3	Neurodevelopmental disorder with dysmorphic facies	Wiedemann-Steiner syndrome (#605130)	*KMT2A*
117	F/0.4	3	Multiple anomalies	Glycosylphosphatidylinositol biosynthesis defect 16 (#617816)	*PIGC*
118	M/3.0	3	Neurodevelopmental disorder with dysmorphic facies	Pitt-Hopkins syndrome (#610954)	*TCF4*
119	F/0.4	3	Congenital myopathy	Central core disease (#117000)	*RYR1*
120	M/7.2	2	Congenital muscular dystrophy	Ullrich congenital muscular dystrophy 1 (#254090)	*COL6A1*
121	M/2.3	3	Mitochondrial disorder	Allan-Herndon-Dudley syndrome (#300523)	*SLC16A2*
122	M/9.3	3	Developmental and epileptic encephalopathy	developmental and epileptic encephalopathy 65 (#618008)	*CYFIP2*
123	F/0.3	2	Spinal muscular atrophy	Spinal muscular atrophy (#313200)	*SMN1*
124	F/1.2	3	Congenital myopathy	Myopathy, myofibrillar, 9, with early respiratory failure (#603689)	*TTN*
125	F/5.7	4	Systemic inflammation	Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome (#615688)	*ADA2*
126	F/0.7	2	Congenital muscular dystrophy	Muscular dystrophy-dystroglycanopathy, type A (#253800)	*FKTN*
127	M/1.1	3	Hypertrophic cardiomyopathy, early-onset progressive	Noonan syndrome 11 (#618499)	*MRAS*
128	M/1.2	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 13 (#614558)	*SCN8A*

129	F/5.1	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 31 (#616346)	*DNM1*
130	M/1.8	3	Neurodevelopmental disorder with microcephaly	Microcephaly 9, primary, autosomal recessive (#614852)	*CEP152*
131	M/13.2	3	Neurodevelopmental disorder with dysmorphic facies	17p13 deletion	
132	M/9.0	4	Neurodevelopmental disorder with progressive rigidity, severe	Neurodevelopmental disorder with spastic diplegia and visual defect (#615075)	*CTNNB1*
133	F/5.0	3	Leigh syndrome	Developmental and epileptic encephalopathy 69 (#618285)	*CACNA1E*
134	M/1.5	3	Neurodevelopmental disorder with dysmorphic facies	Congenital disorder of glycosylation type Ia (#212065)	*PMM2*
135	F/11.0	3	Limb girdle muscular dystrophy	Laing distal myopathy (#160500)	*MYH7*
136	F/5.1	3	Coffin-Siris syndrome	Xp22 deletion	
137	M/8.6	3	Developmental and epileptic encephalopathy	Intellectual developmental disorder, X-lined 106 (#300997)	*OGT*
138	M/1.8	3	Developmental and epileptic encephalopathy	1p34 deletion (including SLC2A1)	
139	F/0.7	3	Joubert syndrome	Joubert syndrome 5 (#610188)	*CEP290*
140	F/3.0	3	Neurodevelopmental disorder, profound	developmental and epileptic encephalopathy 7 (#613720)	*KCNQ2*
141	M/4.3	2	Wiedemann Steiner syndrome	Wiedemann-Steiner syndrome (#605130)	*KMT2A*

142	M/12.3	4	Hypertrophic cardiomyopathy, early-onset progressive, with developmental delay	Hutchinson-Gilford progeria (#176670)	*LMNA*
143	M/0.8	3	Neurodevelopmental disorder	5q14 deletion	
144	M/5.1	3	Neurodevelopmental disorder with dysmorphic facies	Spinocerebellar ataxia, autosomal recessive 11 (#614229)	*SYT14*
145	F/0.6	3	Neurodevelopmental disorder, profound	Segawa syndrome, recessive (#605407)	*TH*
146	F/10.2	4	Progressive cerebellar atrophy	Congenital disorder of glycosylation, type Ia (#212065)	*PMM2*
147	M/10.3	4	Generalized pustulosis, familial	Psoriasis 14, pustular (#614204)	*IL36RN*
148	M/0.3	4	Leukodystrophy, and generalized skin manifestation	Neurodevelopmental disorder with ataxic gait, absent speech, and decreased cortical white matter (#617807)	*RAB11B*
149	M/2.8	3	Neurodevelopmental disorder	Developmental and epileptic encephalopathy 27 (#616139)	*GRIN2B*
150	F/1.9	3	Neurodevelopmental disorder with dysmorphic facies	Lissencephaly 2 (Norman-Roberts type) (#257320)	*RELN*
151	M/3.9	3	Leigh syndrome	Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal	*IARS2*
152	F/2.7	3	Neurodevelopmental disorder with dysmorphic facies	Coffin-Siris syndrome 3 (#614608)	*SMARCB1*
153	M/1.0	3	Neurodevelopmental disorder with macrocephaly and cortical malformation	Macrocephaly/autism syndrome (#605309)	*PTEN*
154	F/15.3	3	Neurodevelopmental disorder with cerebellar atrophy	Spinocerebellar ataxia 6 (#183086)	*CACNA1A*

