JCN Open Access ORIGINAL ARTICLE
pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2016;12(2):181-187 / http://dx.doi.org/10.3988/jcn.2016.12.2.181

Leigh Syndrome in Childhood: Neurologic Progression and Functional Outcome

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Background and Purpose Few studies have analyzed the clinical course and functional outcome in Leigh syndrome (LS). The aim of this study was to determine the clinical, radiological, biochemical, and genetic features of patients with LS, and identify prognostic indicators of the disease progression and neurological outcome.

Methods Thirty-nine patients who had been diagnosed with LS at the Seoul National University Children's Hospital were included. Their medical records, neuroimaging findings, and histological/biochemical findings of skeletal muscle specimens were reviewed. Targeted sequencing of mitochondrial DNA was performed based on mitochondrial respiratory chain (MRC) enzyme defects.

Results Isolated complex I deficiency was the most frequently observed MRC defect (in 42% of 38 investigated patients). Mitochondrial DNA mutations were identified in 11 patients, of which 81.8% were *MT-ND* genes. The clinical outcome varied widely, from independent daily activity to severe disability. Poor functional outcomes and neurological deterioration were significantly associated with early onset (before an age of 1 year) and the presence of other lesions additional to basal ganglia involvement in the initial neuroimaging.

Conclusions The neurological severity and outcome of LS may vary widely and be better than those predicted based on previous studies. We suggest that age at onset and initial neuroimaging findings are prognostic indicators in LS.

Key Words Leigh syndrome, mitochondrial DNA mutation, functional outcome, prognostic indicators.

INTRODUCTION

Leigh syndrome (LS), which is also known as subacute necrotizing encephalopathy, is a rare neurodegenerative disorder that is clinically and genetically heterogeneous. Patients with LS show characteristic radiological brain abnormalities. Dysfunction of the mitochondrial respiratory enzyme complex or pyruvate dehydrogenase complex is the most common cause of LS.[1,2] Because nuclear and mitochondrial DNA encode mitochondrial respiratory chain (MRC) enzyme complexes and their assembly factors, LS can be caused by mutations in either genome.[1,2] Classic LS is characterized by various neurological symptoms that begin in infancy or early childhood and include psychomotor retardation, seizures, hypotonia, dystonia, gait disturbance, and respiratory dysfunction. These symptoms worsen progressively, and patients deteriorate neurologically and usually die in early childhood.[1,2]

Since the first report of LS,[3] the increasing number of patients diagnosed with LS has broadened the clinical spectrum, including cases with late onset and slow progression.[4,5] However, there are few reports on the prognostic outcome according to clinical and/or neuroradiological features.[6,7]

Received July 3, 2015
Revised September 20, 2015
Accepted September 24, 2015

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The aim of this study was to determine the clinical, radiological, biochemical, and genetic characteristics of patients with LS in Korea, and identify clinical factors that act as prognostic indicators of the disease progression and functional neurological outcome. The results may provide clinical guidelines for appropriate patient care.

METHODS

This study included 39 patients (15 males and 24 females) who were diagnosed with LS at the Seoul National University Children's Hospital between May 2001 and January 2010. The diagnosis was established based on the following characteristic clinical features and brain magnetic resonance imaging (MRI) findings: 1) neurodegenerative symptoms, including psychomotor retardation, encephalopathy, hypotonia or spasticity, dystonia, dyskinesia, seizures, ataxia, and brainstem dysfunctions such as dysphagia and ptosis; and 2) symmetric lesions in one or more areas of the central nervous system, including the basal ganglia, thalamus, brainstem, and cerebellum.[1,2] The diagnosis was further supported by biochemical features, including MRC defects. Analyses of arterial blood gas, serum amino acids, urine organic acids, carnitine profile, tandem mass screening, serum copper and ceruloplasmin, and general laboratory tests, including serum ammonia, were performed to exclude other causes of metabolic disorders. None of the patients had any history of perinatal asphyxia or kernicterus. We also performed a thorough medical evaluation to exclude Wernicke encephalopathy, acute necrotizing encephalopathy, Reye syndrome, acute disseminated encephalomyelitis, other types of encephalitis, vasculitis, cerebral infarction, pantothenate-kinase-associated neurodegeneration, and biotin-responsive basal ganglia disease. This study was approved by Seoul National University Children's Hospital institutional review board (IRB No. 1403-087-566), and blood and muscle samples were obtained from enrolled patients who provided informed consent.

