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Identification of Genomic Loci Contributing to Agenesis of the Corpus Callosum

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Agenesis of the corpus callosum (ACC) is a common brain malformation of variable clinical expression that is seen in many syndromes of various etiologies. Although ACC is predominantly genetic, few genes have as yet been identified. We have constructed and analyzed a comprehensive map of ACC loci across the human genome using data generated from 374 patients with ACC and structural chromosome rearrangements, most having heterozygous loss or gain of genomic sequence and a few carrying apparently balanced rearrangements hypothesized to disrupt key functional genes. This cohort includes more than 100 previously unpublished patients. The subjects were ascertained from several large research databases as well as the published literature over the last 35 years. We identified 12 genomic loci that are consistently associated with ACC, and at least 30 other recurrent loci that may also contain genes that cause or contribute to ACC. Our data also support the hypothesis that many ACC loci confer susceptibility to other brain malformations as well as ACC, such as cerebellar hypoplasia, microcephaly, and polymicrogyria. The database presented here provides a valuable resource for diagnosis and management of individuals with ACC and individuals with chromosome rearrangements in whom ACC should be suspected, and of course for identifying ACC causal and contributory genes. Well-defined diagnostic criteria, improved scanning techniques, and increased recognition of associated abnormalities will further facilitate gene mapping and allow definition of distinct syndromes within this heterogeneous group of patients. © 2010 Wiley-Liss, Inc.

Key words: corpus callosum; corpus callosum agenesis; corpus callosum hypoplasia; magnetic resonance imaging; chromosome; copy number variant; brain malformation

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INTRODUCTION

The corpus callosum (CC) is the largest of three forebrain commissures in humans, and originates from the most rostral segment of the developing forebrain. Agenesis of the corpus callosum (ACC) is a common brain malformation with significant variability in expression [Glass et al., 2008] (Fig. 1). Although ACC is commonly associated with genetic disorders [Dobyns, 1996; Schell-Apacik et al., 2008], the underlying genetic causes remain elusive. Recent improvements in molecular and cytogenetic technology have led to a rapid increase in the number and definition of copy number variants (CNVs) [de Smith et al., 2007; Perry et al., 2008] and to a broadening in our understanding of the many chromosomal regions and syndromes associated with ACC. We therefore present and analyze a comprehensive map of ACC loci in the human genome using data generated from 374 patients with ACC and structural chromosome rearrangements, including at least 101 previously unpublished cases. The subjects were ascertained from large research databases maintained by the authors (WBD, EHS), the Californian Birth Defects Monitoring Program (CBDMP—see the Methods Section), three online databases of patients with chromosome rearrangements (DECIPHER, ECARUCA, DGAP—see the Methods Section), and a comprehensive literature review.

Using these combined strategies we identified 12 loci with 6 or more subjects with ACC, and another 18 loci with 3–5 patients with ACC. We also found many other possible loci (17) described in small numbers of patients with ACC, which may represent either

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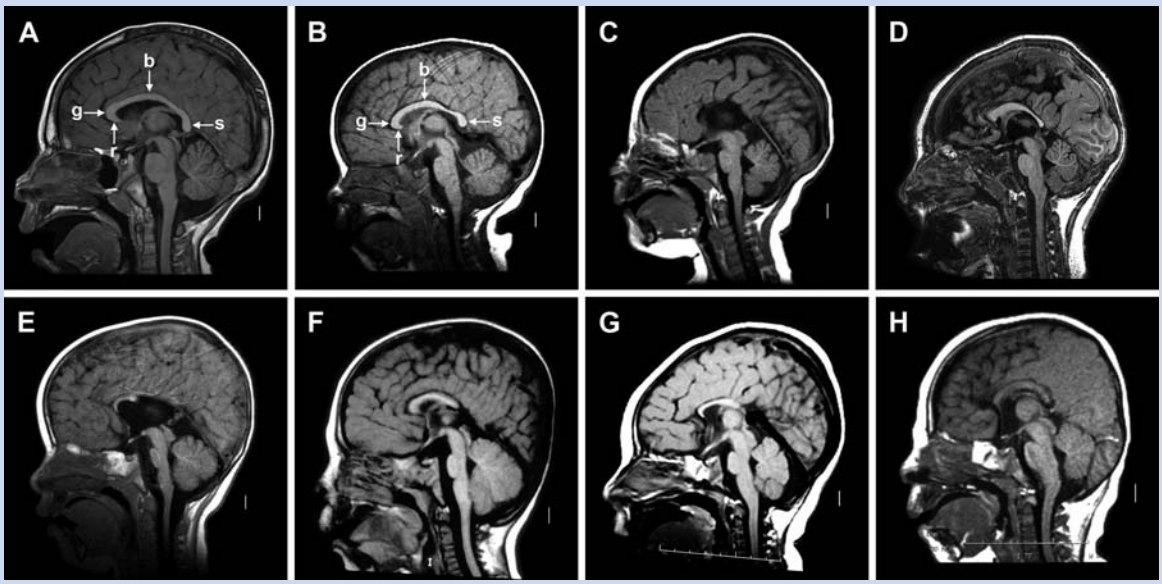