155	F/3.3	3	Neurodevelopmental disorder with microcephaly	Bainbridge-Ropers syndrome (#615485)	*ASXL3*
156	F/8.6	3	Congenital muscular atrophy	Ullrich congenital muscular dystrophy 1 (#254090)	*COL6A2*
157	F/0.9	3	Neurodevelopmental disorder with dysmorphic facies	Congenital contractures of the limbs and face, hypotonia, and developmental delay	*NALCN*
158	F/7.4	3	Cerebellar ataxia, megalencephaly	spastic paraplegia 31, autosomal dominant (#610250)	*REEP1*
159	M/2.6	3	Neurodevelopmental disorder, profound	Allan-Herndon-Dudley syndrome (#300523)	*SLC16A2*
160	F/2.8	4	Neurodevelopmental disorder with post-natal microcephaly and progressive brain atrophy	Pyruvate dehydrogenase E1-alpha deficiency (#312170)	*PDHA1*
161	M/3.6	2	CODAS syndrome	CODAS syndrome (#600373)	*LONP1*
162	F/0.8	4	Central hypotonia, abnormal brain myelination and congenital nystagmus	Leukodystrophy, hypomyelinating 6 (#612438)	*TUBB4A*
163	F/2.4	3	Neurodevelopmental disorder	Mental retardation, autosomal dominant 34 (#616351)	*COL4A3BP*
164	M/0.5	3	Neurodevelopmental disorder with microcephaly and cerebellar atrophy	Neurodevelopmental disorder with cerebellar atrophy and motor dysfunction (#619333)	*GEMIN5*
165	F/0.8	4	Developmental and epileptic encephalopathy	Rett syndrome, congenital variant (#613454)	*FOXG1*
166	M/0.6	4	Neurodevelopmental disorder with generalized osteoporosis and skeletal problems	Congenital disorder of glycosylation type IIm (#300896)	*SLC35A2*
167	M/0.4	3	Neurodevelopmental disorder with central hypotonia	Congenital disorder of glycosylation type IIm (#300896)	*SLC35A2*

168	M/5.8	3	Neurodevelopmental disorder with ataxia	Congenital disorder of glycosylation, type Iii (#613612)	*COG5*
169	M/4.6	4	Profound neurodevelopmental disorder with severe early-onset involuntary	Neurodevelopmental disorder with involuntary movements (#617493)	*GNAO1*
170	M/4.5	3	Neurodevelopmental disorder with megalencephaly	Leukodystrophy, hypomyelinating 6 (#612438)	*TUBB4A*
171	M/6.2	3	Neurodevelopmental disorder with microcephaly	Neurodevelopmental disorder with spastic diplegia and visual defect (#615075)	*CTNNB1*
172	F/7.7	3	Developmental and epileptic encephalopathy	Kleefstra syndrome 2 (#617768)	*KMT2C*
173	M/2.1	3	Neurodevelopmental disorder with central hypotonia	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal	*GRIN1*
174	M/8.8	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, autosomal dominant 5 (#612621)	*SYNGAP1*
175	M/0.8	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 54 (#617391)	*HNRNPU*
176	M/2.2	3	Neurodevelopmental disorder with dysmorphic facies	ZTTK syndrome (#617140)	*SON*
177	M/1.7	3	Neurodevelopmental disorder with Dandy-Walker variant	spinocerebellar ataxia 5 (#600224)	*SPTBN2*
178	M/1.8	4	Unknown neurometabolic or neurodegenerative disease	Brody myopathy (#60003)	*APT2A1*
179	M/1.6	3	Neurodevelopmental disorder with dysmorphic facies	Coffin-Siris syndrome 1 (#135900)	*ARID1B*
180	F/9.2	4	Neurodevelopmental disorder with ataxia	Myasthenia, congenital, 12, with tubular aggregates (#610542)	*GFPT1*