Medical record review

Medical records were reviewed with a focus on the age at onset, initial manifesting symptom or sign, family history, clinical course of the disease, and functional outcome. Lactate and pyruvate levels were measured in the serum and/or cerebrospinal fluid. Echocardiography and cardiology consultation data were reviewed to assess cardiac involvement. Ophthalmological evaluations, including of visual-evoked potentials, were also reviewed, as were initial and serial follow-up MRI findings. A lactate peak in brain magnetic resonance spectroscopy (MRS) was assessed.

Functional outcomes

Clinical functional outcomes were assessed at outpatient clinics, mostly using information provided by the patients' caregivers or from telephone conversations for patients who were unavailable to visit an outpatient clinic due to severe disability. Outcome was assessed in three categories: ambulation, feeding, and respiration. In addition, we used a scoring system to explore the association between clinical course or functional outcome and neuroradiological findings or genetic defects. The scoring system in the present study was simply a highly modified version of the WeeFIM/FIM scoring system that has been used to assess the functional status of patients with mitochondrial disease.[8] The total score for functional outcome varied from 3 points (severe disability) to 8 points (independent daily activity): a score of 5 points or less was considered a poor outcome with moderate to severe functional impairment. Ambulatory status was classified into nonambulatory (scored as 1 point), assisted ambulation (2 points), and independent ambulatory (3 points). Feeding status was categorized into fed through percutaneous gastrostomy or feeding tubes (1 point), fed orally with assistance (2 points), and self-feeding (3 points). Respiratory status was classified into partially or completely dependent on mechanical ventilation (1 point) and self-respiratory without assistance (2 points).

Muscle biopsy

A muscle biopsy was performed to obtain muscle tissue from the rectus femoris muscle. The obtained samples were investigated histologically that included staining with hematoxylin and eosin, modified Gomori trichrome, ATPase, cytochrome C oxidase, and succinate dehydrogenase, and by electron microscopy.

Analysis of mitochondrial respiratory enzyme complex

The activities of respiratory chain complexes in the supernatants from muscle homogenates were measured using a spectrophotometer (DU-730, Beckman Coulter, Fullerton, CA, USA) as described previously.[9] The activity was expressed relative to that of citrate synthase, which is a marker of mitochondrial mass. A reduction in enzyme activity below 15% was considered to be a significant decrease in activity.

Genetic analysis

Total DNA was extracted from muscle samples using the PUREGENE DNA purification kit (Gentra Systems, Minneapolis, MN, USA). Based on the MRC defects, direct targeted sequencing of mitochondrial DNA genes was performed using BigDye Terminator Cycle Sequencing (version 3.1) (Applied Biosystems, Foster City, CA, USA) kits and an ABI

Table 1. Clinical course and functional outcome of the whole cohort of 39 patients