FIG. 1. Agenesis or hypogenesis of the corpus callosum in six patients with various chromosome deletions on T1-weighted midline sagittal magnetic resonance images. A,B: The normal shape of the corpus callosum is shown in two individuals with arrows pointing to the rostrum (r), genu (g), body (b), and splenium (s). C: Agenesis or complete absence of the corpus callosum in a girl with deletion 1q44 (LR05-202). D: Hypogenesis of the corpus callosum with absent rostrum, thin and short body and absent splenium in a boy with deletion 1q44 (LR06-076). E: Severe hypogenesis in a girl with deletion 6q26-q27 (LR06-191). F: Mild hypogenesis with a short, comma-shaped corpus callosum in a boy with deletion 6q26-q27 (LR00-183). G: Hypogenesis in a girl with interstitial deletion 6q25 (LR00-226). H: Mild hypogenesis with a short, comma-shaped corpus callosum in a girl with interstitial deletion 14q13 (LR01-197).

low penetrance ACC loci or incidental findings (Fig. 2 and see supporting information Table I which may be found in the online version of this article). Many of the latter had poorly defined critical regions, other incidental chromosome abnormalities unrelated to the ACC phenotype, or an incorrect diagnosis of ACC. From our analysis of these data, we hypothesize that the human genome contains over 30 loci in which heterozygous loss or gain of gene products causes or contributes to ACC. Furthermore, some of the higher penetrance loci contain two (or more) ACC causative genes, and several ACC loci also confer susceptibility to other brain malformations such as cerebellar hypoplasia, microcephaly, and polymicrogyria. These data provide information that will assist in the interpretation of abnormal karyotypes and microarray results in pre- and postnatal medical and research settings and direct genetic investigation in patients with brain imaging abnormalities involving the CC. It also has the potential to contribute to our knowledge of the genes and gene pathways involved in normal and abnormal brain development.

METHODS

The CC is the principal connection between the right and left cerebral hemispheres. Four contiguous segments can be seen on MRI brain imaging: the rostrum, genu, body, and splenium (Fig. 1A,B). Several different terms have been used in the literature to describe callosal malformations. Complete absence is referred to as ACC. Partial absence, typically involving the anterior rostrum and posterior body and splenium, is preferentially described as hypogenesis although the terms partial agenesis and dysgenesis are also used [Barkovich, 2002; Hetts et al., 2006; Schell-Apacik et al., 2008]. Hypoplasia of the CC describes a thin CC where all the segments are present but abnormally thin, and has sometimes been used when the CC appears short but otherwise normally formed, as well as thin.

Sources of Data

We retrieved data from our own, largely unpublished, research databases (sources (1) and (2) below) and supplemented this with data from several appropriate online databases. We also consulted all available reports of CC anomalies associated with cytogenetic abnormalities in the published medical literature from 1965, with a particular emphasis on reports since the last review in 1996 [Dobyns, 1996]. Our primary sources included:

(1) Lisdb: This is a large database of ~5,400 patients ascertained based on birth defects of the brain and other neurodevelopmental disabilities collected and maintained by WBD. Of these 409 are recorded to have a callosal disorder documented by brain imaging studies, some of which have been the subject of previous publications.
(2) Brain Development Research Program (BDRP): This is a study of cortical malformations lead by EHS, with a focus on callosal anomalies that includes 456 patients with ACC as detected by MRI. Only clinically confirmed cytogenetic data are included from this cohort.
(3) California Birth Defects Monitoring Program (CBDMP) Database (www.cbdmp.org): This is a database maintained by

the State of California Department of Public Health and the March of Dimes Foundation that identifies children with birth defects including ACC. From a review of data between 1993 and 2003, 645 cases of ACC were identified. However, brain imaging studies were not available for children listed in this database.

(4) European Cytogeneticists Association Register of Unbalanced Chromosome Abberations (ECARUCA; agserver01.azn.nl:8080/ecaruca/ecaruca.jsp). This is an online, searchable database of over 4,000 patients with chromosomal rearrangements. Some, but not all, have microarray-based information.

(5) DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER; http://decipher.sanger.ac.uk). This is an online, searchable database of patients with chromosomal rearrangements defined using microarray data.

(6) Developmental Genome Anatomy Project (DGAP; www.bwhpathology.org/dgap). This is an online searchable database of apparently balanced chromosomal rearrangements in patients with multiple congenital anomalies.

(7) PubMed search, using EndNote(R) as a search engine, 1996–2008 using the terms corpus callosum, absent corpus callosum or corpus callosum agenesis, dysgenesis or hypoplasia. This search obtained ~2,000 references, which were then reviewed by title and abstract. The relevant papers were then reviewed in their entirety to obtain more detailed information. Published images confirmed the presence of ACC in only a small minority of papers.

