資料6

資料7

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Autosomal dominant optic atrophy with *OPA1* gene mutations accompanied by auditory neuropathy and other systemic complications in a Japanese cohort

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Purpose: This study aimed to describe the genetic and clinical characteristics of four Japanese patients with autosomal dominant optic atrophy (DOA) accompanied by auditory neuropathy and other systemic complications (i.e., DOA-plus disease).

Methods: Four patients from four independent families underwent comprehensive ophthalmic and auditory examinations and were diagnosed with DOA-plus disease. The disease-causing gene variants in the *OPA1* gene were identified by direct sequencing. The genetic and clinical data of 48 DOA patients without systemic complications—that is, with simple DOA—were compared to those of DOA plus patients.

Results: DOA-plus patients noticed a decrease in vision before the age of 14 and hearing impairment 3 to 13 years after the development of visual symptoms. Two patients had progressive external ophthalmoplegia, and one patient had vestibular dysfunction and ataxia. The DOA-plus phenotypes accounted for 13.3% (4/30) of the families with the *OPA1* gene mutations. Each DOA plus patient harbored one of the monoallelic mutations in the *OPA1* gene: c.133-1G>A, p.R145H, c.1618A>C, p.T540P, and c.892A>C, p.S298R. Missense mutations accounted for 100% (4/4) of the DOA-plus families and only 11.5% (3/26) of the families with simple DOA.

Conclusions: All the patients with the DOA-plus phenotype carried one of the missense mutations in the *OPA1* gene. They all had typical ocular symptoms and signs of DOA in their first or second decade, and other systemic complications—such as auditory neuropathy, vestibular dysfunction, and ataxia—followed the ocular symptoms. We should consider the occurrence of extraocular complications in cases with DOA, especially when they carry the missense mutations in the *OPA1* gene.

Autosomal dominant optic atrophy (DOA; OMIM 165500) is one of the major causes of inherited optic nerve disorders and is characterized by a slow, progressive reduction of visual acuity, by central visual field defects, and by the temporal pallor of the optic disc. Abnormalities in the *OPA1* gene (Gene ID: 165500; OMIM 605290) are a major cause of DOA [1-4], and mutations in the *OPA1* gene account for 32.1–89.5% of all DOA cases [3,5-10]. *OPA1* encodes a dynamin-related GTPase that is located in the mitochondrial intermembrane space, and it plays a key role in controlling the balance of mitochondrial fusion and fission. To date, more than 200 *OPA1* variants have been reported to cause DOA [11], including missense mutations, nonsense mutations, insertion/deletion, splice site mutations, and large-scale *OPA1* rearrangements [5-9,12,13].

The severity of DOA varies considerably, and the visual acuity ranges from normal to hand motion [10,14]. This variability is observed both within and among families. It should be noted that there is a subset of patients with DOA who have extraocular symptoms, such as, auditory neuropathy, ataxia, myopathy, neuropathy, and progressive external