Patient	Age/Sex	Onset age (months)	Functional outcome			Neurologic course	Radiologic findings		MRC deficiency	Molecular genetics
			Amb	Feed	Resp		Initial	F/U		
1	6 yr*/M	2				Deterioration	BG/T/BS/MB	Atr	I	
2	5 mo*/M	2				Deterioration	BG/MB/WM		normal	
3	6 yr/F	3	B	O	S	Deterioration	BG	Atr	I	
4	8 yr/F	3	B	T	MV	Deterioration	BG		I+III+IV	
5	4 yr/F	4	B	T	MV	Deterioration	BG/T/Atr	Atr/WM	I	m.8993T>G
6	6 yr/M	5	S	S	S	Stable	BG	NC	I	
7	19 yr/M	5	A	O	S	Deterioration	BG/MB	Cbll/Atr	I+III	
8	2 yr†/F	6				Deterioration	BG/MB		I	
9	8 yr/F	6	B	O	S	Deterioration	T/AQ/Atr		Normal	
10	2 yr/M	6	B	T	S	Deterioration	BG/MB		I+III	m.14459G>A
11	9 yr/M	6	S	O	S	Stable	BG		Normal	
12	10 yr/M	7	B	T	S	Deterioration	BG/T	MB/Atr	I+III+IV	
13	7 yr/F	7	B	T	S	Deterioration	BG/T/MB/Cbll		I	
14	19 mo†/F	8				Deterioration	BG/Atr		I+III+IV	
15	4 yr/F	8	A	O	S	Deterioration	BG/MB	Atr	I+III+IV	
16	2 yr/F	8	B	O	S	Deterioration	BG/Atr		I+III+IV	
17	12 yr/F	8	A	O	S	Deterioration	BG	NC	III	
18	17 mo*/F	9				Deterioration	AQ/3V		I+III	
19	19 mo/F	11	B	T	MV	Deterioration	BG/Cbll/WM	T	I+III+IV	
20	5 yr†/M	12				Deterioration	BG/MB		I	m.13513G>A
21	7 yr/F	12	A	O	S	Stable	BG		Normal	
22	6 yr/F	14	A	O	S	Deterioration	BG/MB/WM	Atr	I	
23	6 yr/F	16	S	S	S	Stable	BG	Atr	I	m.10197G>A
24	7 yr/M	18	A	O	S	Deterioration	BG/T/MB	C (MELAS)	I	m.10158T>C
25	12 yr/F	18	A	O	S	Deterioration	BG	MB/Atr	I+III+IV	
26	4 yr/F	18	S	O	S	Stable	BG	NC	II+III	
27	4 yr/M	20	A	O	S	Stable	BG/MB	NC	I	
28	4 yr/M	26	A	O	S	Deterioration	BG/T/MB/WM	Atr	I	m.14487T>C
29	16 yr/M	27	A	O	S	Deterioration	BG	MB	I	m.10197G>A
30	8 yr/M	27	A	O	S	Deterioration	BG		Normal	
31	11 yr/F	28	A	O	S	Deterioration	BG/BS/T/MB	BG/Atr	Not done	m.8993T>G
32	13 yr/F	36	S	S	S	Stable	BG	Atr	I	m.10197G>A
33	7 yr/F	53	S	S	S	Stable	BG	Inc	II+III	
34	17 yr/F	60	B	T	S	Deterioration	BG	C/T (MELAS)	I	m.10191T>C
35	12 yr/F	60	S	S	S	Stable	BG	NC	I	m.14487T>C
36	11 yr/F	60	S	S	S	Stable	BG	NC	I+III	
37	17 yr/M	96	B	T	S	Deterioration	BG	C/BS/Atr (MELAS)	I+III	
38	13 yr/M	122	B	T	MV	Deterioration	BG/BS/MB/WM	Inc	II+III	
39	29 yr/F	252	A	S	S	Deterioration	BG/MB/AQ/Cbll		Normal	

*Age of the patients at last FU, †Age of the expired patients.
A: with assist, Amb: ambulation, Atr: atrophy, AQ: periaqueductal gray matter, B: bedridden, BG: basal ganglia, BS: brainstem, C: cerebral cortex, Cbll: cerebellum, Feed: feeding, Inc: increased, MB: midbrain, MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, MRC: mitochondrial respiratory chain, MV: mechanical ventilation, NC: no change, O: assited oral, Resp: respiration, S: self, T: PEG or feeding tube, T: thalamus, WM: white matter, 3V: near third ventricle.

PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). If no mutations were identified in the targeted regions, sequencing of other regions of mitochondrial DNA (mtDNA) was performed. Sequence changes were detected by comparisons with MITOMAP (http://www.mitomap.org/MITOMAP) and the Human Mitochondrial Genome Database.[10]

Table 2. Initial manifestations in the whole cohort of 39 patients

Abnormalities	Number of patients
Developmental delay	15 (38%)
Delay since birth	9
Arrest without inciting event	4
Arrest or regression after inciting event	2
Seizure	9 (23%)
Infantile spasms	4
Complex partial seizure with secondary generalization	3
Convulsive status epilepticus	2
Lethargy, poor sucking	6 (15%)
Ataxia, tremor	6 (15%)
Stroke like episode	3 (8%)
Dystonia	3 (8%)
Weakness	2 (5%)
Choreoathetosis	2 (5%)
Spasticity	2 (5%)
Dysphasia	2 (5%)
Cranial nerve palsy	1 (3%)

