Identification of Genomic Copy Number Variants Associated with Childhood Apraxia of Speech (CAS)

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Childhood Apraxia of Speech (CAS) is a rare, severe, and persistent subtype of pediatric speech sound disorder which shows high heritability, but very little is known about its genetic causes. We hypothesize that for a subset of patients with CAS, copy number abnormalities of speech-related genes could be responsible for the abnormal phenotype. To test this hypothesis, we performed high resolution array Comparative Genomic Hybridization (aCGH) analysis in a group of patients with confirmed diagnosis of CAS.

Methods

Patients were recruited through an ongoing collaborative IRB approved research study in pediatric speech sound disorders (National Institute on Deafness and other Communication Disorders DC000496). Each patient completed a two-hour assessment protocol that included measures of speech, prosody, voice, intellectual function, language, orofacial structure and function, and developmental history. aCGH testing was performed with custom designed high density oligonucleotide-based arrays (Roche NimbleGen Systems Inc., Madison, WI). The arrays contained 385,000 oligonucleotide probes, with increased probe density for the regions previously associated with CAS (*FOXP2* gene, chromosomal regions 16q23.2, 4q35.2 and others), and a median interprobe distance of approximately 6kb for the rest of the genome. DNA labeling, hybridization, post-hybridization washes and array scanning were performed according to the manufacturer's recommendations (Roche NimbleGen Systems Inc., Madison, WI). Data was extracted using NimbleGen's NimbleScan software and viewed with NimbleGen's SignalMap data browser software. Additional analysis was performed using the OGT Cytosure software (Oxford Genomic Technologies).

Results

aCGH testing of 23 patients with CAS detected one case with a 562-kb deletion affecting the 16p11.2 microdeletion syndrome critical region on chromosome 16 (Figure 2). Copy number variants (CNVs) which do not correspond to benign changes reported in the Database of Genomic Variants (http://projects.tcag.ca/variation/) were also observed at several candidate chromosomal regions, including 2p14, 2q24.1, 2q31.2, 5q35.1, 6p11.2p12.1, 12q24.23, 14q23.2 and 16p13.2 (Listed in the table below). Additional studies are in progress to determine the clinical significance of some of the detected CNVs.

Subject	aCGH Findings	Affected Genes
01	arr 2q31.1(172,500,884-174,354,110)x1	*HAT1, AC015976.3, DLX1, DLX2, AC104801.4, ITGA6, PDK1, Y_RNA, AC018712.5, RAPGEF4, ZAK, CDCA7, AC073465.5-1, AC073465.5-2*
02	16p11.2(29,531,556-30,099,861)x1	See Figure 2.
03	arr 2q31.2(178,467,013-178,649,476) x1	*PDE11A, AC011998.8-1, U6*
04	arr 2q24.1(158,644,817-159,312,243) x1	*UPP2, CCDC148, AC008070.4, PK4P, AC005042.2*
05	arr 16p13.2(8,725,553-8,963,020)x1	*ABAT, TMEM186, PMM2, CARSHP1, and USP7*
06	arr 9q32(114,786,772-114,857,326)x1	*ZFP37*
07	arr 6p12.1(56,611,129-57,325,976)x3	*DST, RP11-472M19.3, U6, BEND6, RP11-129K24.3, RP11-129K24.4, KIAA1586, ZNF451, BAG2, RAB23, PRIM2*
08	arr 4p15.1(33,734,758-33,825,986) x3,arr 17q23.2(52,748,147-52,801,291) x1	*MSI2*

16p11.2 Microdeletion and CAS

Deletion of the 16p11.2 critical region was detected in a patient with significant persistent speech and expressive language impairment. Standardized perceptual and acoustic measures of the competence, precision, and stability of the patient's speech, prosody, and voice confirmed the diagnosis of CAS (Figure 1).
Although speech and language delay has been described as a common clinical feature of the 16p11.2 deletion, most published reports are not informative on the specific subtype(s) of the associated speech disorder. We speculate that the prevalence of CAS in individuals with 16p11.2 microdeletion may be considerably higher than currently recognized.

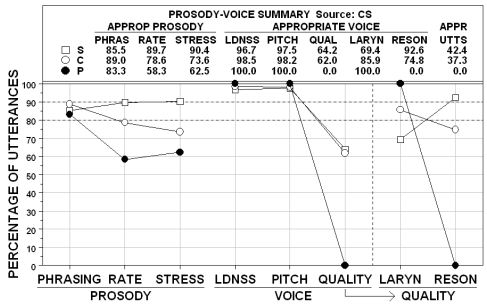

Figure 1. Prosody and voice findings for a patient with a 16p11.2 microdeletion and CAS. The patient's profile (filled circles) on seven prosody-voice domains are shown together with the means on these domains from two groups of speakers with speech/sound disorders: 36 speakers with CAS (open circles) and 20 speakers with Speech Delay (open squares). The patient's profile is consistent (i.e. is generally more severe) with the averaged profile of speakers with CAS.

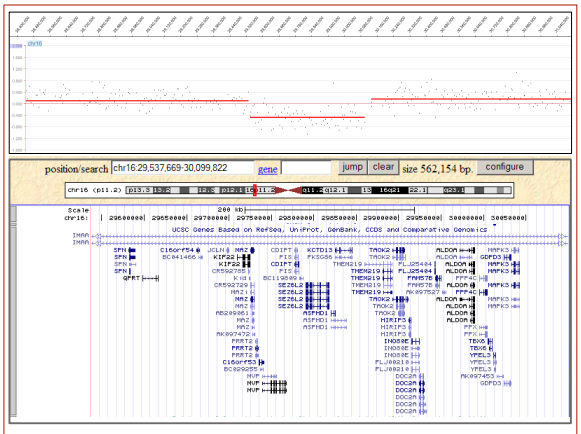

Figure 2. The 562 kb deletion detected by aCGH testing; (A) the close view of the deleted segment from the SignalMap software from Roche-NimbleGen (B) known genes within the 562kb deleted region, as determined using the UCSC Genome Browser (http://genome.ucsc.edu/).

Summary

Our preliminary studies show that aCGH testing detects likely pathogenic deletions and duplications in patients with CAS , and that genomic copy number abnormalities may play a role in susceptibility to this pediatric motor speech disorder. Additionally, we describe the first case of the 16p11.2 microdeletion in a patient with a confirmed diagnosis of CAS. Evaluation by a speech pathologist may be warranted for all patients with 16p11.2 deletion, to determine if the associated speech delay meets the diagnostic criteria for CAS.

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