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Journal
Brain, 137(6)

ISSN
0006-8950

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Publication Date
2014-06-01

DOI
10.1093/brain/awt358

Peer reviewed

doi:10.1093/brain/awt358 Brain 2014: 137; 1579–1613 | 1579

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes

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The corpus callosum is the largest fibre tract in the brain, connecting the two cerebral hemispheres, and thereby facilitating the integration of motor and sensory information from the two sides of the body as well as influencing higher cognition associated with executive function, social interaction and language. Agenesis of the corpus callosum is a common brain malformation that can occur either in isolation or in association with congenital syndromes. Understanding the causes of this condition will help improve our knowledge of the critical brain developmental mechanisms required for wiring the brain and provide potential avenues for therapies for callosal agenesis or related neurodevelopmental disorders. Improved genetic studies combined with mouse models and neuroimaging have rapidly expanded the diverse collection of copy number variations and single gene mutations associated with callosal agenesis. At the same time, advances in our understanding of the developmental mechanisms involved in corpus callosum formation have provided insights into the possible causes of these disorders. This review provides the first comprehensive classification of the clinical and genetic features of syndromes associated with callosal agenesis, and provides a genetic and developmental framework for the interpretation of future research that will guide the next advances in the field.

Keywords: corpus callosum; axon guidance; neuronal specification; neurogenesis; midline patterning
Abbreviations: ACC = agenesis of the corpus callosum; MCPH = autosomal recessive primary microcephaly

Introduction

The corpus callosum is the largest of the interhemispheric white matter tracts in the brain. It comprises >190 million topographically organized axons, each forming homotopic or heterotopic connections, often between distant regions of cerebral cortex (Wahl *et al*., 2007, 2009). These connections participate in an array of cognitive functions including language, abstract reasoning, and the integration

Received May 25, 2013. Revised September 25, 2013. Accepted October 14, 2013. Advance Access publication January 28, 2014