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資料8

①盲ろうサポートTOP画面（一般の方・医療関係者　共通画面）

②盲ろうサポートTOP2画面（一般の方・医療関係者　共通画面）

③検索画面（一般の方・医療関係者　共通画面）

④検索結果一覧画面（一般の方・医療関係者　共通画面）

⑤詳細結果ページ（一般の方用）

⑤詳細結果ページ（医療関係者用）
※担当科・医師名・担当曜日表示

資料9

患者の遺伝子検査

↓

初回カンファレンス　原因候補の遺伝子変異の情報
患者と家族の臨床情報　} 検討

↓

詳細な検討を行う変異の選別

第2回カンファレンス　追加検査結果の情報
ACMG基準による病的意義　} 検討

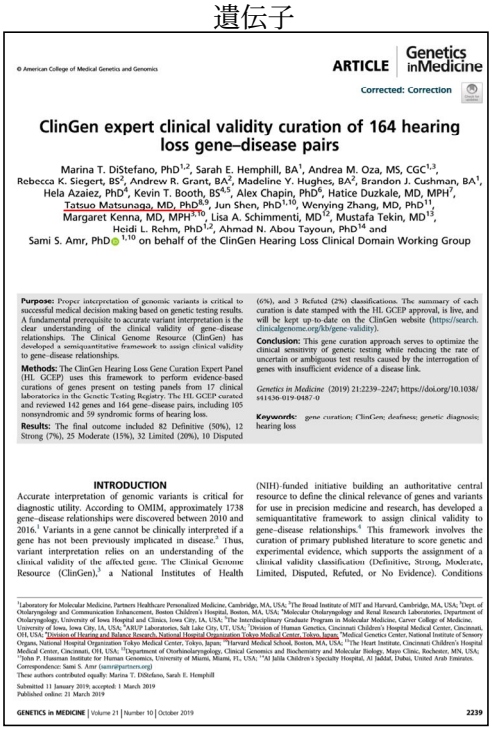
↓

原因診断

（3ヶ月で報告）

資料10

遺伝子



ARTICLE Genetics inMedicine

Corrected: Correction

ClinGen expert clinical validity curation of 164 hearing loss gene–disease pairs

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Purpose: Proper interpretation of genomic variants is critical to successful medical decision making based on genetic testing results. A fundamental prerequisite to accurate variant interpretation is the clear understanding of the clinical validity of gene–disease relationships. The Clinical Genome Resource (ClinGen) has developed a semiquantitative framework to assign clinical validity to gene–disease relationships.

Methods: The ClinGen Hearing Loss Gene Curation Expert Panel (HL GCEP) uses this framework to perform evidence-based curations of genes present on testing panels from 17 clinical laboratories in the Genetic Testing Registry. The HL GCEP curated and reviewed 142 genes and 164 gene–disease pairs, including 105 nonsyndromic and 59 syndromic forms of hearing loss.

Results: The final outcome included 82 Definitive (50%), 12 Strong (7%), 25 Moderate (15%), 32 Limited (20%), 10 Disputed (6%), and 3 Refuted (2%) classifications. The summary of each curation is date stamped with the HL GCEP approval, is live, and will be kept up-to-date on the ClinGen website (https://search.clinicalgenome.org/kb/gene-validity).

Conclusion: This gene curation approach serves to optimize the clinical sensitivity of genetic testing while reducing the rate of uncertain or ambiguous test results caused by the interrogation of genes with insufficient evidence of a disease link.

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Keywords: *gene curation; ClinGen; deafness; genetic diagnosis;* hearing loss

INTRODUCTION

Accurate interpretation of genomic variants is critical for diagnostic utility. According to OMIM, approximately 1738 gene–disease relationships were discovered between 2010 and 2016.[1] Variants in a gene cannot be clinically interpreted if a gene has not been previously implicated in disease.[2] Thus, variant interpretation relies on an understanding of the clinical validity of the affected gene. The Clinical Genome Resource (ClinGen),[3] a National Institutes of Health (NIH)-funded initiative building an authoritative central resource to define the clinical relevance of genes and variants for use in precision medicine and research, has developed a semiquantitative framework to assign clinical validity to gene–disease relationships.[4] This framework involves the curation of primary published literature to score genetic and experimental evidence, which supports the assignment of a clinical validity classification (Definitive, Strong, Moderate, Limited, Disputed, Refuted, or No Evidence). Conditions