Table 3. Overall clinical features of the whole cohort of 39 patients

Abnormalities	Number of patients
Neurologic manifestations	
Central nervous system other than brainstem	
Developmental delay, regression	33 (85%)
Seizure	12 (31%)
Dystonia	10 (26%)
Ataxia	4 (10%)
Hemiparesis	3 (8%)
Nystagmus	2 (5%)
Cortical blindness	2 (5%)
Brainstem	
Spasticity	6 (15%)
Dysphagia	5 (13%)
Dysphasia, dysarthria	5 (13%)
Failure to thrive	3 (8%)
Apnea	2 (5%)
Peripheral nervous system	
Weakness	6 (15%)
Cranial nerve palsy	1 (3%)
Non-neurologic	
Cardiomyopathy	5/36 (14%)
Retinitis pigmentosa	3/26 (12%)
Optic atrophy	2/26 (8%)

Statistical analysis

Statistical analyses were performed using SPSS (version 21, SPSS Inc., Chicago, IL, USA). Mann-Whitney U tests were applied to continuous variables, and chi-squared analyses or Fisher's exact tests were applied to categorical variables. Multivariate logistic regression was used to examine the association between independent variables and functional outcome among the patients included in this study. The cutoff for statistical significance was set at $p<0.05$.

RESULTS

Clinical characteristics and functional outcome

The mean age at onset was 28 months of age (range, 2 months to 21 years). The age at disease onset was younger than 2 years in 27 patients (69%) (Table 1). Various initial manifestations of the disease were found, including delay, arrest, or regression of development, seizures, encephalopathic features, ataxia, dystonia, generalized muscle weakness, ophthalmoplegia, hemiparesis, and spasticity (Table 2). The most common associated nonneurological manifestations were ophthalmological findings and cardiac involvement (Table 3). Five patients (13%) had a positive family history of LS.

The mean follow-up duration was 4.0 years (range, 2 months to 19 years). As indicated in Table 1, progressive neurological deterioration was observed in 29 patients (74%), while the other 10 patients remained neurologically stable during follow-up. Data on functional outcomes were available for 33 patients, since 3 patients died during follow-up because of septic shock or respiratory arrest, and another 3 patients were lost during the follow-up period. The mean age at the end of follow-up was 9 years 8 months (range, 20 months to 29 years), and the mean score for the functional outcome was 5.7 points (range, 3 to 8 points). As indicated in Table 1, eight patients (24%) were capable of independent self-ambulation and 13 patients (39%) could walk with assistance, although some gait imbalance was present. Twenty-four patients (73%) were fed orally, of which seven patients could feed themselves independently. Twenty-nine patients (88%) could breathe without a mechanical ventilator, whereas four patients (12%) were either partially or completely dependent on mechanical ventilator support via a tracheostomy tube due to brainstem dysfunction with recurrent episodes of apnea or poor respiratory control.

We attempted to identify the clinical factors that were as-

sociated with neurological deterioration and worse functional outcome (score <6 points). Early onset (before 1 year of age) and the presence of seizures at presentation were significantly associated with poor functional outcome (p=0.01 and 0.003, respectively). In addition, patients with an onset before 1 year of age or with seizures were likely to experience neurological deterioration during the follow-up (p=0.141 and 0.158, respectively).