The retrieved data were reviewed to document the individual karyotypes, which were recorded using ISCN nomenclature [Shaffer and Tommerup, 2005], which often required modification. We excluded papers where published cytogenetic data were incomplete, for example, when the breakpoints were not given or could not be determined from illustrations. Where additional FISH or microarray studies were performed, we used these data to update the karyotype. We calculated the size of rearrangements using the UCSC database (http://genome.ucsc.edu/cgi-bin/hgGateway) considering any involved bands as deleted in their entirety. We extracted key data regarding the phenotype and separated these into neurodevelopmental and other abnormalities. The former includes brain malformations, specific developmental disabilities and neurological conditions such as seizures. The latter includes abnormal growth, structural defects of other systems and dysmorphic features. Where figures of brain imaging studies or postmortem data were included in the publication, we were able to confirm the presence of a callosal abnormality.

Inclusion Criteria

Patients from literature reports or online cytogenetic databases with ACC were included. The CC is easily seen on mid-sagittal magnetic resonance imaging (MRI) scans. It is less easily, and less reliably, visualized using other imaging modalities, such as ultrasound and computerized tomography (CT) scans. Complete ACC is a relatively straightforward diagnosis but subtle variation in callosal width or length is subject to the interpretation and experience of the reporting physician. Where brain imaging figures or postmortem results were published, we attempted to use these to confirm whether CC abnormalities were present and looked for evidence of other brain malformations. Several different terms were used to describe CC abnormalities without any obvious consensus. These included "absent," "agenesis," "dysgenesis," "hypogenesis," "hypoplasia," "thin," and "partial agenesis." For this reason, we have used ACC as an umbrella term to cover all of these descriptions.

We identified many patients from literature reports or online cytogenetic databases such as DECIPHER, which usually did not contain photos or scan images. In these instances we relied on the documented reports of ACC.

Exclusion Criteria

CC abnormalities are found in severe forebrain malformations such as holoprosencephaly, a part of more general CNS disruption such as neural tube defects, and have been described as a part of degenerative conditions such as Andermann syndrome and some metabolic disorders. In these disorders, the callosal abnormalities are likely to be secondary to different pathological processes than in cases of isolated or complex ACC, which were more common. Reports of these disorders were excluded from this study.

Construction of the Database

Each patient was entered once for each separate cytogenetic rearrangement. Most of these consisted of CNVs, but we found 10 apparently balanced rearrangements. So, for example, patients with inverted duplication deletions were entered twice, once for the deletion and again for the duplication. Three patients had three or more rearrangements. Thus, the total number of entries greatly exceeds the number of patients (see supporting information Table I which may be found in the online version of this article).

We first organized all entries by chromosome, type of abnormality (breakpoint, deletion or duplication, rarely triplication or quadruplication), and segment involved, all derived directly from the karyotype. These data were hand curated to identify the shortest regions of overlap between patients with overlapping deletions or duplications; all apparently balanced breakpoints were included with the deletions, while triplications and quadruplications were included with duplications. Deletions (plus breakpoints) and duplications were treated separately, even when the same regions were involved. We then sorted all entries based firstly on the individual chromosome, then the critical region, then the type of abnormality, and finally the specific segment involved, which could be larger than the critical region.

Classification of Critical Regions (CR)

- Class 1 CR consist of regions with six or more patients, where at least one, and usually two or more, were confirmed by our review of brain imaging studies. When images from only one patient were available for review (e.g., 1p36), we required confirmation by independent reports from several different groups.
- Class 2 CR consist of regions with 3–5 patients reported, the majority of which we could confirm in *at least* one patient by review of brain imaging.
- Class 3 or possible CR consist of two patients including at least one with confirmation of brain imaging, *or* three or