181	F/1.1	3	Neurodevelopmental disorder with glaucoma and respiratory muscle incoordination	2q25 deletion	
182	M/6.1	4	Profound neurodevelopmental delay with Rett syndrome phenotypes	KBG syndrome (#148050)	*ANKRD11*
183	F/7.4	3	Neurodevelopmental disorder with Rett syndrome phenotypes	Intellectual developmental disorder, autosomal dominant 23 (#215761)	*SETD5*
184	M/1.3	3	Neurodevelopmental disorder with dysmorphic facies	Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart (#616975)	*RERE*
185	M/3.0	3	Neurodevelopmental disorder	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal	*GRIN1*
186	M/1.0	2	Tay-Sachs disease	Tay-Sachs disease (#272800)	*HEXA*
187	M/1.4	2	Spinal muscular atrophy	spinal muscular atrophy (#313200)	*SMN1*
188	M/1.5	3	Neurodevelopmental disorder with dysmorphic facies	Wieacker-Wolff syndrome (#314580)	*ZC4H2*
189	F/0.7	3	Developmental and epileptic encephalopathy	Myasthenic syndrome, congenital, 18 (#616330)	*SNAP25*
190	F/2.8	2	PIK3CA-related disorder	Megalencephaly-capillary malformation-polymicrogyria syndrome, somatic (#602501)	*PIK3CA*
191	F/10.2	4	Unknown neurodegenerative disease	Spastic paraplegia 3A, autosomal dominant (#182600)	*ATL1*
192	F/3.1	4	Unknown neurodegenerative disease with multiple anomalies	Rahman syndrome (#617537)	*HIST1H1E*
193	F/2.0	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, autosomal dominant 41 (#616944)	*TBL1XR1*

194	M/1.9	3	Neurodevelopmental disorder with microcephaly	Intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia (#300749)	*CASK*
195	M/3.3	4	Unknown leukodystrophy	Joubert syndrome 21 (#615636)	*CSPP1*
196	M/12.2	3	Neurodevelopmental disorder with microcephaly	Intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia (#300749)	*CASK*
197	F/0.9	2	GM1-gangliosidosis	GM1-gangliosidosis type I (#230500)	*GLB1*
198	F/2.0	3	Neurodevelopmental disorder with microcephaly	Cornelia de Lange syndrome 3 (#610759)	*SMC3*
199	M/8.6	3	Neurodevelopmental disorder with simplified gyral pattern	Developmental and epileptic encephalopathy 65 (#618008)	*CYFIP2*
200	F/12.0	3	Meyer-Golin syndrome	Meier-Gorlin syndrome 1 (#613804)	*CDT1*
201	F/2.5	3	Developmental and epileptic encephalopathy	2q31 deletion	
202	F/6.8	3	Neurodevelopmental disorder with dysmorphic facies	Ogden syndrome (#300855)	*NAA10*
203	F/6.6	3	Movement disorder, early-onset	Neurodevelopmental disorder with involuntary movements (#617493)	*GNAO1*
204	M/6.1	3	Neurodevelopmental disorder, profound with microcephaly	CRASH syndrome (#303350)	*L1CAM*
205	M/3.0	4	Unknown hemoglobinopathy	Methemoglobinemia, beta type (#617971)	*HBB*
206	M/2.2	2	Alternating hemiplegia, (ATP1A3-related)	Alternating hemiplegia of childhood 2 (#614820)	*ATP1A3*