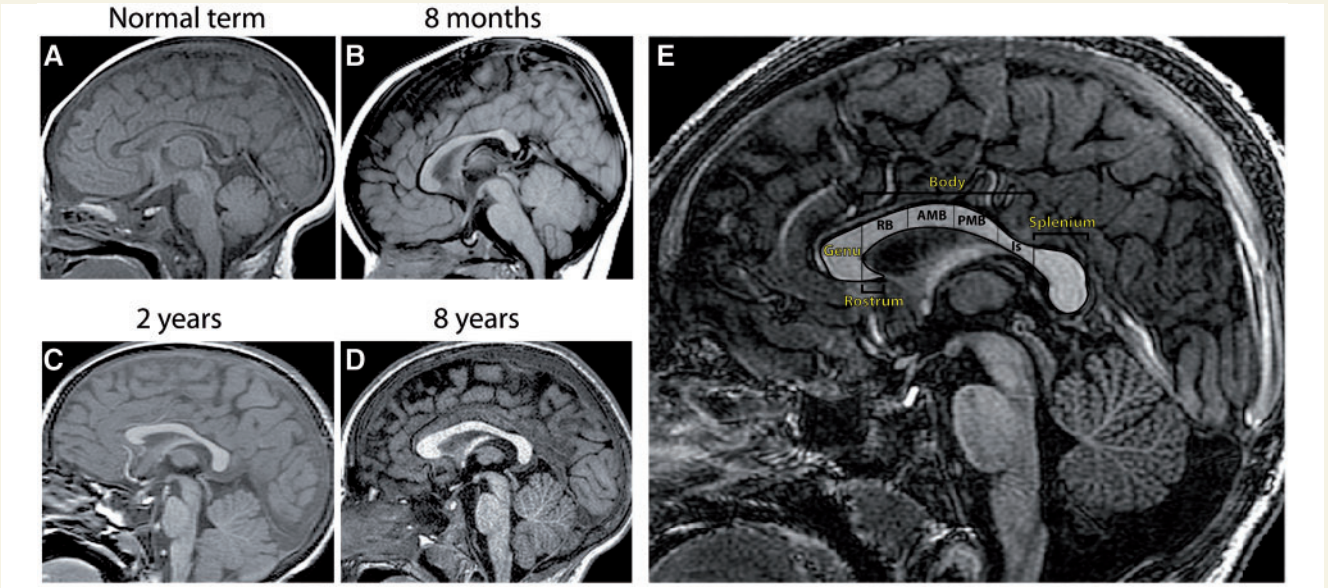

Figure 1 T_1-weighted sagittal MRI scans showing the structure of the normal human corpus callosum in the full-term infant (**A**), 8-month-old (**B**), 2-year-old (**C**), 8-year-old (**D**) and adult (**E**). (**A**) At birth, the corpus callosum has assumed its general shape but is thinner throughout. The thickness of the corpus callosum (vertical dimension) increases generally throughout childhood and adolescence. Growth in the anterior sections is most pronounced within the first 10 years of life (compare **C** with **D**), and posterior growth predominates during adolescence (compare **D** with **E**). There is also marked interindividual variation in corpus callosum size and shape. (**E**) Normal adult corpus callosum, showing subdivisions established by Witelson (1989). The corpus callosum is initially divided into genu, rostrum, body and splenium. The body can be further subdivided into the isthmus, and the anterior, middle and posterior segments. RB = rostral body; AMB = anterior midbody; PMB = posterior midbody; Is = isthmus.

of complex sensory information between the hemispheres (Brown *et al*., 1999; Paul *et al*., 2003). The corpus callosum is classically divided into four distinct segments based on early histological studies (Witelson, 1989; see Fig. 1). Recent advances in diffusion tensor imaging and tractography have provided remarkable insight into the diversity of interhemispheric callosal connections within each segment, and has helped to clarify what happens to these connections when embryonic or foetal development is disturbed (Wahl *et al*., 2007, 2009).

Agenesis of the corpus callosum (ACC) is an exceedingly heterogeneous condition that can result from disruption of numerous developmental steps from early midline telencephalic patterning to neuronal specification and guidance of commissural axons. It can occur as an isolated finding on MRI, but is more commonly associated with a broader disorder of brain development (Schell-Apacik *et al*., 2008; Tang *et al*., 2009). Accordingly, the cognitive and neurological consequences in patients with ACC vary considerably from mild behavioural problems to severe neurological deficits. Deficits in problem solving and social skills are common, and these often fall within the autistic spectrum (Lau *et al*., 2013; Siffredi *et al*., 2013). Interestingly, isolated ACC predominantly carries a favourable prognosis (Moutard *et al*., 2003; Sotiriadis *et al*., 2012) and these individuals exhibit a different cognitive outcome from the disconnection syndrome characterized in commissurotomy patients (Paul *et al*., 2007). Individuals with ACC therefore provide a unique opportunity to study not only the mechanisms of callosal development, but also the broader principles that determine how the brain responds to disruptions in neurodevelopment.

The increased use and resolution of comparative genomic hybridization have implicated many more genes and genomic loci in corpus callosum development (O'Driscoll *et al*., 2010), and have revealed a great diversity of genetic causes for ACC syndromes. At present, however, the cause of 55–70% of cases with ACC cannot be identified by clinical evaluation (Bedeschi *et al*., 2006; Schell-Apacik *et al*., 2008). The apparently sporadic nature of ACC makes genetic studies difficult (Sherr *et al*., 2005; Schell-Apacik *et al*., 2008), and it is possible that the cause of ACC in a proportion of these patients is non-genetic, such as foetal exposure to alcohol. Indeed, it is often the associated brain abnormalities found on imaging that point to the underlying developmental process that is disturbed.

Syndromes incorporating ACC can be broadly classified by the stage in development that is primarily affected using an approach similar to previous classifications of cortical malformations (Barkovich *et al*., 2012). ACC can occur in association with disorders of neuronal and/or glial proliferation, neuronal migration and/or specification, midline patterning, axonal growth and/or guidance, and post-guidance development. Much of what is known about normal corpus callosum formation has emerged from studies using mouse models of callosal agenesis. Indeed, our understanding of the processes underpinning callosal development in mice has served as a foundation for much of what is currently known about human patients with ACC. The purpose of this review is to systematically outline the clinical features of all human syndromes associated with ACC, and relate these to the genetic causes and developmental processes likely to be disturbed.