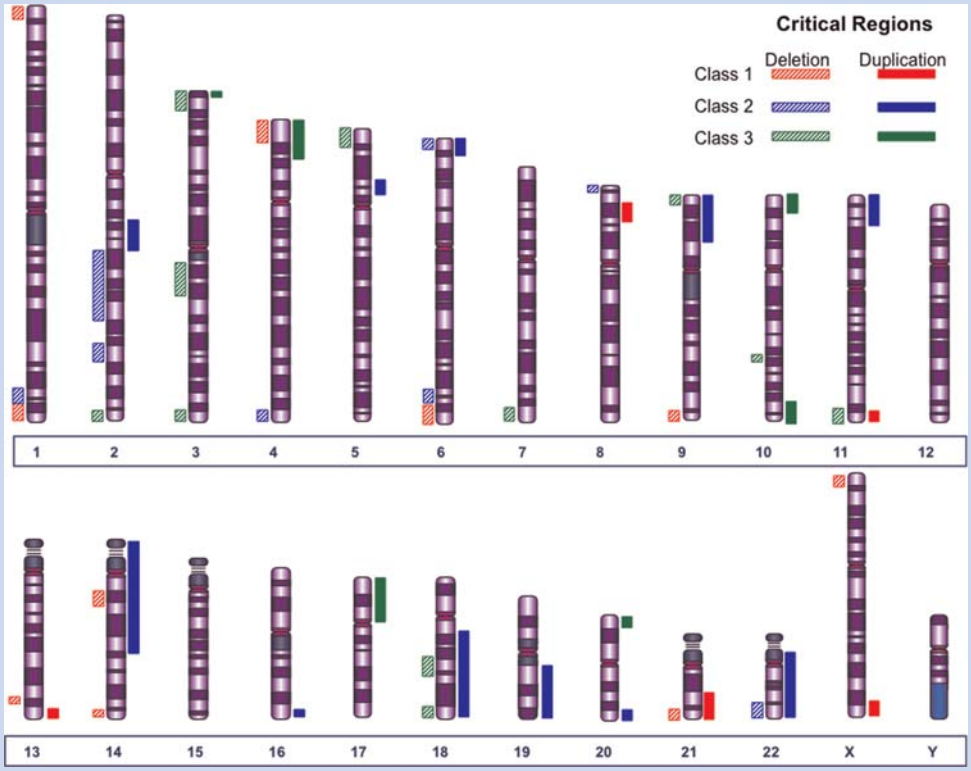

FIG. 2. Chromosome ideograms at 550 band resolution illustrating the class 1–3 loci. Deletions are represented on the left-hand side of the ideogram with hatched boxes. Duplications are represented on the right-hand side of the ideogram with solid boxes. Class 1 loci are in red, class 2 in blue, and class 3 in green.

more patients with no available imaging studies to confirm the presence of ACC.

RESULTS

Cytogenetic Rearrangements

We identified 374 patients with reported or confirmed ACC and documented cytogenetic rearrangements, including at least 101 previously unpublished individuals. Most cytogenetic abnormalities were CNVs, and many comprised complex rearrangements with more than one chromosome segment involved, so our analysis contains 420 entries. These data are summarized in Table I and Figure 2, and our complete data set is available online (see supporting information Table I which may be found in the online version of this article).

We identified 12 class 1 CR spread over 10 chromosomes, with 10 due to deletions and 2 to duplications. The size of the CR varied from 3.67 to 16.4 Mb. The only ACC causative gene identified from one of these regions thus far is *AKT3* from 1q43-q44 [Boland et al., 2007], although recent data suggest that *FOXG1* in 14q12 may be another [Shoichet et al., 2005; Ariani et al., 2008]. We designated another 18 loci as class 2 CR, with 8 due to deletions and 10 to duplications. The size of these CR ranged from 1.6 to 78.4 Mb, in general larger than for class 1 CR. Several of these regions are associated with common deletion or duplication syndromes in humans that have not generally been considered to be ACC loci, including deletions 5p13 and 22q13, and duplication 22q11.2. We interpret these as common CNV syndromes with low penetrance ACC.

We found many other possible loci with weaker support that we designate as class 3 loci. Some of these are likely to be rare CNV with high penetrance ACC, and others common CNV with low penetrance ACC, including loci that result in ACC only in combination with other factors. Some of the remainder may be real CNV that are unrelated to ACC, in which case the reported ACC is likely to have a different cause. This phenomenon is being seen more often in microarray studies, as a subset of patients have multiple potentially pathogenic CNV. Finally, the clinical criteria for ACC differ from center to center, so that some putative loci unsupported by imaging or pathological data might not be included were these data available for us to review. Where we encounter a published report of ACC with no image of the CC we classify this as "provisional."

The penetrance of ACC appears to be high, although never 100%, for some loci, especially deletions of 1q43-q44 (33/38 patients with images shown in published reports) and 6q26-q27 (8/12 patients with scans from our unpublished data) and inversion duplication deletions of 8p. Penetrance appears to be higher among patients with deletion or duplication of two ACC critical regions. The best examples here are extended deletions of 1q42-q44 [Bedeschi et al., 2006; Boland et al., 2007] and 6q25-q27 [Shen-Schwarz et al., 1989; Rubtsov et al., 1996; Desai et al., 1999; Sukumar et al., 1999;

