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Clinical Report

Agenesis of the Corpus Callosum, Optic Coloboma, Intractable Seizures, Craniofacial and Skeletal Dysmorphisms: An Autosomal Recessive Disorder Similar to Temtamy Syndrome

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Agenesis of the corpus callosum (ACC) is a common brain anomaly with a birth incidence of at least 1 in 4,000. ACC can occur as an isolated malformation or as a component of a syndrome. Here, we report on an autosomal recessive syndrome with ACC, optic coloboma, craniofacial dysmorphism, skeletal anomalies, and intractable seizures in a brother and sister from a consanguineous family. Homozygosity mapping excluded three genes, *VAX1*, *ASXL2*, and *ZNF462*, which have previously been implicated in ACC with optic coloboma. This case presents many features similar to Temtamy syndrome and will help in establishing the spectrum of this disorder. © 2007 Wiley-Liss, Inc.

Key words: agenesis of the corpus callosum (ACC); Temtamy syndrome; optic coloboma; homozygosity mapping; MRI

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INTRODUCTION

Agenesis of the corpus callosum (ACC) is a common brain anomaly with an incidence of approximately 1 per 4,000 live births [Talisetti et al., 2003]. There are only a few genes in humans that, when inactivated, repeatedly result in a syndrome with ACC [Mowat et al., 2003]. In mice, the corpus callosum is derived from axons arising from cortical neurons in layers 2, 3, and 5, and there is evidence that the cingulate cortex provides pioneer axons for midline crossing [Rash and Richards, 2001; Richards et al., 2004]. Previous studies have shown that deletion of *VAX1* results in ACC and optic coloboma in mice [Bertuzzi et al., 1999]. Additionally, *ASXL2* and *ZNF462* were identified at the breakpoints of a balanced chromosomal translocation in a patient with ACC and optic colobomata [Ramocki et al., 2003; Talisetti et al., 2003].

Here, we report on an autosomal recessive condition with ACC, optic coloboma, craniofacial and skeletal anomalies, profound cognitive impairment, and intractable seizures in a brother and sister from a consanguineous family of Middle Eastern origin. Brain magnetic resonance imaging showed

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Jiang Li and Shilpa Shivakumar contributed equally to this work.

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the proposita had complete ACC and the older brother had partial ACC. Both siblings have colpocephaly and Probst bundles. This report further expands the spectrum of Temtamy syndrome, (ACC, bilateral optic colobomata, craniofacial and skeletal dysmorphisms) [Temtamy et al., 1996], and may lead to identification of the causative gene.

CLINICAL REPORT AND RESULTS

Patient 1

Patient 1 is a 15-year-old female who was the fifth child of consanguineous healthy parents of Middle Eastern descent. The mother was 36 years old at the time of her birth and the father was 43 years old (Fig. 1). Her callosal agenesis was diagnosed by prenatal ultrasound at 22 weeks gestation. She was born at term with a birth weight of 3.4 kg. Her early development was delayed. She sat at 1 year and crawled at 2 years. She currently has severe cognitive impairment. She is able to make sounds but she has no words. She communicates by gesturing, touching, and making sounds. She is completely dependent on others for her daily activities. She has a generalized seizure disorder that began at 2 years of age and remains intractable to multiple anticonvulsants. EEG revealed grossly abnormal recordings on the left hemisphere suggesting a structural abnormality. She was noted to have left microphthalmia and had surgery for esotropia. She has also had a bilateral Achilles tendon release, and gingival resection for anti-convulsant-induced gum hyperplasia.

Physical examination showed that her height was 147 cm (5th centile), weight was 38.7 Kg (5th centile), and head circumference (OFC) was 54.5 cm (50th centile). She had dolichocephaly, left hemifacial atrophy, coarse facial features, and thick lips (Fig. 2). She had small epicanthal folds and inner canthal distance (ICD) measured 3.25 cm (50th centile), interpupillary distance (IPD) was 7.6 cm (>97th centile), and outer canthal distance (OCD) was 10.8 cm (>97th centile). Her ear length was 6 cm (50th centile).

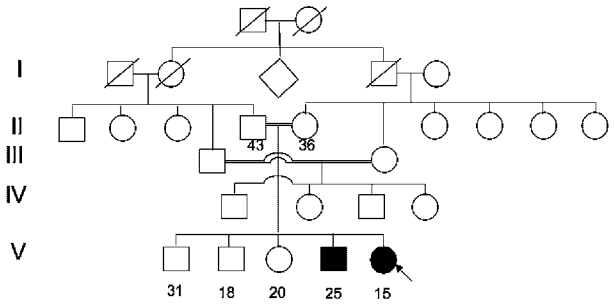

FIG. 1. Family pedigree. The proband (arrow; patient 1) is a 15-year-old female and patient 2 is a 25-year-old male who are the fifth and second children of consanguineous healthy parents. Four children were born in a parallel consanguineous brother–sister marriage and are healthy.