207	F/2.3	3	Developmental and epileptic encephalopathy	Neurodevelopmental disorder with hyperkinetic movements and dyskinesia (#619651)	*ADCY5*
208	M/4.8	4	Neurodevelopmental disorder with unexplained progressive spasticity	Spastic paraplegia 4, autosomal dominant (#182601)	*SPAST*
209	M/2.2	4	Primordial dwarfism with multiple anomalies and intellectual disability	Floating-Harbor syndrome (#136140)	*SRCAP*
210	M/3.5	3	Developmental and epileptic encephalopathy	Developmental delay and seizures with or without movement abnormalities (#617836)	*DHDDS*
211	M/1.8	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, autosomal dominant 26 (#615834)	*AUTS2*
212	F/2.9	3	Neurodevelopmental disorder with microcephaly	Congenital contractures of the limbs and face, hypotonia, and developmental delay	*NALCN*
213	M/2.8	3	Hereditary spastic paraplegia	Spastic paraplegia 3A, autosomal dominant (#182600)	*ATL1*
214	F/2.9	3	Developmental and epileptic encephalopathy (+cleft palate)	multiple congenital anomalies-hypotonia-seizures syndrome 1 (#614080)	*PIGN*
215	F/9.3	3	Developmental and epileptic encephalopathy	developmental and epileptic encephalopathy 36 (#300884)	*ALG13*
216	M/2.5	4	Profound developmental delay with episodic generalized paralysis	Sifrim-Hitz-Weiss syndrome (#617159)	*CHD4*
217	M/3.7	3	Neurodevelopmental disorder with dysmorphic facies	6q27 duplication	
218	M/2.9	3	Neurodevelopmental disorder	Allan-Herndon-Dudley syndrome (#300523)	*SCL16A2*
219	M/2.8	3	Neurodegenerative disorder	Neurodevelopmental disorder with involuntary movements (#617493)	*GNAO1*

220	M/1.4	3	Syndromic short stature	Angelman syndrome (#105830)	*UBE3A*
221	M/2.3	3	Developmental and epileptic encephalopathy	developmental and epileptic encephaloapathy 46 (#617162)	*GRIN2D*
222	M/1.8	3	Developmental and epileptic encephalopathy	mitochondrial complex IV deficiency, nuclear type 6 (#615119)	*COX15*
223	M/8.8	3	Developmental and epileptic encephalopathy	Intellectual developmental disorder, autosomal dominant 62 (#618793)	*DLG4*
224	F/2.1	3	Hypophosphatemic rickets, familial	Xp22 duplication	
225	F/1.8	3	Episodic ataxia	Infantile-cerebellar-retinal degeneration (#614559)	*ACO2*
226	M/3.8	3	Neurodevelopmental disorder with dysmorphic facies	2q24 deletion	
227	F/4.1	3	Neurodevelopmental disorder with dysmorphic facies	Pitt-Hopkins syndrome (#610954)	*TCF4*
228	F/1.9	3	Neurodevelopmental disorder and failure to thrive	Intellectual developmental disorder, autosomal dominant 5 (#612621)	*SYNGAP1*
229	F/2.3	3	Generalized ichthyosis, infantile-onset alopecia, and photophobia	Ichthyosis, follicular, with atrichia and photophobia syndrome 2 (#619016)	*SREBF1*
230	F/10.9	4	Overgrowth and unknown connective tissue disease	Intellectual developmental disorder, X-linked, Turner type (#309590)	*HUWE1*
231	M/5.5	3	Cockayne syndrome	Cerebrooculofacioskeletal syndrome 3 (#616570)	*ERCC5*
232	F/1.1	3	MECP2 negative Rett syndrome	Microcephaly2, primary, autosomal recessive, with or without cortical malformation (#604317)	*WDR62*

233	M/8.8	3	Neurodegenerative disease	Alkuraya-Kucinskas syndrome (#617822)	*KIAA1109*
234	M/3.1	3	Neurodevelopmental disorder with multiple anomalies	Ardoleda-Tham syndrome (#616268)	*KAT6A*
235	M/5.8	2	PIK3CA related disorder	Megalencephaly-capillary malformation-polymicrogyria syndrome, somatic (#602501)	*PIK3CA*
236	F/5.5	3	Hypomelanosis of Ito and hemihypertrophy	Smith-Kingsmore syndrome (#616638)	*MTOR*
237	F/2.7	3	Hypophosphatemic rickets	Hypophosphatemic rickets, X-linked dominant (#307800)	*PHEX*
238	M/3.1	3	Neurodevelopmental disorder with microcephaly	Wiedemann-Steiner syndrome (#605130)	*KMT2A*
239	F/15.5	3	Neurodevelopmental disorder	Intellectual developmental disorder, autosomal dominant 29 (#616078)	*SETBP1*
240	M/5.8	4	Unknown neuromuscular disease (neuromuscular junction or motor neuron)	Cowshock syndrome (#310490)	*AIFM1*
241	M/1.1	3	Neurodevelopmental disorder with cerebellar hypoplasia	Congenital disorder of glycosylation, type IIg (#611209)	*COG1*
242	M/4.3	3	Neurodevelopmental disorder with microcephaly	Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1 (#614388)	*DNM1L*
243	F/1.4	3	Neurodevelopmental disorder with multiple anomalies	Developmental and epileptic encephalopathy 85, with or without midline brain defect (#301044)	*SMC1A*
244	M/6.0	3	Joubert syndrome (ciliopathy)	Joubert syndrome 3 (#608629)	*AHI1*
245	F/1.4	4	Profound global developmental delay, intractable seizures, rapidly-progressive	Ceroid lipofuscinosis, neuronal, 1 (#256730)	*PPT1*