TABLE I. Summary of ACC Critical Regions

Class	Chr	Region	CNV type	ACC	Two loci	ACC confirmed	CBL	PMG	NOS
1	1	1p36	del	8		1	0	1	2
2	1	1q42	del	3	5 (1 confirmed)	3	0	0	1
1	1	1q43-q44	del	35	5 (1 confirmed)	8	5	0	15
2	2	2q14.3-q21	dup	4		2	1	0	2
2	2	2q22-q31	del	4		1	0	0	3
2	2	2q33	del	3		1	1	1	2
3	2	2q37.3	del	2		1	0	0	0
3	2	3p26.3-p25	del	2		1	0	0	1
3	2	3p26.3-26.2	dup	2		1	1	0	1
3	3	3q13.1-q13.3	del	4		0	0	0	0
3	3	3q29	del	2		1	0	0	1
1	4	4p16.1-p16.3	del	15		1	1	1	2
3	4	4p16.3-p15.2	dup	3		0	0	1	1
2	4	4q35	del	3		1	1	1	0
2	5	5p13.3-p13.1	dup	3		1	1	0	1
3	5	5p15.33-p15.2	del	2		1	2	0	0
2	6	6p25	del	5		2	2	1	3
2	6	6q25.3-q24.1	dup	3		2	0	0	2
2	6	6q25.3-q25.1	del	3	8 (1 confirmed)	1	1	0	1
1	6	6q26-q27	del	12	8 (1 confirmed)	7	7	8	6
3	7	7q36.1-q36.3	del	4		0	0	0	0
1	8	8p22-p21.3	dup	21	38 (6 confirmed)	5	1	1	11
2	8	8p23.3	del	4	38 (6 confirmed)	1	0	0	9
3	9	9p24	del	3		0	0	0	0
2	9	9p24.3-p21.1	dup	4		1	1	0	2
1	9	9q34.3	del	6		1	0	0	3
3	10	10p15.3-p14	dup	4		0	0	0	0
3	10	10q23.2	del	2		1	0	0	1
3	10	10q26.1-q26.3	dup	3		0	0	0	1
2	11	11p15.1-p15.5	dup	3		1	1	1	1
1	11	11q25	dup	10		2	3	1	2
3	11	11q24.1-q25	del	3		0	0	0	2
1	13	13q32.3-q33.1	del	14		2	3	0	3
1	13	13q34	dup	22		1	0	0	2
2	14	14p13-q22	dup	4		1	0	0	3
1	14	14q12-q13.1	del	8	1 (0 confirmed)	1	0	0	5
1	14	14q32.3	del	9	1 (0 confirmed)	4	1	0	3
2	16	16q24.3	dup	4		1	0	0	0
3	17	17p13.3-p11.2	dup	3		0	0	0	0
2	18	18q12-q23	dup	3		1	0	0	0
3	18	18q21.1-q21.2	del	2	4 (0 confirmed)	0	0	0	0
3	18	18q23	del	2	4 (0 confirmed)	0	0	0	0
2	19	19q13	dup	3		1	0	0	0
3	20	20p13.3	dup	3		0	0	0	0
2	20	20q13.3	dup	3		1	1	0	0
1	21	21q22.11-q22.3	dup	11		1	0	0	2
1	21	21q22.2-q22.3	del	10		3	0	3	0
2	22	22q11.2-q13.3	dup	5		1	0	0	0
2	22	22q13.31-q13.33	del	5		1	0	0	2
1	X	Xp22.3	del	6		2	1	0	1
1	X	Xp27.3-q28	dup	6		2	1	0	1

Chr, chromosome; CNV, copy number variant; ACC, patients with agenesis of the corpus callosum; ACC confirmed, patients with ACC confirmed on brain imaging by the authors (see the Methods Section); CBL, cerebellar malformation; PMG, polymicrogyria; NOS, brain malformation not otherwise specified; del, deletion; dup, duplication.

Yamanouchi et al., 2005]. Patients have also been identified with CNVs on two different chromosomes encompassing identified critical regions, including records 4 and 5 (Lisdb subjects DP89-003a1/a2), 28, 36, 132, 141 [Rott et al., 1972; Yamanouchi et al., 2005; Boland et al., 2007; Poot et al., 2007] from supporting information Table I (supporting information Table I may be found in the online version of this article).

Several of our ACC loci overlap with critical regions for other brain malformations, especially cerebellar malformations and the cortical malformation polymicrogyria based on our published [Dobyns et al., 2008] and unpublished (K.J. Millen, K. Aldinger, W.B. Dobyns, unpublished cerebellar loci) data. We found nine loci in common between our ACC and cerebellar malformation databases, and four loci in common with our ACC and PMG databases. Deletions of chromosomes 1q43-q44 and 6q26-q27 are associated with all three malformations, although this appears robust only for deletion 6q26-q27. All three malformations have been reported with a few other loci, such as deletion 2q31-q33, which could be real or reflect an unrecognized cryptic abnormality of another candidate region. The loci are summarized in Table II.

Phenotype Data

We collated data on brain malformations other than ACC where they were available. We were able to confirm the presence of a callosal abnormality from published images or autopsy data, or from our own data in only 74 of 374 (20%) patients, including 20 from our primary patient database. For many other patients, additional brain malformations were described but not shown. Cerebellar malformations were reported in 14 (10.8%) and polymicrogyria in 9 (6.7%) individuals with ACC class 1–3 loci. These are estimated values as a small number of patients with unclassified CNVs had cerebellar and cortical malformations together with ACC.

