

A Girl with Greig Cephalopolysyndactyly Contiguous Gene Deletion Syndrome: The Importance and Usefulness of DNA Microarray Analysis

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Abstract

Greig cephalopolysyndactyly syndrome (GCPS) is an autosomal dominant disease, characterized by polysyndactyly, macrocephaly and facial dysmorphisms. GCPS can appear both by point mutations of *GLI3* or contiguous gene deletion of 7p13 (GCPS-CGS). We report a 2-year-old girl with GCPS-CGS. DNA microarray analysis revealed 6.2 Mb deletion of 7p12.3p14.1 including *GLI3*, *CCM2* and *GCK*. She manifests multiple cerebral cavernous malformations by deletion of *CCM2*. Also it is revealed that she has a high risk of developing maturity onset diabetes of the young type 2 by deletion of *GCK*. DNA microarray provide a definitive diagnosis and clarify the genes involved in the deletion for the proper management of the complications.

Keywords: Greig cephalopolysyndactyly syndrome; Cerebral cavernous malformations; Maturity onset diabetes of the young type 2; Contiguous gene deletion; DNA microarray

Abbreviations: ACLS: Acrocaslosal Syndrome; CCM2: Cerebral Cavernous Malformations 2; GCPS: Greig Cephalopolysyndactyly Syndrome; GCPS-CGS: GCPS-Contiguous Gene Deletion Syndrome; MODY2: Maturity Onset Diabetes of the Young Type 2; PHS: Pallister-Hall Syndrome; SHH: Sonic Hedgehog.

Introduction

Greig cephalopolysyndactyly syndrome (GCPS, MIM #175700) is an autosomal dominant disease, characterized by preaxial polydactyly with syndactyly and facial dysmorphisms including macrocephaly, frontal bossing, hypertelorism and downslanted palpebral fissures. Its incidence is estimated as 1–9/1,000,000, and *GLI3* (GLI family zinc finger 3) is an only causative gene for GCPS [1]. GCPS can appear both by point mutations of *GLI3* or by contiguous gene deletion syndrome of 7p13 (GCPS-CGS) [2]. The majority of the former is intellectually normal and degree of polysyndactyly and facial dysmorphisms are highly variable. *GLI3* point mutations are also detected in patients with the milder phenotype as non-syndromic postaxial polydactyly [3]. In contrast, GCPS-CGS manifests relatively uniform symptoms; *i.e.* typical facial appearance, polysyndactyly (especially partial duplication to preaxial polydactyly of the great toe), and moderate to severe mental retardation are consistently observed [2,4]. Also, GCPS-CGS manifests unique symptoms by haploinsufficiency of surrounding genes depending on the extent of the deletion.

Case Report

A two-year-old girl was referred to our clinic for detailed examination of developmental delay and multiple congenital anomalies. She was born at 41 gestational weeks by uneventful natural vaginal delivery with a birth weight of 4050 g (+2.63SD). Soon after birth, she was noticed preaxial polydactyly and cutaneous syndactyly of first to fourth toes in both feet, and cutaneous syndactyly of second to fourth fingers in left hand (Figure 1A). Overgrowth was observed in early infancy. Her height and weight were around +2SD until 10-month-old, then reduced to +1.5SD after that. Her developmental milestone was delayed. She gained head control, sitting and crawling at 5, 14 and 20-month-old respectively. When she visited us, she did not walk alone and spoke no word, but followed the simple orders and showed her intention to others by some gestures. She had macrocephaly

(+2.3SD) with frontal bossing and hypertelorism (Figure 1B). Brain magnetic resonance image showed multiple cerebral cavernous malformations, ventricular dilatation and hypogenesis of corpus callosum (Figure 1C). She had no history of febrile seizure and epilepsy. From these phenotypes, she was suspected with GCPS-CGS, and DNA microarray analysis was performed with Genome-Wide Human single nucleotide polymorphism (SNP) 6.0 array (Affymetrix). Consequently, 6.2 Mb deletion was detected on short arm of chromosome 7. The microarray karyotype of the patient is designated as arr[hg19] 7p14.1p12.3(41,076,615-47,282,889)x1. This deletion includes 85 genes but only six genes, *GLI3*, *BLVRA*, *PGAM2*, *GCK*, *OGDH* and *CCM2* are linked to known phenotypes (Table 1). Of these, *BLVRA*, *PGAM2* and *OGDH* are autosomal recessive traits and single allele deletion causes no effect as long as there is no mutation in the remaining allele. *GLI3* is a causative gene of GCPS, and *CCM2* and *GCK* are causative gene of cerebral cavernous malformations 2 (*CCM2*, MIM #603284) and maturity onset diabetes of the young type 2 (*MODY2*, MIM #125851) respectively. Therefore, the patient has GCPS and multiple CCM at the same time as consequence of contiguous deletion of these genes. Although laboratory test of the patient showed negative urine sugar and normal glycated hemoglobin value, she has a high risk of developing MODY and careful follow up is required. Written informed consent was obtained from the parents of the patient after genetic counseling, and the study design was approved by the ethics review board of Kanazawa Medical University.