246	F/4.0	4	Multi-systemic inflammatory disorder	Immunodeficiency, common variable 10 (#615577)	*NFKB2*
247	M/2.4	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, autosomal dominant 35 (#616355)	*PPP2R5D*
248	M/6.9	3	Spinocerebellar ataxia, early-onset	Dystonia 4, torsion, autosomal dominant (#128101)	*TUBB4*
249	F/3.3	3	Movement disorder	choreoathetosis, hypothyroidism, and neonatal respiratory distress (#610978)	*NIKX2-1*
250	F/2.8	3	Leigh syndrome	Mitochondrial disease	*m.A8344G*
251	F/1.6	3	Neurodevelopmental disorder with microcephaly and failure to thrive	Wiedemann-Steiner syndrome (#605130)	*KMT2A*
252	F/4.2	4	Neurodevelopmental disorder with episodic ataxia	Charcot-Marie-Tooth disease, type 2A1	*KIF1B*
253	F/1.6	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy (#613477)	*SPTAN1*
254	F/2.3	3	Leukodystrophy	GM1-gangliosidosis type I (#230500)	*GLB1*
255	M/3.2	3	Motor neuron disease	Charcot-Marie-Tooth disease, axonal, type 2A2A (#609260)	*MFN2*
256	F/7.7	3	Cerebellar ataxia	spinocerebellar ataxia 6 (#183083)	*CACNA1A*
257	M/2.6	3	Neurodevelopmental disorder with progressive focal dyskinesia	Dystonia-11, myoclonic (#159900)	*SGCE*
258	F/16.0	3	Developmental and epileptic encephalopathy	Non-genetic (acquired hypoxic damage)	

259	M/2.7	4	Profound global developmental delay, severe hypotonia with dysmorphic face	Floating-Harbor syndrome (#136140)	*SRCAP*
260	F/1.9	3	Neurodevelopmental disorder with macrocephaly	Macrocephaly/autism syndrome (#605309)	*PTEN*
261	F/12.2	3	Hereditary spastic paraplegia	Spastic paraplegia, intellectual disability, nystagmus, and obesity (#617296)	*KIDINS220*
262	F/1.8	4	Multi-systemic inflammatory disease	Muckle-Wells syndrome (#191900)	*NLRP3*
263	F/3.8	3	Charcot-Marie-Tooth disease	Charcot-Marie-Tooth disease, axonal, type 2K (#607831)	*GDAP1*
264	M/3.3	3	Developmental and epileptic encephalopathy	Developmental and epileptic encephalopathy 11 (#613721)	*SCN2A*
265	F/3.2	3	Leigh syndrome	Mitochondrial disease Neurofibromatosis type 1 (#162200)	*m.G3697A NF1*
266	F/16.3	3	Movement disorder	Neurodevelopmental disorder with involuntary movements (#617493)	*GNAO1*
267	F/8.7	3	MECP2-negative Rett syndrome	Pitt-Hopkins syndrome (#610954)	*TCF4*
268	M/5.5	3	Mucopolysaccharidosis	Mucopolysaccharidosis type IIIA (#252900)	*SGSH*
269	F/2.3	4	White matter vanishing disease, episodic encephalopathy aggravated by infection	Leukoencephalopathy with vanishing white matter (#603896)	*EIF2B3*
270	M/7.3	3	Hereditary spastic paraplegia	Spastic paraplegia 4, autosomal dominant (#182601)	*SPG4*
271	M/4.0	3	Developmental and epileptic encephalopathy	Non-genetic (congenital infection)	