Other cortical malformations such as periventricular nodular heterotopia, hydrocephalus, and brainstem abnormalities were also reported. Hydrocephalus, ventriculomegaly (VM), and colpocephaly were reported in numerous individuals. We were often unable to differentiate between these abnormalities based on the limited data provided, so they are listed together as VM in supporting information Table I (supporting information Table I may be found in the online version of this article). As expected, the incidence of seizures and mental retardation are high, particularly when other cortical malformations are present.

Descriptions of microcephaly and macrocephaly are common in individuals with ACC. Despite this, few reports provided occipitofrontal circumference (OFC) or percentile/*z*-score data, making estimation of the severity difficult to determine. We included data regarding microcephaly or macrocephaly when this was mentioned in the report (see supporting information Table I which may be found in the online version of this article), but could not correlate either of these with ACC. The only exception was for deletions of 1q43-q44, which have been more consistently phenotyped. Of 37 published patients with deletion 1q4 and ACC for whom sufficient information is available, 30 had microcephaly (OFC <2.5 SD) of either postnatal onset or congenital onset with striking postnatal progression [Boland et al., 2007]. Macrocephaly was rarely documented with only five individuals found in the database, all with apparently isolated ACC.

The phenotype descriptions from both published and database reports varied greatly. No information on physical features other than ACC was available for approximately 20% of individuals included in this report. More comprehensive data is available for class 1 and 2 loci based on numerous reports, and we summarize data supporting inclusion of some of the critical regions below.

TABLE II. Co-Occurrence of ACC Loci With Cerebellar Malformations and Polymicrogyria

Locus	ACC	CBL[a]	PMG[b]
1p36	8	—	13
1q43-q44	35	6	1
3q24-q25.3	2	10	—
6p25	5	10	—
6q26-q27	12	7	8
8p21-p22	59	1	—
9p24-p11.2	3	15	—
11q23-q25	9	2	—
13q32.3-q33.1	14	8	—
21q22.3	10	—	2
22q13.2-q13.33	5	4	—

CBL, cerebellar malformation; PMG, polymicrogyria.

[a]W.B. Dobyns, K.J. Millen, K. Aldinger, unpublished cerebellar loci.
[b]Data from Dobyns et al. [2008].

Deletion 1p36

Deletion 1p36 (OMIM 607872) is the most common terminal deletion syndrome associated with a clinically recognizable phenotype. While callosal abnormalities have been reported with deletion of 1p36, many reports give few specific details regarding the CC and show no images. In most, the CC was described as thin but not absent. Three recent reviews of ~190 patients with deletion 1p36 reported callosal abnormalities in only 5.8% [collated numbers from: Gajecka et al., 2007; Bahi-Buisson et al., 2008; Battaglia et al., 2008]. Therefore we do not consider this to be a strong ACC candidate region. In a recent report of 13 patients with polymicrogyria and deletion of 1p36, midline sagittal images show a mildly short CC in one patient, while three others have a thin but complete CC [Dobyns et al., 2008]. In this paper, Figure 1A,E,I shows a thin CC, while Figure 1M shows a short CC. A similar situation exists for callosal abnormalities in deletions of 4p16, some of which appear to cause a thin but intact CC in the presence of a diffuse reduction in white matter volume [Righini et al., 2007].

Deletion 1q4

We found reports of 35 patients with ACC and deletion (or a translocation breakpoint at) 1q4 that collectively support two or possibly three ACC causative loci in this region. One report describes three patients from one family with ACC and interstitial deletion 1q42 that does not overlap with the more distal deletions [Puthuran et al., 2005]. The major locus was delineated by reports of 29 patients with deletion 1q43-q44, ACC of variable severity,

and consistent postnatal microcephaly (Fig. 1C,D). Several other patients with deletion of this region have a normal CC, supporting incomplete penetrance. Studies from three groups have attributed the ACC to heterozygous loss of function of the *AKT3* gene based on its deletion in 27/29 patients, a balanced translocation breakpoint located just 20 kb upstream of exon 1, and supportive data from two mouse knockouts [Eash et al., 2005; Tschopp et al., 2005; Boland et al., 2007; Hill et al., 2007; Merritt et al., 2007]. However, two patients, one with total ACC and another with reported callosal hypoplasia, had 1q44 deletions beginning ~0.6 to 1 Mb telomeric to *AKT3* [Poot et al., 2007; van Bon et al., 2008]. We attribute this to either a positional effect on *AKT3* expression or a third ACC locus in 1q4. Another five patients have had larger deletions of 1q42-q44 that include both or all of these loci.

Deletions 6p25 and 6q2

We found five individuals with callosal abnormalities and deletions of distal 6p (see supporting information Table I which may be found in the online version of this article), but these account for only a small proportion of patients reported with 6p25 deletions. However, many of them have not had brain imaging [Gould et al., 2004]. The phenotype, which includes ocular anterior segment abnormalities, has been ascribed to deletion of the FOXQ1-FOXF2-FOXC1 gene cluster, especially FOXC1 [Maclean et al., 2005]. Imaging in multiple patients with similar deletions has shown ventricular enlargement and Dandy–Walker malformation as well as callosal abnormalities, suggesting a common developmental pathway with variable expressivity [Descipio et al., 2005; Maclean et al., 2005].

