Comprehensive genetic analysis confers high diagnostic yield in 16 Japanese patients with corpus callosum anomalies

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【Summary】
Corpus callosum anomalies (CCA) is a common congenital brain anomaly with various etiologies. Although one of the most important etiologies is genetic factors, the genetic background of CCA is heterogenous and diverse types of variants are likely to be causative. We analyzed 16 Japanese patients with corpus callosum anomalies to delineate clinical features and the genetic background of CCAs. Whole exome sequencing revealed genetic alterations in 9 of the 16 patients (56.3%), including 8 de novo alterations (2 copy number variants and variants in *ARID1B*, *CDK8*, *HIVEP2*, and *TCF4* and a recessive variant of *TBCK*. Patient with *TBCK* was also identified with an additional *de novo* variant in *CDH2*, which gene was recently reported as an associated with corpus callosum anomalies. *A de novo TCF4* variant and somatic mosaic deletion at 18q21.31-qter encompassing TCF4 suggest an association of TCF4 abnormalities with CCAs.

Method

16 patient with corpus callosum anomalies (CCA)

Female:13, Male:3

Whole exome analysis

Single Nucleotide variants (**SNVs**) Small insertions/deletions (**Indels**)

a. Excluding the common variants with alle frequency ≥ 1% in public database
b. High prediction scores by pathogenicity prediction tools

MuTect2

Detection of somatic mosaic SNVs and Indels

Copy Number variants (**CNVs**)

XHMM (eXome Hidden Markov Model)

Comprehensive CNV analysis of all chromosomes

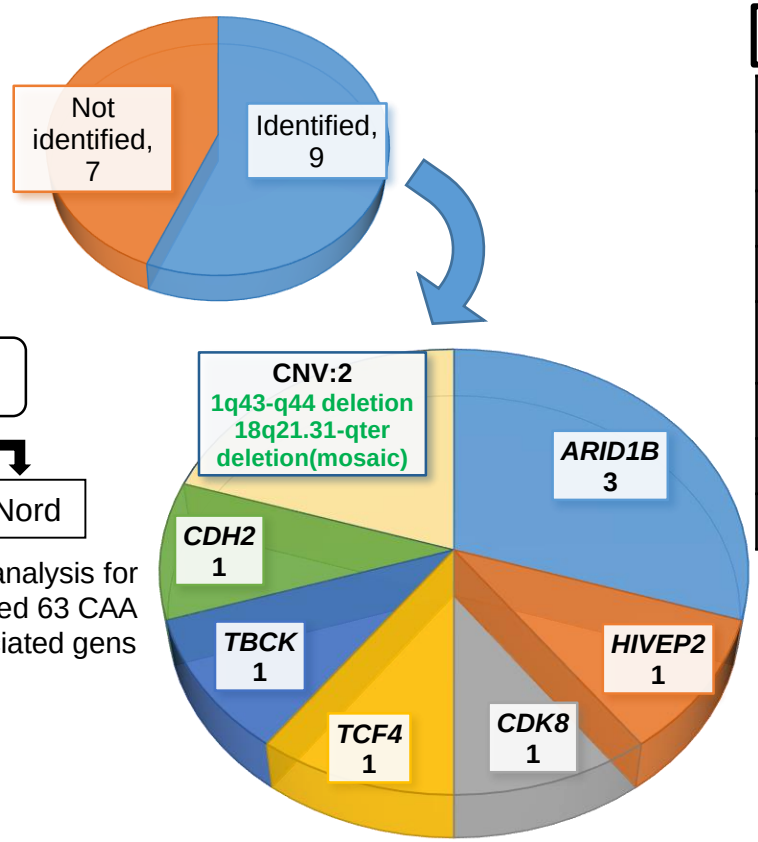
H^3M^2

Detection of Runs of homozygosity

Nord

CNV analysis for selected 63 CAA Associated gens

Identified genetic variants



Clinical summary of 16 individuals

Neurological phenotype

Seizures	60% (9/15)
Seizure onset (age)	1day ～2years and 11months
Drug efficiency	57.1% (4/7)
Intellectual disability	100 % (16/16)
Motor developmental delay	93.8% (15/16)
Speech delay	93.8% (15/16)
Hypotonia	68.8% (11/16)
Autism	18.8% (3/16)

Brain MRI findings

total ACC	14
corpus callosum dysplasia	2
Colpocephaly	84.6% (11/13)
Enlarged supracerebellar cistern	41.7% (5/12)

Extra phenotype

Short stature	43.8% (7/16)
Facial dysmorphisms	50% (8/16)
Other dysmorphisms	50% (8/16)

Conclusion

- We confirmed that both nucleotide and chromosomal alterations were important genetic factors of CCAs.
- Comprehensive genetic analyses using WES could contribute the high diagnostic yields of CCA patients and further understanding for pathogenesis of CCA.