Imaging and classifying agenesis of the corpus callosum

ACC encompasses either total absence (complete ACC) or absence from birth of at least one, but not all, of the anatomically defined regions of the corpus callosum (partial ACC), which results in a shorter anterior-posterior length (Fig. 2). Hypoplasia denotes a corpus callosum that is thinner than usual, but has a normal anterior–posterior extent (Fig. 2). Routine sonography remains the primary tool for identifying ACC from mid-trimester onwards, when widening of the interhemispheric fissure, absence of the cavum septum pellucidum and colpocephaly can be identified (Santo *et al*., 2012). Sonography, however, often fails to detect more subtle cases of partial ACC or callosal hypoplasia (Ghi *et al*., 2010; Paladini *et al*., 2013), as well as associated white matter dysgeneses. For this reason, prenatal MRI remains the preferred imaging modality for direct visualization of the corpus callosum in cases with suspected ACC, and associated abnormalities not detected by sonography. This is particularly important for offering early counselling to parents, as additional cerebral abnormalities identified by MRI might suggest broader disorders of neurodevelopment that are linked with more severe neurological impairment (Tang *et al*., 2009).

Advances in tractography based on diffusion tensor imaging have significantly improved our understanding of how the corpus callosum connects with the cortex in normal individuals, and how these connections are disturbed and re-routed in patients with ACC. Of particular interest are the so-called 'sigmoid bundles', which asymmetrically connect the frontal lobe with the contralateral occipitoparietal cortex. Sigmoid bundles have been reported in patients with partial ACC (Fig. 3), and may represent a pathologic plasticity that has so far not been associated with the better characterized longitudinal bundles of Probst, which exhibit conserved topographical organization, albeit confined to the ipsilateral cortex (Tovar-Moll *et al.*, 2007; Wahl *et al*., 2009). The mechanisms that account for this apparent plasticity of interhemispheric wiring in patients with partial ACC, and whether these patterns of heterotopic connections are compensatory or detrimental, remain areas of current research.

Mouse models of callosal development

Mouse models of ACC have proven invaluable in characterizing the cellular and molecular processes underpinning corpus callosum development and the individual genes involved. However, phenotypes in mice cannot always be correlated with human syndromes as it is not usually clear whether developmental mechanisms are conserved between species. Neuroimaging approaches are bridging this gap and provide a means to examine human brain