Two individuals with ring chromosome 6 have deletions of both the 6p25 and 6q26-q27 loci (see supporting information Table I which may be found in the online version of this article). Many patients with a distal 6q2 deletion have been described with a variable brain phenotype including periventricular nodular heterotopia, PMG, cerebellar malformations, hydrocephalus, and ACC [Eash et al., 2005; Sherr et al., 2005]. These data support the presence of two ACC loci on distal chromosome 6q, as two apparently non-overlapping ACC loci have been identified, consisting of a class 1 locus on 6q26-q27 and a class 2 locus in 6q25 (Table I).

Rearrangements of 8p

The largest individual group of patients in this report has rearrangements of chromosome 8p (Table I). The majority of these were 8p inverted duplication deletions thought to be due to non-allelic homologous recombination at a common inversion polymorphism located between two low copy repeat (LCR) sites [Sugawara et al., 2003], although several different rearrangements have been reported [Ciccone et al., 2006; Giorda et al., 2007]. In this series, ACC has been associated with terminal deletions, various pure duplications, and the common inverted duplication deletions of 8p (Table I; see supporting information Table I which may be found in the online version of this article). These reports collectively suggest either one gene that can cause ACC when deleted or duplicated, or the presence of at least two ACC loci, one associated with deletions and the other with duplications. The penetrance appears to be high as we were able to confirm ACC in 25% of individuals. However the true penetrance is unknown given the lack of published images.

Deletion 13q

Deletions of 13q32 have been reported in association both with neurodevelopmental abnormalities and malformations of other systems such as the eye, limbs, and gastrointestinal tract [Ballarati et al., 2007]. We found 14 published reports of ACC and deletions of 13q, three of which also had a cerebellar malformation. This allows the identification of a critical region within 13q (13q32.3-q33.1) that is consistently associated with ACC. One of these had a balanced translocation between 1q43-q44 and 13q32 in which the breakpoint on 1q43-q44 disrupts the AKT3 gene [Boland et al., 2007]. ZIC2 has been suggested as a candidate gene on 13q32 for other brain malformations including holoprosencephaly [Brown et al., 1998; Ballarati et al., 2007; Dubourg et al., 2007]. ZIC2 is located within the class 1 critical region identified here, on 13q32.3. This class 1 critical region is 5.6 Mb in size and contains around 14 genes. Further work will be required to identify other candidate genes within the region.

Deletion 14q

We have identified two discrete regions on chromosome 14q associated with ACC (Table I). Terminal deletions of 14q have been associated with several brain malformations, including callosal abnormalities, PMG, heterotopia, and microcephaly [Masada et al., 1989; Maurin et al., 2006; Ravnan et al., 2006; Schneider et al., 2008]. Proximal deletions of 14q have also been associated with ACC and microcephaly. One study suggested that deletion of *GARNL1* in 14q13.1 was responsible for the brain malformations, although this has not been confirmed [Schwarzbraun et al., 2004]. Cranial MRI in the original patient in whom the deletion was described had no specific brain malformation [Petek et al., 2003a]. Two patients with mutations in *FOXG1B* on 14q12 and hypoplasia of the CC have recently been described with microcephaly, seizures, severe mental retardation, and callosal abnormalities [Ariani et al., 2008]. A single patient with ACC and a translocation involving *FOXG1* [Shoichet et al., 2005] has also been reported, making *FOXG1* the more likely candidate gene for ACC in this region.

Common Trisomies

Included in the database are 10 patients with trisomy 21 (Down syndrome), 18 with trisomy 13 (Patau syndrome), and 23 with trisomy 18 (Edward syndrome) associated with ACC. All patients with partial trisomy (duplication) of these three chromosomes had an additional deletion of a class 1 or 2 critical region. The presence of ACC in these patients may be the result of two relatively common abnormalities, ACC and non-disjunction, occurring within the same individual.

DISCUSSION

We have used a comprehensive search strategy to identify numerous chromosomal regions contributing to ACC (Table I and Fig 2). We reasoned that a comprehensive database of patients with established pathogenic CNVs would identify numerous loci containing highly penetrant ACC causal genes, even if the regions proved to be large. Our analysis of 374 individuals with abnormalities of the CC and structural chromosome rearrangements

has identified 12 ACC loci supported by 6 or more subjects, another 18 loci supported by 3–5 subjects, and numerous other possible loci. These data confirm the strong genetic contribution to ACC reported previously [Dobyns, 1996; Schell-Apacik et al., 2008].