Examination of the extremities showed contractures of hands with hyperextensible joints, persistent fetal finger pads, and normal palmar creases. Palm length was 9.2 cm (3rd–25th centile). The third finger length was 6.2 cm (<3rd centile), consistent with brachydactyly. Her feet were small, with a length of 15.5 cm (<3rd centile), and showed bilateral clinodactyly with overlapping of the 2nd and 4th toes on the 3rd toe. Motor examination revealed decreased muscle bulk, increased tone, and brisk reflexes. A direct fundoscopic examination showed left microophthalmia with retinal and iris colobomata.

Investigations showed that the patient had a 46,XX karyotype, and subtelomeric FISH testing was normal as was a basic metabolic screen including serum amino acid profiles, urine organic acids, carnitine (total and free), and electrolyte panel. Her MRI showed complete ACC, and associated colpocephaly and Probst bundles (Fig. 4). An interhemispheric lesion bright on T1 and T2 was interpreted as a colloid cyst, and a small anterior commissure, hypoplastic left optic nerve and chiasm, and a small hypothalamus, cerebella vermis, and thin brain stem were also observed.

Patient 2

Patient 2 is a 25-year-old male who is an elder brother to the proposita. He was born at 44 weeks by normal spontaneous vaginal delivery. Birth weight was 3.6 kg. He had severe mental retardation and was nearly completely dependent on others for his daily activities; however, he can feed himself and was able to attend special school until 18 years of age. Additional medical details of his early life are not available. A genetics evaluation early in life noted upslanting palpebral fissures, with epicanthal folds, hypertelorism, and high arched and narrow palate. His seizures began at 3 years of age and he currently has multiple daily short myoclonic spells that are partially controlled by Depakote.

On examination (Fig. 3), height was 150 cm (<5th centile), weight was 70.4 kg (50th centile), and OFC was 59.7 cm (>99th centile). He had slightly coarse facial features with drooling and no speech or verbal comprehension. He had a left esotropia, his OCD was 12 cm (>98th centile), ICD was 2.5 cm (3rd centile), and IPD was 6.2 cm (80th centile). His ear length was 6.8 cm (>99th centile).

Examination of the extremities revealed his palm length was 9.5 cm (14th centile), finger length was 6.9 cm (25th centile), and foot length was 21.5 cm (<3rd centile). Limb deformities include severe bilateral pronation of the feet treated with braces. He had a normal male karyotype (46,XY) and a basic metabolic screen was also normal. A head computerized tomography (CT) scan demonstrated the absence of the splenium and part of the posterior