Radiological findings

Initial brain MRI findings were available for all patients. The initial MRI revealed that the structures involved other than the basal ganglia included the midbrain (38%), thalamus (21%), white matter (13%), brainstem (8%), and cerebellum (8%), as listed in Table 1. Patients with lesions additional to basal ganglia involvement in the initial neuroimaging were likely to have a poor functional outcome (p=0.114). The presence of other lesions in addition to those in the basal ganglia was significantly associated with severe neurological deterioration during follow-up (p=0.001). Among the three patients who had brainstem lesions in the initial neuroimaging, one was bedridden and required tube feeding and mechanical ventilation, one had a good outcome, and the third was lost to follow-up. A patient who developed brainstem lesions during the follow-up showed a poor outcome. However, the presence of brainstem lesions on initial or follow-up imaging did not significantly influence either the functional outcome (p=0.54) or the respiratory status (p=0.33) of the patients. MRS was performed in 19 patients; a lactate peak was present in all cases but the serum lactate level was normal in 15 patients. Follow-up MRI was performed in 25 patients at a mean time of 53 months (range, 3 months to 16 years 11 months). Multiple cerebral cortical infarctions on follow-up were found in three cases, of which two had mitochondrial DNA mutations (m.10158T>C and m.10191T>C in the *ND3* gene). Radiological progression, including brain atrophy, the appearance of new lesions, or an increased extent of previous lesions, was observed in 19 patients (76%). However, the brain MRI findings had not changed relative to the initial findings in six patients (24%). Clinical progression was evident in 16 (84%) of the 19 patients with radiographic progression. Only one (17%) of the six patients without radiographic progression showed clinical progression (Fisher's exact test, p=0.006). A two-tailed Mann-Whitney U test revealed that the functional outcome varied significantly between patients with and without radiological progression (U=21.5, p=0.023).

Muscle biopsy findings

Muscle biopsies were performed in all patients. There were nonspecific light-microscopy findings in all specimens, including variable size changes, atrophic changes, and perimysial or endomysial fibrosis. Electron microscopy revealed sarcoplasmic accumulation of either normally or abnormally shaped mitochondria in 17 (46%) of the 37 examined patients. Large or swollen mitochondria with or without abnormal cristae were found in eight patients (22%), whereas nonspecific degenerative findings were detected in another eight patients (22%).

Biochemical and genetic analyses

A mitochondrial respiratory enzyme complex assay was performed in 38 patients. Deficiency of the respiratory chain complex was identified in 32 patients (84%): isolated complex I deficiency was the most common type (16 patients), followed by complex I+III+IV combined deficiency (7 patients), complex I+III combined deficiency (5 patients), complex II+III combined deficiency (3 patients), and isolated complex III deficiency (1 patient). The clinical course and functional outcome did not differ significantly between patients with and without isolated complex I deficiency.

Based on the biochemical results, specifically targeted mtDNA gene sequencing was performed. mtDNA mutations were identified in 11 (28%) of the 39 patients: m.10158T>*C/MT-ND3* (n=1), m.10191T>*C/MT-ND3* (n=1), m.10197G>*A/MT-ND3* (n=3), m.13513G>*A/MT-ND5* (n=1), m.14487T>*C/MT-ND6* (n=2), m.14459G>*A/MT-ND6* (n=1), and m.8993T>*G/MT-ATP6* (n=2). Eight of the nine patients with mutations in *ND* genes had isolated complex I deficiency, and the other patient had combined complex I+III deficiency. All patients without mutations identified in the targeted sequencing based on the MRC defects had no mutations in other regions of mtDNA. The clinical course and outcome did not differ significantly between patients with and without mtDNA mutations. Additionally, there was no correlation between neuroradiological findings and either the presence or absence of mtDNA mutations.

DISCUSSION

LS is a devastating neurodegenerative disorder that typically presents in infancy or early childhood (<2 years of age) and progresses rapidly, resulting in death,[1,11,12] although several studies have found significant clinical heterogeneity in LS.[4,5] The disease onset occurred before 2 years of age in 69% of the patients in the present study,[7,11] while three patients presented with seizures or ataxia at ages of 8, 10, and 21 years, which supports the wide spectrum of clinical features reported recently.[7] A few of the patients described in the literature exhibited mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes/Leigh overlap syndrome (MELAS/LS).[13,14] Three patients in the present study presented with

LS that subsequently progressed to overlap with MELAS,[13] of which two had mtDNA mutations that have not been previously reported as being associated with the MELAS/LS overlap phenotype. These two cases expand the phenotypic spectrum of the mtDNA mutations m.10158T>C and m.10191T>C.