We hypothesize that most if not all of the 30 class 1 and class 2 loci contain ACC causal genes, and that some of the many class 3 and unclassified regions also contain ACC causal genes. Here it is likely that separation of true from false loci will be aided by increasing reports of patients with ACC and CNV, but complicated by an increasing number of CNV regions identified per patient. We anticipate that our data will prove important in evaluating the significance of new and smaller loci found in the future. This analysis is strengthened by recent data supporting the *AKT3* gene in 1q43-q44 and the *FOXG1* gene in 14q12 as putative ACC causal genes as both are located in class 1 critical regions. We expect that we have identified many of the highly penetrant ACC loci associated with heterozygous copy number changes in the human genome, but expect that we have missed many low penetrance loci associated with heterozygous copy number changes and also most autosomal recessive forms of ACC.

Our data further supported by a recent report of chromosomal aberrations in association with a number of different central nervous system malformations that identified several potential causative chromosomal regions in the etiology of ACC [Tyshchenko et al., 2008]. These include duplication of 8p22-p21 and deletions of 14q11.2-q13 and 1q42-q44, all of which we classified as class 1 loci. They also identified deletions of 3q13.1-q21 in association with ACC, which includes 3q13.1-q13.3, a class 3 loci in this report. They suggested the gene *DISPA* as a candidate gene on 1q42 but note that a recent study of patients whose deletions included this gene had no callosal malformations on MRI brain imaging [Shaffer et al., 2007]. As some of the patients included in this study have been identified from the ECARUCA database used in the study by Tyshchenko et al. [2008] some patients may be included in both of these reports. However, it is not clear whether those patients had ACC in combination with other malformations that we excluded from this study, namely holoprosencephaly and lissencephaly.

It is difficult to estimate the overlap of ACC with microcephaly or macrocephaly. From the authors' experience these are often concurrent malformations, for example, microcephaly of postnatal onset is frequently described in patients with 1q44 deletions. Macrocephaly is a useful diagnostic marker in recognizable syndromes where a proportion of patients have also been reported to have ACC; for example, Gorlin [Ozturk et al., 2003; Kimonis et al., 2004] and Soto [Schaefer et al., 1997; Chen et al., 2002; Bedeschi et al., 2006; Park et al., 2006] syndromes. Birth and serial OFC measurement can be a useful diagnostic indicator in many disorders as well as providing prognostic information. Therefore consistent reporting of head size in publications of patients with brain malformations will prove to be useful in differentiating different syndromes.

The same issues surrounding diagnostic accuracy of ACC also apply to cerebellar and other cortical malformations. However, other brain malformations are common in patients [Hetts et al., 2006] with ACC and their presence may be useful in the differentiation of single gene and microdeletion/duplication syndromes. More regions have been linked to ACC than other malformations given the relative ease of diagnosis on a variety of imaging techniques [Dobyns et al., 2008] (unpublished CBL data). One of the authors (EHS) maintains a large database of patients with ACC as part of the Brain Development Research Program (BDRP). In a previous report using this resource the MRI scans of 142 patients with ACC were reviewed by the authors. Overall 73 of 142 patients within this cohort had additional cortical malformations including PMG and heterotopia [Hetts et al., 2006]. They concluded that callosal abnormalities are infrequently truly isolated. There is considerable discrepancy between these figures and the data collated here which may reflect patient selection and differences in image interpretation.

The presence or absence of a callosal abnormality in patients with similar CNVs is likely to represent variation in penetrance and expressivity of causative genes, as well as, in some cases, inconsistencies in reporting. A further potential mechanism in a small number of patients may be the positional effects of CNVs on neighboring genes; for example, the presence of ACC and 1q43-44 abnormalities not including AKT3 [Boland et al., 2007]. Both cerebellar malformations and PMG have been consistently reported with cytogenetic rearrangements, several of which overlap with the ACC loci reported here (Table II). Of particular interest are deletions of chromosome 6q26-q27 in which patients have other malformations such as heterotopia and hydrocephalus alongside polymicrogyria and cerebellar abnormalities. However, as for the 1q4 region, substantial evidence supports the existence of two ACC loci on distal 6q with variable penetrance and expression of ACC as well as cerebellar and cortical malformations. The consistent association of ACC with other developmental brain malformations seen in these reports (see supporting information Table I which may be found in the online version of this article) suggests that the same genes, or those expressed as part of the same pathways, confer susceptibility to more than one recognizable malformation of brain development.

Consistent diagnostic criteria, improved scanning techniques and increased recognition of associated abnormalities will facilitate gene mapping and allow definition of syndromes within this heterogeneous group of patients. It will also allow clinicians to tailor investigation and management strategies for individuals with CNVs overlapping ACC critical regions. The increasing availability of high-resolution array comparative genome hybridization has already greatly improved our ability to identify potentially pathogenic CNVs, and in the future the number of potential ACC loci is likely to expand significantly.

The database should provide a valuable resource for the clinical diagnosis and management of patients with ACC as well as those with chromosomal rearrangements in whom ACC should be suspected. We expect it to facilitate research projects aimed at identifying new ACC causal genes.

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