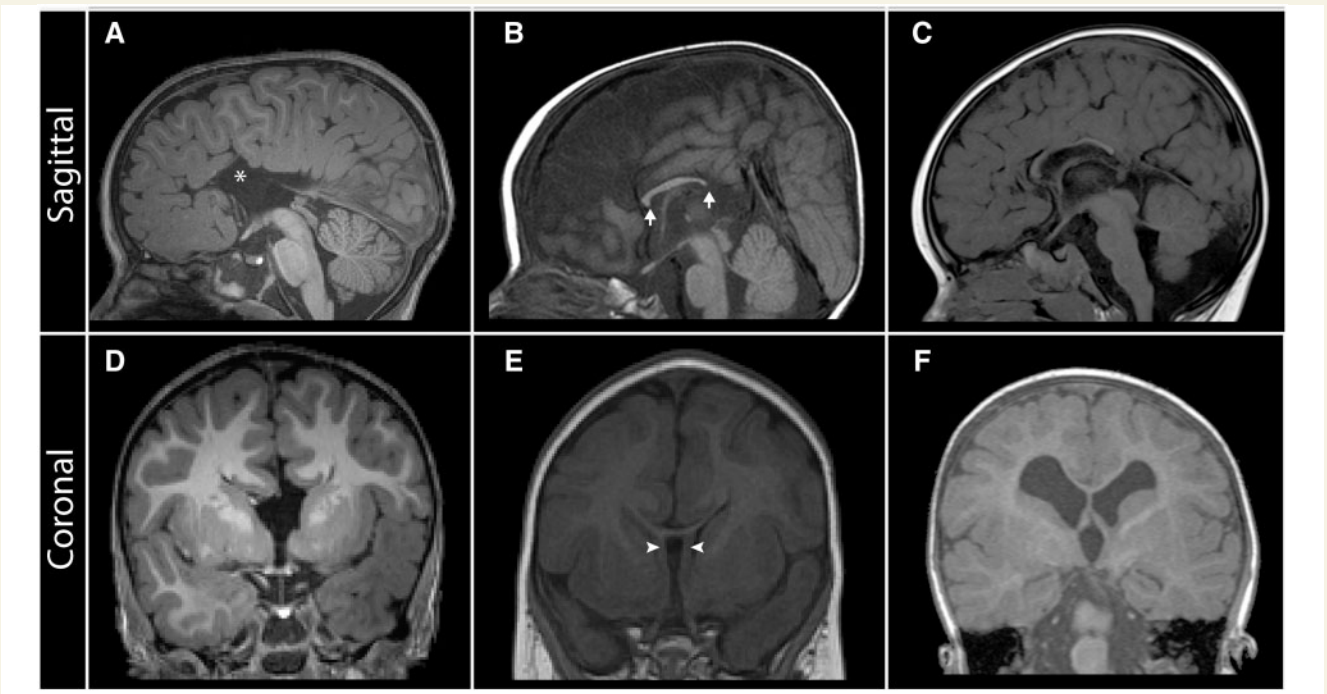

Figure 2 Neuroanatomical features revealed by T_1-weighted midsagittal and coronal MRI in patients with corpus callosum abnormalities. (**A** and **D**) Patient with complete ACC associated with dorsal expansion of the third ventricle (asterisk), absence of the cingulate gyrus and sulcus, and absence of the septum pellucidum. (**B** and **E**) Patient with partial ACC; the splenium is absent and the rostrum is not fully formed (arrows). In addition, the leaves of the septum pellucidum are unfused (**E**; arrowheads). (**C** and **F**) Patient with hypoplasia of the corpus callosum. All segments are present but are diffusely thinned; there is also markedly reduced cerebral white matter volume (**F**).