272	M/13.8	3	Developmental and epileptic encephalopathy	Intellectual developmental disorder, autosomal dominant 5 (#612621)	*SYNGAP1*
273	M/3.9	3	Anhidrotic ectodermal dysplasia	Ardoleda-Tham syndrome (#616268)	*EDA*
274	M/5.1	3	Neurodevelopmental disorder with dysmorphic facies	Angelman syndrome (#105830)	*UBE3A*
275	F/4.6	3	Neurodevelopmental disorder with microcephaly	microcephaly 18, primary, autosomal dominant (#617520)	*WDFY3*
276	M/2.9	2	Pelizaeus-Merzbacher disease	Pelizaeus-Merzbacher disease (#612080)	*PLP1*
277	M/3.3	3	Neurodevelopmental disorder with microcephaly	1q24 deletion	
278	M/4.3	2	Mucopolysaccharidosis III	Mucopolysaccharidosis type IIIA (#252900)	*SGSH*
279	F/3.7	3	Overgrowth-intellectual disability	Marshall-Smith syndrome (#602535)	*NFIX*
280	F/5.5	2	Spinal muscular atrophy	spinal muscular atrophy (#313200)	*SMN1*
281	F/12.8	3	Hereditary spastic paraplegia	Spastic paraplegia 30, autosomal dominant (#610357)	*KIF1A*
282	M/14.0	3	Cerebellar ataxia	Neurodegeneration with brain iron accumulation 3 (#606159)	*FTL*
283	F/6.8	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, X-linked, Turner type (#309590)	*HUWE1*
284	F/10.8	4	Infantile-onset movement disorder	Visser-Bodmer syndrome (#619033)	*CNOT3*

285	F/9.2	3	Neuromuscular disorder	Myasthenia, congenital, 12, with tubular aggregates (#610542)	*CFPT1*
286	F/6.0	3	Neurodevelopmental disorder with macrocephaly	generalized epilepsy with febrile seizures plus, type 9 (#616172)	*STX1B/SCN2A*
287	F/2.5	2	Dermatomyositis	Nongenetic (dermatomyositis)	
288	F/5.9	3	Neurodevelopmental disorder with Rett-like phenotypes	CEBALID syndrome (#618774)	*MN1*
289	M/11.3	4	Neurodevelopmental disorder with episodic severe dystonia	Alternating hemiplegia of childhood 2 (#614820)	*ATP1A3*
290	M/2.9	3	Leigh syndrome	Mitochondrial disease	*m.G3697A*
291	M/3.4	3	Mitochondrial disorder	Combined oxidative phosphorylation deficiency 23 (#616198)	*GTPBP3*
292	M/3.8	3	Alternating hemiplegia	Alternating hemiplegia of childhood 1 (#104290)	*ATP1A2*
293	M/16.2	4	Unknown peripheral neuropathy	spinal muscular atrophy, X-linked 2, infantile (#301830)	*UBA1*
294	M/7.4	3	Leigh syndrome	Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal	*IARS2*
295	M/0	3	Epilepsy and multiple anomalies	Multiple congenital anomalies-hypotonia-seizures syndrome 3 (#615398)	*PIGT*
296	F/10.8	3	Overgrowth-intellectual disability	Intellectual developmental disorder with autistic features and language delay, with or without seizures (#618906)	*TANC2*
297	M/16.5	3	X-linked neuromuscular disorder	Nemaline myopathy 5, Amish type (#605355)	*TNNT1*

298	M/4.2	2	Metachromatic leukodystrophy	Metachromatic leukodystrophy (#250100)	*ARSA*
299	M/5.2	3	Congenital muscular dystrophy	Non-genetic (anti-SRP ab myositis)	
300	M/17.4	3	Noonan syndrome	Kabuki syndrome 1 (#147920)	*KMT2D*
301	F/5.6	2	Cystic fibrosis	Cystic fibrosis (#219700)	*CFTR*
302	M/9.3	3	Neuronal ceroid lipofuscinosis	Ceroid lipofuscinosis, neuronal 6A (#601780)	*CLN6*
303	M/5.8	2	Duchenne muscular dystrophy	Becker muscular dystrophy (#300376)	*DMD*
304	M/8.8	3	Limb-girdle muscular dystrophy	Becker muscular dystrophy (#300376)	*DMD*
305	F/15.7	3	Progressive dystonia	Paramyotonia congenita (#168300)	*SCN4A*
306	F/4.6	3	Neurodevelopmental disorder with cerebellar hypoplasia	Multiple congenital anomalies-hypotonia-seizures syndrome 3 (#615398)	*PIGT*
307	M/13.3	2	GLUT1 deficiency	GLUT1 deficiency syndrome 2, childhood onset (#612126)	*SLC2A1*
308	F/6.4	3	Mitochondrial disorder	Mitochondrial disorder	*m.A8344G*
309	F/6.1	3	Limb-girdle muscular dystrophy	Becker muscular dystrophy (#300376)	*DMD*
310	F/9.8	3	Leukodystrophy	Leukodystrophy, hypomyelinating, 11 (#616494)	*POLR1C*