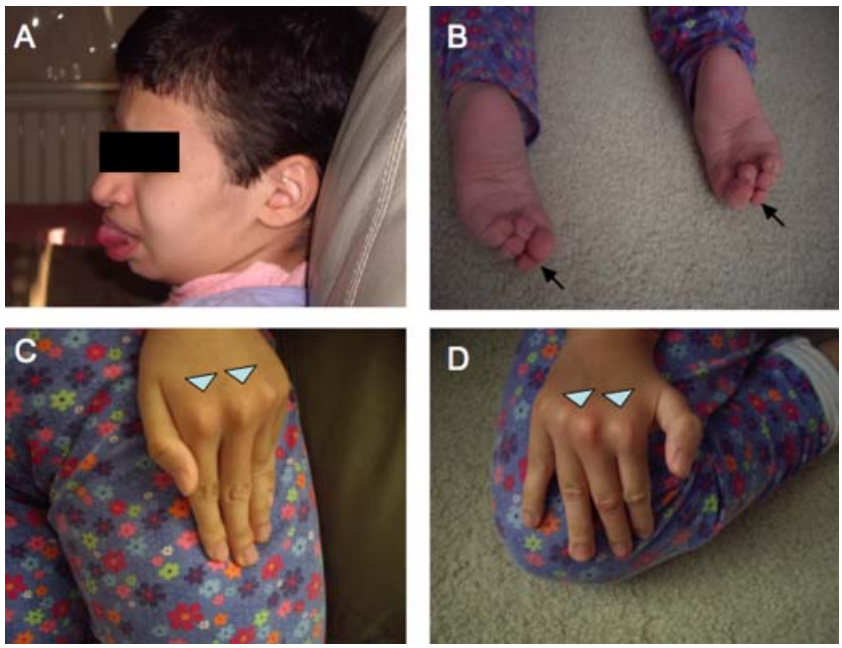

FIG. 2. Patient 1 at the age of 15. **A**: Left side view. Note that she has left hemifacial atrophy, with coarse facial features and thick lips, elongated head. **B**: Bilateral clinodactyly with overlapping of the 2nd and 4th toes with the 3rd toe (arrow). **C** and **D**: Contractures of both hands with hyperextensible joints. (arrow head). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

body of the corpus callosum. Colpocephaly is also noted (Fig. 4).

Homozygosity mapping. Blood samples were obtained from the five siblings and mother, and genomic DNA was extracted from peripheral blood leukocytes using the Puregene DNA Purification Kit (Gentra, Minneapolis, MN). All the protocols have been approved by the committee on human research at the University of California, San Francisco. Homozygosity mapping for the genes *VAX1*, *ASXL2*, and *ZNF462* were undertaken by PCR with10 cM spaced microsatellite markers that flank the three

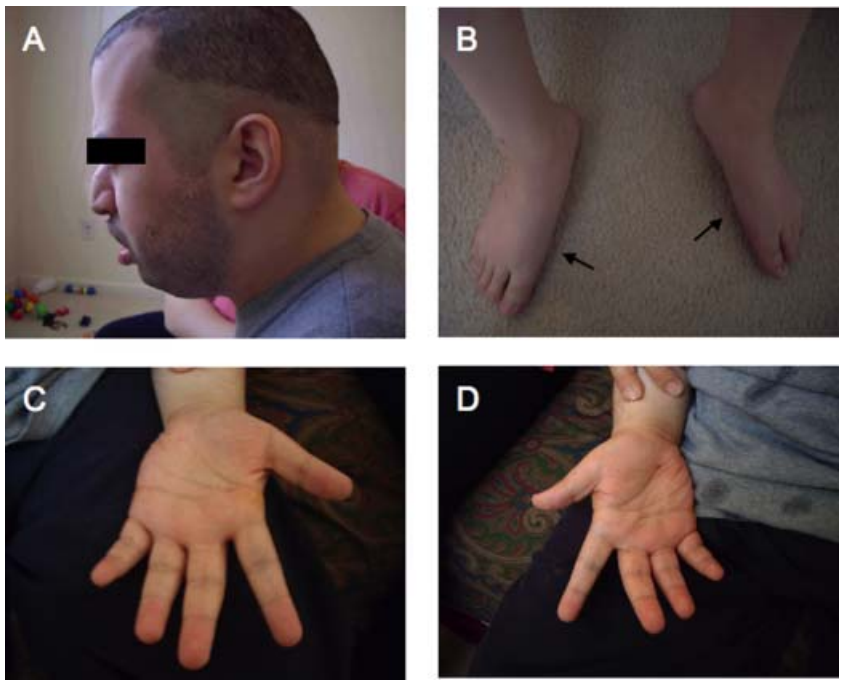

FIG. 3. Patient 2 at the age of 25. **A**: Left side view. Note that he has a slightly coarse facial features with drooling. **B**: Severe bilateral pronation of the feet (arrow). **C**, **D**: Short finger length of both hands. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

