ARID1B gene mutation in a patient with Coffin-Siris syndrome and Autism Spectrum Disorder

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ABSTRACT
Various factors may contribute to the emergence of Autism Spectrum Disorder (ASD). Genetic factors are particularly prominent in the etiology of ASD, and genetic syndromes may frequently accompany the disorder. Coffin-Siris syndrome is a genetic condition characterized by mental retardation, coarse facial appearance, hirsutism/hypertrichosis or skin with sparse hair, distal phalanx aplasia or hypoplasia, and fifth-finger and nail abnormalities. This genetic syndrome is accompanied by numerous different cardiac, genitourinary, gastrointestinal, ophthalmological, and craniofacial systemic abnormalities. ARID1B gene mutation is thought to be involved both in Coffin-Siris syndrome and in the etiology of autism. Although common genetic factors are involved in the etiologies of both diseases, our review of the literature revealed only one case report demonstrating an association between Coffin-Siris syndrome and ASD. This report describes a male patient aged 2 years and 10 months with ARID1B mutation showing Coffin-Siris syndrome and ASD comorbidity. It may be beneficial for clinicians to remember the coexistence of genetic syndromes in patients diagnosed with ASD and to request consultations from relevant departments for early diagnosis and treatment.

Keywords: Autism, ARID1B, Coffin-Siris syndrome, genetic

INTRODUCTION
Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired social interaction, stereotyped repetitive behaviors, and a limited field of interest (1). Many significant factors play a role in the etiology of autism, including genetic factors (2). In recent years, numerous studies have investigated genetic factors, and many cases have been reported in the context of the relationship between different genetic syndromes and autism (3-5). Coffin-Siris syndrome is a genetic condition characterized by mental retardation, a coarse facial appearance, hirsutism/hypertrichosis or skin with sparse hair, distal phalanx aplasia or hypoplasia, and fifth-finger and nail abnormalities. Accompanying congenital abnormalities, cardiac, genitourinary, gastrointestinal and craniofacial abnormalities, ophthalmological problems, hearing abnormalities, and nutrition difficulties may also be present (6). The genetic transition of Coffin-Siris syndrome often occurs with de novo mutations. There is also an autosomal dominant transmission, at a lower level, caused by the heterozygous mutations of ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1, and SOX11 genes (6). ARID1B gene mutation is one of the most common de novo mutations of Coffin-Siris syndrome (7). ARID1 is also one of the genes thought to be associated with
the etiology of autism (7). However, we encountered only one case report concerning the coexistence of Coffin-Siris syndrome and ASD (8). This report describes a male patient aged 2 years and 10 months with ARID1B mutation and comorbid Coffin-Siris syndrome and autism.

**CASE**

A.K., aged 2 years and 10 months, was the subject of a consultation with the child and adolescent psychiatry outpatient clinic requested by the genetics department. History taken from the family revealed limited eye contact, failure to look when called, absence of focus of interest, unwillingness to point to any desired object, lack of interest in his peers, and ‘flapping’ motions when excited. Mental status examination revealed that he exhibited very little social interaction, lack of eye-to-eye contact, restricted facial expression, and repetitive movements such as ‘flapping’ when he was excited. The childhood autism assessment scale (CARS) was used for psychometric assessment. The case was assessed as severe autism with a CARS score of 38. ASD was diagnosed based on psychometric testing, DSM-based interview, and the history taken from the family. Coffin-Siris syndrome was diagnosed by the genetics department, and heterozygous c.4176del(p.Tyr1392*) mutation in the ARID1B gene (6q25.3, NM_020732.3) was revealed by whole-exome sequencing. Following psychological assessment, the neurology, ophthalmology, and otorhinolaryngology departments were consulted to investigate potential comorbid diseases. The patient’s threshold of hearing was within normal ranges, while ophthalmological examination revealed no visual impairment, and neurological examination showed no additional neurological disease. Psychoeducation concerning ASD was provided for the family. Special education support was recommended for the autism symptoms. Together with this special education, follow-up at three-monthly intervals was scheduled.

**DISCUSSION**

This report discusses a case of ASD and Coffin-Siris syndrome in a patient aged 2 years and 10 months. The number of case reports concerning the coexistence of genetic syndromes and autism is growing (9,10,11). However, case reports concerning the coexistence of ASD and Coffin-Siris syndrome are very limited. Hersh et al. (8) reported a case of a six-year-old girl with ASD and Coffin-Siris syndrome in 1982. Seventh-degree consanguinity was present between her parents. Chromosomal analysis was performed at genetic analysis, but the de novo mutations were not assessed. In the present case, heterozygous c.4176del(p.Tyr1392*) mutation in the ARID1B gene (6q25.3, NM_020732.3) was determined by whole-exome sequencing. There was no consanguinity between the parents. Both cases met the criteria for ASD in DSM-5 (8,12). Coffin-Siris syndrome is a genetic syndrome caused by mutations at ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1 and SOX11 heterozygous pathogenic variants (4). ARID1B gene mutation is the most common cause of the syndrome (5). ARID1B is by far the most frequently mutated gene (76%) in Coffin-Siris syndrome (13). ARID1B mutations are rare in autism, although the incidence has not so far been reported (14). ARID1B is also one of the common mutations in autism spectrum disorders (5). The ARID-1 gene is responsible for regulating histone relaxation through the SWI/SNF protein complex. Mutations occurring in the ARID1B gene affect the SWI/SNF protein complex, thus resulting in Coffin-Siris syndrome (15). A group of proteins known as the SWI/SNF chromatin-remodeling complex is responsible for DNA packaging. DNA forms chromatin by coiling up with proteins known as histones. The SWI/SNF protein complex is involved in “neural stem cell/precursor generation, proliferation, and neuronal subtype specification, differentiation, and migration” in the neurodevelopmental process. Dysfunction of the SWI/SNF protein complex affects the neurodevelopmental process and plays a role in the development of neurodevelopmental disorders (16,17). Genes involved in the etiology of autism are associated with neuronal communication, synapse development, and chromatin remodeling/transcription regulation (18-20). Sanders et al. (21) reported that 65 genes encoding either chromatin regulators or synaptic proteins were related to the risk of ASD. The authors suggested that mutations in ARID1 may be associated with ASD due to its presence in the chromatin remodeling/transcription regulation pathway, but that further studies on the subject were needed (16).

ASD is a common neurodevelopmental disorder (22). Identifying the genetic syndromes associated with ASD will contribute to a better understanding of the mechanisms involved in the etiology of ASD. For example, the discovery of MeCP2 gene mutation in Rett syndrome has revealed its critical role in astrocyte production during neurodevelopment (23,24). Many genetic syndromes comorbid with ASD are also seen in systemic diseases. The early diagnosis of these systemic
diseases is important in terms of the clinical care needs of patients diagnosed with ASD, too. Thus, an early tumor follow-up program in cases diagnosed with ASD with PTEN mutation, as well as early diagnosis of systemic diseases in tuberous sclerosis patients, and early diagnosis of congenital abnormalities, cardiac, genitourinary, gastrointestinal and craniofacial abnormalities, ophthalmological problems, and hearing abnormalities in patients with Coffin-Siris syndrome may affect the course of the disease (8,25,26). Genetic consultation should be requested for patients diagnosed with ASD in order to identify these diseases. Clinicians should therefore be aware of genetic syndromes in patients diagnosed with ASD (27). Requesting genetic consultation for patients diagnosed with ASD will improve our understanding of the etiology of ASD and is important in terms of early diagnosis of and intervention in systemic diseases (28).

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REFERENCES