Discussion

The *GLI3* protein is a zinc finger transcription factor located at the downstream of sonic hedgehog (SHH) pathway which involved in morphogenesis of the neural tube, craniofacial structures, the limbs, the

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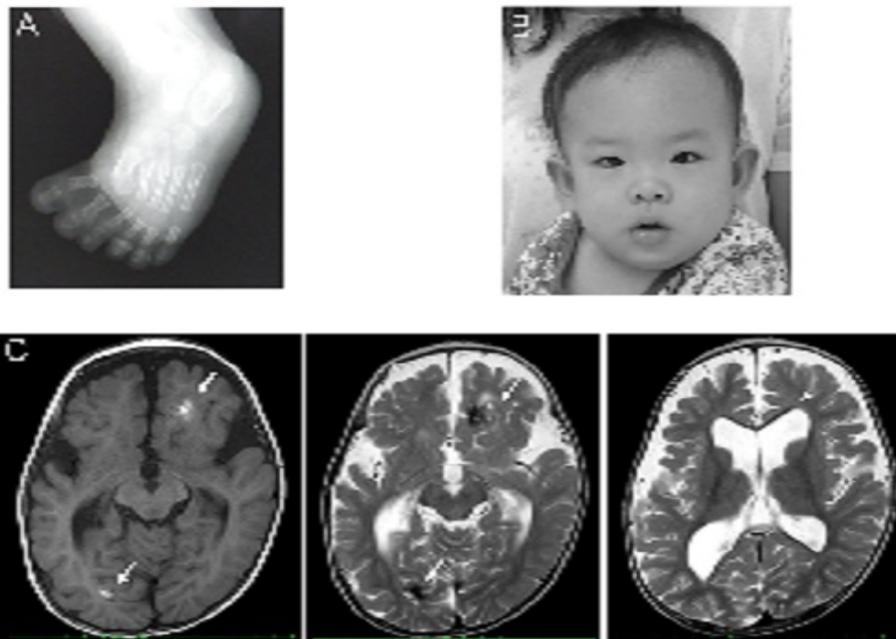


Figure 1: A) Left foot X-ray shows preaxial polydactyly of the great toe. A facial appearance of the patient. B) Note the macrocephaly and hypertelorism resembling to Sotos syndrome. C) Axial T1- (left) and T2- (center and right) MR images revealing multiple CCMs (arrows), ventricular dilatation and hypogenesis of corpus callosum (arrow head).

start bp	stop bp	Cytological location	Gene symbol	Gene Description	Related disease	MIM number	Inheritance
42000547	42277469	7p13	<i>GLI3</i>	GLI family zinc finger 3	Greig cephalopolysyndactyly syndrome (GCPS)	175700	AD
43798272	43846941	7p13	<i>BLVRA</i>	biliverdin reductase A	Hyperbiliverdinemia	614156	AR
44102326	44105186	7p13-p12	<i>PGAM2</i>	phosphoglycerate mutase 2 (muscle)	Glycogen storage disease X	261670	AR
44183870	44229022	7p15.3-p15.1	<i>GCK</i>	glucokinase (hexokinase 4)	MODY, type II	125851	AD
44646104	44748669	7p14-p13	<i>OGDH</i>	oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)	Alpha-ketoglutarate dehydrogenase deficiency	203740	AR
45039345	45116069	7p13	<i>CCM2</i>	cerebral cavernous malformation 2	Cerebral cavernous malformations-2 (CCM2)	603284	AD

AD: Autosomal Dominant; AR: Autosomal Recessive

Table 1: Genes with known phenotypes within the 6.2Mb deletion of 7p13 detected in the patient.

lung and other organs. Loss of function mutations of *GLI3* cause GCPS as mentioned above, on the other hand, gain of function mutation of *GLI3* cause phenotypically different disease called Pallister-Hall syndrome (PHS, MIM# 146510). PHS is characterized by polydactyly, hypothalamic hamartoma, bifid epiglottis or laryngeal cleft, and pulmonary segmentation anomalies. In the absence of *SHH*, *GLI3* protein is proteolytically processed and translocate to the nucleus then repressed downstream genes. *GLI3* nonsense or frameshift mutations in this processing domain cause PHS. The truncated *GLI3* mutated protein is considered to act constitutionally as repressor independent of *SHH* pathway control [5].

Recent advantage of DNA microarray technology revealed haploinsufficiency of several genes around *GLI3* causes the additional phenotypes of patients with 7p13 deletion. *CCM2* is one of the causative gene of inherited CCM with *CCM1* (MIM# 116860) caused by *KRIT1* mutation and *CCM3* (MIM# 603285) caused by *PDCD10* mutation. CCM was previously reported in two patients with GCPS-CGS and caused seizures in both [6,7], also one of them developed MODY by *GCK* deletion at the same time [7].

Acrocasilloal syndrome (ACLS, NIM#200990) is autosomal recessive condition caused by *KIF7* mutation. Patients with ACLS also manifests macrocephaly, preaxial or postaxial polydactyly and mental retardation; and virtually indistinguishable to GCPS-CGS from the phenotype [2]. This makes a problem on the genetic counseling. ACLS has 25% of recurrence risk to siblings, by contrast, most cases of GCPS-CGS are caused by de novo deletion and recurrence to siblings can be negligible. On brain MRI, ventricular dilatation and hypogenesis to agenesis of corpus callosum are common findings in both syndromes, but if CCM is found, it strongly suggests GCPS-CGS. Definitive diagnosis is made by DNA microarray test, and proper management of the complications are required, after clarified the genes involved in the deletion.

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