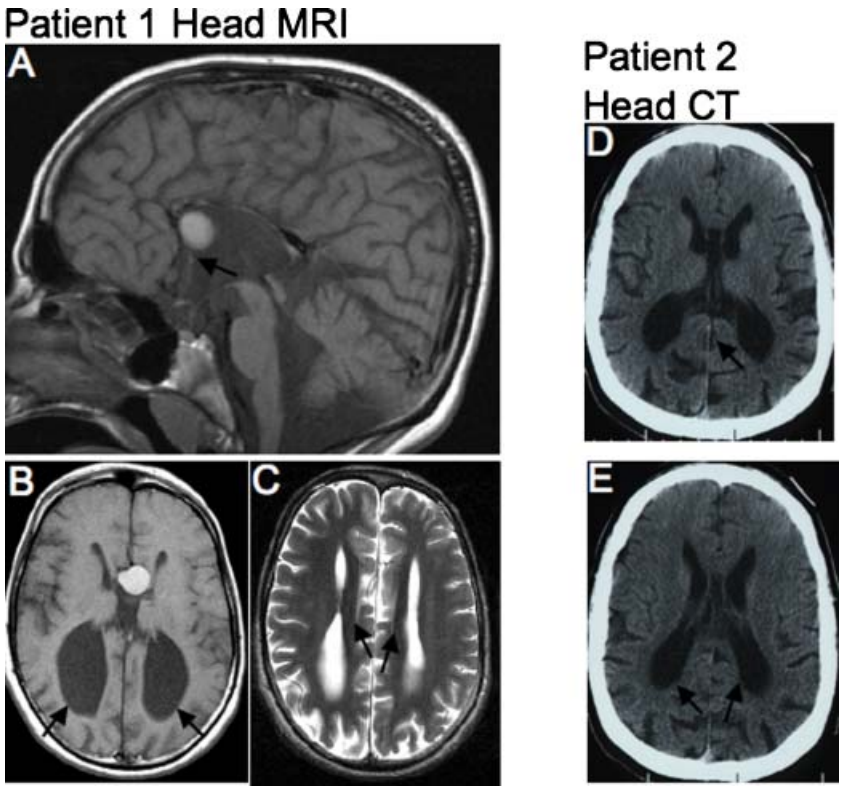

FIG. 4. Images from brain MRI of patient 1 (1183-0A) (**A–C**) and brain CT from patient 2 (1183-4A) (**D–E**). A: Sagittal view shows a colloid cyst, absence of the corpus callosum, thin brainstem, and a small anterior commisure beneath the colloid cyst (arrow). B: Axial T1-weighted sequence shows colpocephaly (arrows). C: Axial T2-weighted images show bilateral Probst bundles (arrows in C). The CT scan of patient 1183-4A (D) demonstrates partial agenesis of the corpus callosum (ACC), with the absence of the splenium and part of the posterior body (arrow). E: Dilated occipital horns and trigones (colpocephaly) are also noted (arrows).

genes by 40 cM on each side (see the online Table I at http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html). PCR products were resolved on an ABI 377 sequencer and analyzed using ABI PRISM Genescan analysis software (Applied Biosystems, Foster City, CA).

Analysis of the marker alleles demonstrates that at no locus were the two affected children homozygous while the three healthy siblings were either heterozygous or homozygous for a different allele. Therefore, assuming the absence of two recombinations between markers, these data exclude the possibility that a recessive alelle for this ACC syndrome resides at these three loci (see the online Table I at http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html).

Comparative genomic hybridization (CGH) arrays. The arrays used in the study were prepared and hybridized as described previously [Ishkanian et al., 2004]. The Tiling Path Array (HumArray 3.2) was obtained from the UCSF Cancer Center Array Core (http://cc.ucsf.edu/microarray/) and it contains over 32,000 human BAC clones spotted in singlets with continuous, overlapping coverage of the genome (~25% overlap between contiguous clones).

We compared gender-matched DNA to the affected female sibling (patient 1) and did not identify any clear deletions or duplications equal to or greater than two BACs in size. Moreover, we found no evidence of any copy number variation that would be consistent with an autosomal recessive pattern of inheritance (data not shown).

DISCUSSION

Temtamy et al. [1996] described three siblings, whose parents were first cousins, with ACC and cerebral ventricular enlargement, iris, retina and chorioid colobomata, craniofacial dysmorphism with macrodolichocephaly, an elongated face, hypertelorism, a prominent nose, low-set and simple ears, micrognathia, and skeletal anomalies including brachydactyly of the hands and feet, genu vara, and pes planus. Subsequently, similar findings were reported in a boy [Chan et al., 2000] and a girl [Ramocki et al., 2003; Talisetti et al., 2003]. Our case has many features consistent with the initial patients reported by Temtamy et al. including complete and partial ACC, optic colobomata, skeletal anomalies including brachydactyly in the first sib and mild craniofacial dysmorphism. However, the patients here differ from that first report given their profound