311	M/8.2	3	Movement disorder (dyskinesia)	GLUT1 deficiency syndrome 2, childhood onset (#612126)	*SLC2A1*
312	M/8.4	2	Dystonia, early-onset, progressive	Dystonia-1, torsion (#128100)	*DYT1*
313	M/8.0	2	Paroxysmal kinesigenic dyskinesia	Episodic kinesigenic dyskinesia 1 (#128200)	*PRRT2*
314	F/7.5	4	Unknown neurodegenerative disease	Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures	*IRF2BPL*
315	F/14.5	3	Neurodevelopmental disorder	Rett syndrome, atypical (#312750)	*MECP2*
316	F/10.1	3	Generalized dystonia	Dystonia 28, childhood-onset (#617284)	*KMT2B*
317	M/13.6	3	Unknown myopathy	Glycogen storage disease II (#232300)	*GAA*
318	M/15.3	4	Multiple endocrine dysfunction, sensorineural hearing loss and frequent skin lesions	Bjornstad syndrome (#262000)	BCS1L
319	F/13.1	4	Leukodystrophy and peripheral neuropathy, progressive	Mitchell syndrome (#618960)	ACOX1
320	M/11.2	3	Neurodegenerative disorder	Neurodegeneration with brain iron accumulation 4 (#614298)	C19orf12
321	F/10.7	3	Neurodevelopmental disorder with dysmorphic facies	Intellectual developmental disorder, autosomal dominant 30 (#616083)	ZMYND11
322	M/16.7	3	Charcot-Marie-Tooth disease	Pontocerebellar hypoplasia type 1A (#607596)	VRK1
323	F/10.7	2	MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes)	Mitochondrial disease (MELAS)	m.A3243G

324	F/15.0	3	Cerebellar ataxia	Macrocephaly/autism syndrome (#605309)	PTEN
325	M/13.1	2	Rapid-onset dystonia and parkinsonism	Alternating hemiplegia of childhood 2 (#614820)	ATP1A3
326	M/12.8	3	Neurodevelopmental disorder with dysmorphic facies and multiple anomalies	16p22 deletion	
327	M/16.9	4	Movement disorder with dysmorphic face and sensorineural hearing loss	Mohr-Tranebjaerg syndrome (#304700)	TIMM8A

감사의 글

의학의 길에 들어선 이래 지속적으로 가르침을 주시고 저를 소아신경학의 길로 이끌어 이 자리에 있게 해 주신 채종희 지도교수님께 마음 깊이 감사드립니다. 또한 환자를 대하는 신실함과 연구자로서의 성실함을 몸소 보여주신 임병찬 선생님, 의사과학자로서 객관적인 시각과 꾸준한 노력의 중요성을 가르쳐 주신 채수안 선생님, 다양한 방면에서 연구를 바라볼 수 있게 하시고 본 학위 논문 연구에 지속적인 가르침을 주신 김한준, 피지훈 선생님께도 진심으로 감사드립니다. 선생님들이 계셔서 연구를 계획하고, 수행하여 좋은 결과를 낼 수 있었습니다. 그리고 제가 한 사람의 의사가 되는데 있어 이정표가 되어 주신 김기중 선생님께도 이 자리를 빌어 깊은 감사의 말씀을 전합니다.

공부를 할 수 있도록 물심양면으로 지원해주시고 언제나 제 편이 되어 주신 양가 부모님께 이 자리를 빌어 감사의 말씀을 전합니다. 또한 제가 지치고 힘들 때마다 진심으로 격려해주고 여러 조언을 아끼지 않은 남편 강창경과, 언제나 삶의 활력소가 되어주는 두 아들 재민, 재언에게 변치 않는 사랑을 보냅니다.

마지막으로, 이 학위를 받기까지 모든 과정에 함께 하시며 용기와 지혜를 주신 하나님께 모든 영광을 돌립니다.