The muscle biopsies performed in the present study did not reveal any ragged red fibers, which may serve to dispel the common misperception among many clinicians that muscle biopsies are absolutely required for the diagnosis of mitochondrial disease. MRC defects were identified in 84% of the patients, which is a higher rate than that reported previously (50%).[1] This finding suggests that the MRC assay remains a useful diagnostic tool if performed using a standardized method and if compared with an enzyme that is not involved in the electron transport chain.[15] On the other hand, the possibility should be considered that some patients with LS can have normal MRC activity in muscle specimens due to the presence of mitochondrial heteroplasmy. We found that isolated complex I deficiency was the most common MRC defect in our Korean patients with LS, which is consistent with findings in Chinese patients.[16,17] Nine of our 16 patients with isolated complex I deficiency harbored mtDNA mutations (56%), which is consistent with the proportion found in a recent study (60.5%).[18] Mutations of *ND* genes, which encode enzyme subunits of complex I, were the most common mutations identified (9 out of 11, 82%). Most of the patients with mutations in *ND* genes had isolated complex I deficiency, as expected. It is surprising that none of the patients had isolated complex IV deficiency, which is one of the most common causes of LS, although we could not confirm the absence of *SURF1* mutations since nuclear DNA sequencing was not performed. Mitochondrial DNA mutations were identified in 28% of the patients in the present study, which is consistent with the findings of a previous study that sequenced the entire mitochondrial genome.[19] Additionally, patients without mutations identified in the targeted sequencing did not carry any mutations in other regions of mtDNA. We assume that targeted mtDNA sequencing based on MRC results increases the genetic diagnostic yield of LS and allows time and money to be saved in the genetic diagnosis of LS. However, a molecular diagnosis was not made in 72% of our patients because most pathogenic mutations that result in mitochondrial dysfunction involve nuclear genes. We are in the process of identifying the genetic causes in these patients.

The long-term outcome of LS is very poor, and often fatal in early childhood.[1] However, only three patients in the present study died from septic shock or sudden respiratory arrest. In addition, the functional outcome of the surviving patients was better than that found in previous studies.[1,11] About two-thirds of the surviving patients remained ambulatory with or without assistance. Regarding feeding, about three-quarters were fed orally and about one-fifth fed themselves independently. Only 12% of the patients were on mechanical ventilator support. We used a scoring system with three domains to evaluate the functional status of surviving patients in this study.[8] Twenty-one of 33 patients (64%) had a relatively good functional outcome, with a total score above 5 points. We investigated which clinical factors were associated with rapid neurological deterioration and worse functional outcome; these factors included an age at onset of younger than 1 year and the presence of seizures at presentation. Multivariate logistic regression confirmed that an age at onset of younger than 1 year was a statistically significant prognostic factor.

MRS revealed a lactate peak in all of the 19 cases in this study, suggesting that the presence of a lactate peak in MRS is more sensitive than the level of serum lactate.[2] Patients with lesions additional to basal ganglia involvement in the initial neuroimaging tended to have a poor functional outcome and show severe neurological deterioration during follow-up. These findings suggest that the presence of lesions additional to basal ganglia involvement on brain MRI at the time of initial diagnosis reflects a greater extent of mitochondrial dysfunction; this leads to cellular damage and therefore predicts a poor functional outcome and neurological deterioration. Brain MRI performed at presentation can be considered as suitable for revealing prognostic factors predicting the functional outcome and neurological course. In addition, an increased extent of involvement of brain MRI findings was significantly associated with the neurological progression of LS, as expected. Neuroradiological progression on follow-up MRI may indicate worsening of the clinical course.[6,11] The prognostic factors of functional outcome identified in this study, such as age at onset and initial neuroimaging findings, were consistent with the predictors of survival found in a recent multicenter study.[7]

In conclusion, this relatively large and long-term follow-up study investigated the clinical, radiological, biochemical, and genetic features of children with LS. Several prognostic factors of the clinical course and functional outcome were identified. Isolated complex I deficiency was the most common MRC defect observed in our patients with LS. The targeted sequencing of mitochondrial DNA led to the identification of mutations in 28% of the patients, among which mutation of the *ND* genes was most common. The present results suggest that the clinical functional outcome of LS can be better than that expected based on the results obtained in previous studies. We suggest that an onset before 1 year of age and the involvement of lesions additional to those in the basal ganglia in the initial neuroimaging are prognostic indicators of a poor clinical course and functional outcome in LS.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgements

This study was supported by a grant of the Korea Healthcare Technology R&D project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry for Health & Welfare, Republic of Korea (Grant No. HI12C0066).

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