TABLE II. Autosomal Recessive Disorders With ACC and Iris Colobomata

Syndrome/author name	Temtamy syndrome	Temtamy-like syndrome [t(2:9)(p24:q32)]	Aicardi syndrome	Donnai–Barrow syndrome	Baraitser–Winter syndrome	Patient 1	Patient 2
Structural brain anomalies	ACC, dilated cerebral and 4th ventricles, slight dilation of cortical sulci	ACC, ventriculomegaly	ACC, periventricular & subcortical heterotopia, pachygyria, vermian anomalies, choroids plexus papilloma, & cysts	ACC	Pachygyria, agyria, band heterotopia, ventricular dilatation, microcephaly	ACC, associated colpocephaly and Probst bundles, interhemispheric colloid cyst, small hypothalamus, cerebella vermis, and thin brain stem	Partial ACC, absence of the callosal splenium and part of the posterior body, colpocephaly
Ocular anomalies	Colobomata of iris, retina, and choroid, lens dislocation, myopia, hypertelorism	Iris and chorioretinal colobomas	Chorioretinal lacunae, coloboma of optic disc, microphthalmia	Hypertelorism, myopia, iris coloboma, retinal detachment	Iris and choroidal colobomata, microphthalmia, microcornea	Left microophthalmia with retinal and iris coloboma	–
Craniofacial anomalies	Frontal bossing, elongated face, arched eyebrows, downslanting palpebral fissures, beaked nose, low-set and dysplastic ears, long philtrum, short upper lip, micrognathia	Frontal bossing, peaked eyebrows, ptosis, malformed low-set ears, depressed nasal bridge, and long philtrum	–	Large anterior fontanel, downslanting palpebral fissures, short nose, posterior angulated ears	Trigonocephaly, hypertelorism, ptosis, epicanthal folds, broad nasal bridge short nose with upturned tip, thin upper lip	Left hemifacial atrophy, coarse facial features, and thick lips	Slightly coarse facial features with drooling
Mental retardation	+	Profound	Profound	+	–	Profound	Profound
Seizures	–	+	Infantile spasms	–	–	Intractable seizures	Intractable seizures
Connective tissue and skeletal anomalies	Exaggerated digital markings	–	Vertebral abnormalities, rib anomalies, scoliosis	–	–	Contractures of the hands with hyperextensible joints, bilateral clinodactyly with overlapping of the 2nd and 4th toes with the 3rd toe	Severe bilateral pronation of the feet
Cardiovascular	Aortic dilation and regurgitation	PDA, VSD	–	VSD, double superior vena cava	–	–	–
Other system anomalies	Dental and gingival abnormalities	Unilateral renal agenesis, neurogenic bladder, and hydronephrosis	–	Sensorineural deafness, diaphragmatic hernia	–	–	–

PDA, patent ductus arteriosus; VSD, ventricular septal defect.

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mental retardation, intractable seizures, and the interhemispheric colloid cyst. These findings may indicate a more severe disruption of brain development. Moreover, our patients lack the cardiac anomalies previously identified in the family described by Temtamy et al. [1996], comprising enlargement of the left ventricle and aortic dilation and regurgitation.

Other syndromes that form part of the differential diagnosis for ACC and optic colobomata include Aicardi syndrome [Aicardi, 2005], Donnai–Barrow syndrome [Donnai and Barrow, 1993] and Baraitser–Winter syndrome [Ganesh et al., 2005], but each of these syndromes has unique features that distinguish them from Temtamy syndrome (Table II). For example, the features in Donnai–Barrow syndrome include diaphragmatic hernia, omphalocele, myopia, and sensorineural deafness and Aicardi syndrome includes infantile spasms, and is inherited as a sporadic condition that only occurs in females or XXY males. In Baraitser–Winter syndrome, the cerebral malformations are distinctive and include evidence of abnormal neuronal migration such as pachygyria, agyria, or subcortical band heterotopia and microcephaly, without evidence of callosal agenesis. Comparison of the different conditions associated with ACC and colobomata indicated that the case we report here most closely resembles Temtamy syndrome, but may constitute a new or unique syndrome in this family.

The genetic etiology of Temtamy syndrome is unknown. Talisetti et al. [2003] reported a 5-year-old female with features similar to the sibs of Temtamy et al. This girl had a de novo balanced chromosome translocation [karyotype 46,XX, t(2; 9)(p24; q32)]. Physical mapping of the break points has identified two zinc-finger like genes, *ASXL2* and *ZNF462*. There is evidence for the production of a novel fusion transcript from the conjunction of these two genes. However, homozygosity mapping indicated that these two genes along with *VAX1*, a gene that causes ACC when its homologue is inactivated in mice, are not the cause of the ACC syndrome observed in our patients if an autosomal recessive mode of inheritance is operant in this family. This suggests that a different gene is likely responsible for the ACC in this family, and possibly also in Temtamy syndrome. CGH is a widely used method to detect genomic copy number change. In this family, there is no detectable chromosomal duplication or deletion to account for the findings observed here. Thus, identification of additional families and genome wide mapping are needed to identify the causative gene.

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