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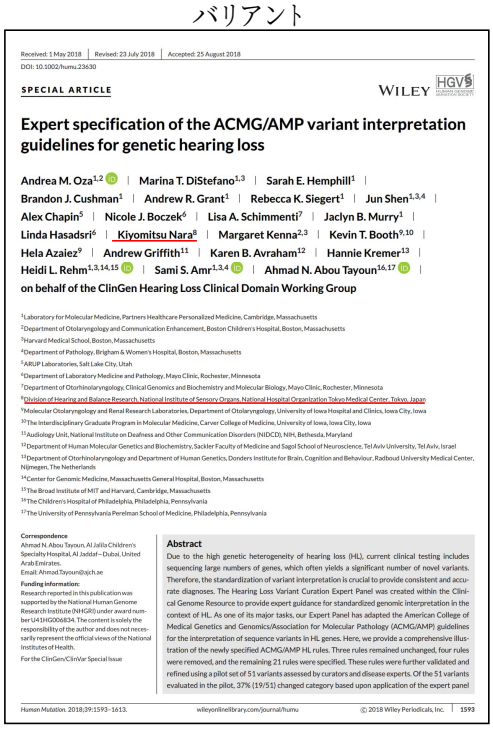
バリアント



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SPECIAL ARTICLE

WILEY HGVS

Expert specification of the ACMG/AMP variant interpretation guidelines for genetic hearing loss

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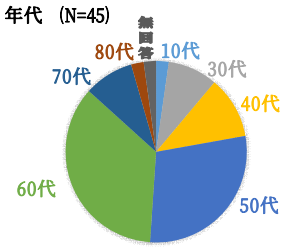
For the ClinGen/ClinVar Special Issue

Abstract

Due to the high genetic heterogeneity of hearing loss (HL), current clinical testing includes sequencing large numbers of genes, which often yields a significant number of novel variants. Therefore, the standardization of variant interpretation is crucial to provide consistent and accurate diagnoses. The Hearing Loss Variant Curation Expert Panel was created within the Clinical Genome Resource to provide expert guidance for standardized genomic interpretation in the context of HL. As one of its major tasks, our Expert Panel has adapted the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines for the interpretation of sequence variants in HL genes. Here, we provide a comprehensive illustration of the newly specified ACMG/AMP HL rules. Three rules remained unchanged, four rules were removed, and the remaining 21 rules were specified. These rules were further validated and refined using a pilot set of 51 variants assessed by curators and disease experts. Of the 51 variants evaluated in the pilot, 37% (19/51) changed category based upon application of the expert panel

Human Mutation. 2018;39:1593–1613. wileyonlinelibrary.com/journal/humu © 2018 Wiley Periodicals, Inc. 1593

資料11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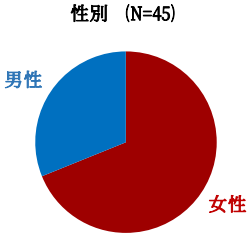
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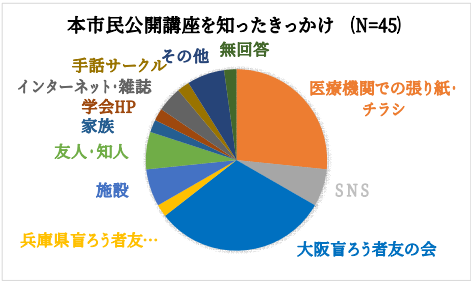
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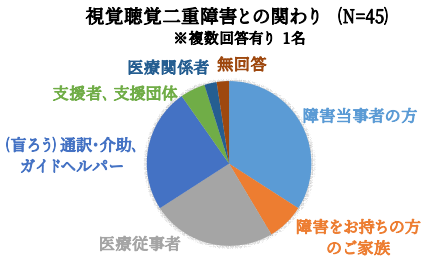
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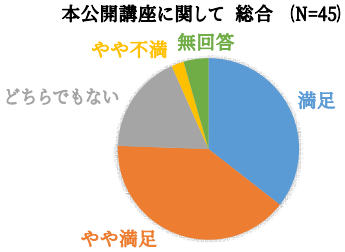
障害をお持ちの方のご家族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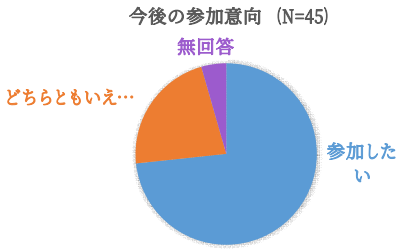
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