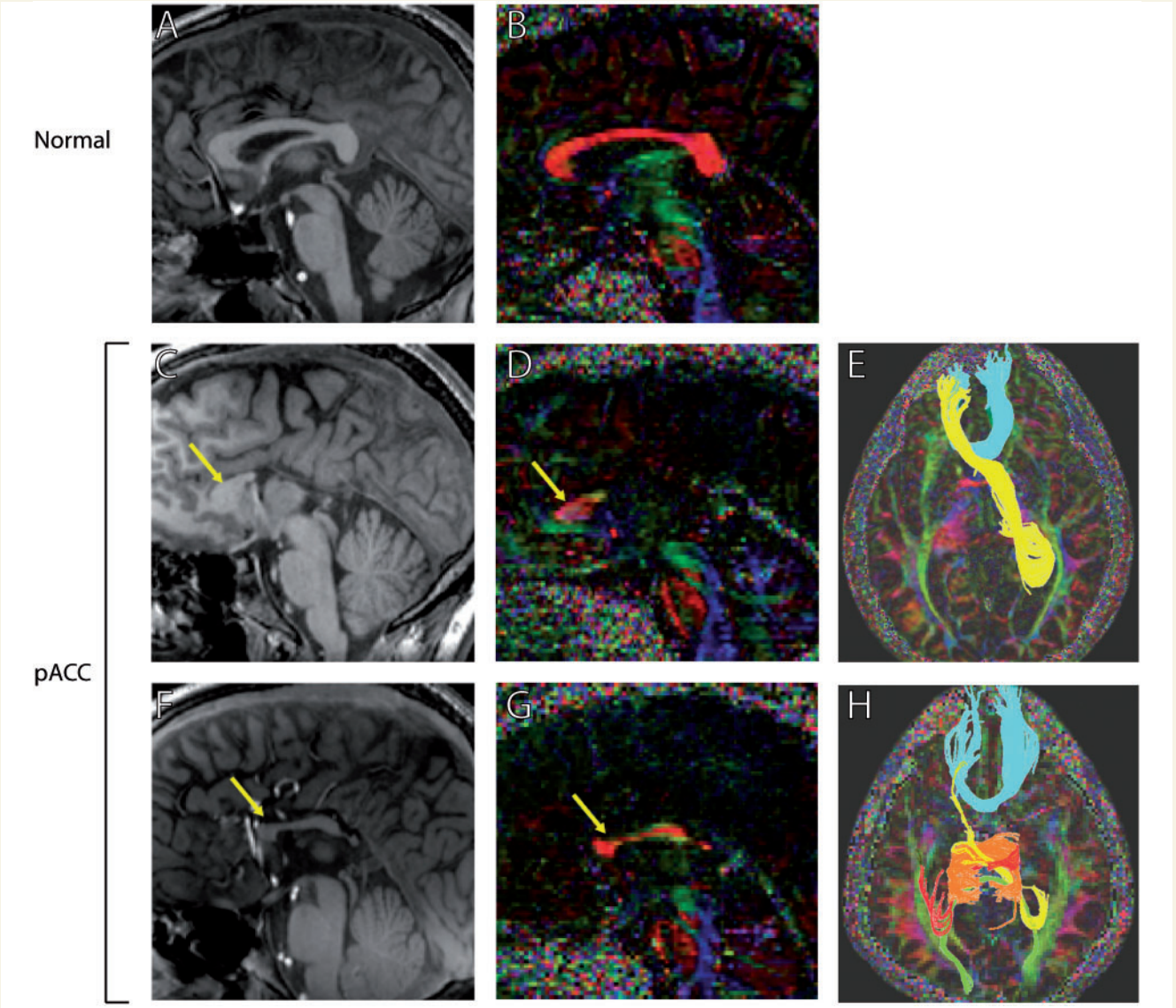

Figure 3 T_1-weighted midsagittal MRI and diffusion tensor imaging tractography of two patients with partial ACC (pACC) and a normal corpus callosum control. (**A**, **C** and **F**) T_1-weighted midsagittal MRI scans. (**B**, **D** and **G**) High-angular-resolution diffusion imaging. Arrows indicate callosal fragments present in partial patients with ACC. (**E** and **H**) Q-ball tractography of partial patients with ACC reveals callosal connections between homotopic and heterotopic cortical regions. Homotopic connections between anterior frontal lobes are conserved in both partial patients with ACC (blue streamlines in **E** and **H**; orange streamlines in **H**), but the degree of temporal and occipital connectivity varies. Both patients also show 'sigmoid bundles' (yellow streamlines in **E** and **H**), which connect the anterior frontal lobe with the contralateral parieto-occipital region. Images adapted from Wahl *et al*. (2009).

development and structure. A major issue in translating mouse models to humans has been that many single gene mouse models result in embryonic or early post-natal lethality, as the genes regulate multiple developmental processes. These genes may act in a similar manner in humans so patients that completely lack such a gene are not normally seen in the clinic. Instead, point mutations in such genes (both inherited and *de novo*) are likely to be more common in patients and may decrease or impede the function of the gene without being completely non-functional. Given this, candidate gene approaches, translating directly from mouse null mutations, have not been as successful in identifying the cause of human ACC as might have been expected. However, mouse models have been instrumental in defining the critical processes involved in callosal development and there is reasonable evidence from direct analysis of human foetal brain tissue that similar processes and molecules are involved in human corpus callosum development (Rakic and Yakovlev, 1968; Lent *et al.*, 2005; Ren *et al.*, 2006). Many of the molecules involved in commissure formation throughout the brain and spinal cord are highly evolutionarily conserved across invertebrates and vertebrates (Tessier-Lavigne and Goodman, 1996), providing further compelling evidence for their conservation in humans.

The formation of the corpus callosum follows clear and well-orchestrated developmental events for which we now have a

reasonable understanding, even if we are yet to discover the molecular mechanisms underlying these processes. Neurons that give rise to the axons of the corpus callosum reside principally in neocortical layers II/III and V, but also in layer VI (Wise and Jones, 1976; Fame *et al.*, 2011). Disruption of the mechanisms that regulate the production and migration of these neurons causes brain malformations such as microcephaly or pachygyria, which are usually independent of, and occur developmentally before, corpus callosum formation. These processes are therefore discussed in later sections of this review only insofar as they relate to syndromes involving ACC. Perhaps the first step in corpus callosum formation is patterning of the midline, which provides a substrate for callosal axons to traverse. All telencephalic commissures initially cross the midline within a distinct anatomical region termed the commissural plate. In mice, four distinct molecular subdomains of the commissural plate have been identified, through which distinct commissural projections pass (Fig. 4). Expression of the secreted morphogen *Fgf8* is crucial in the initial patterning of the forebrain and subsequent development of the commissural plate, and appears to act as an upstream regulator of many midline patterning molecules (Hayhurst *et al.*, 2008; Okada *et al.*, 2008) that correlate anatomically with specific commissures (Moldrich *et al.*, 2010). Dorsally, the corpus callosum passes through an *Emx1*- and *Nfia*-expressing domain; the hippocampal commissure passes through domains expressing *Nfia*, *Zic2* and *Six3*, and the anterior commissure passes through a *Six3*-expressing domain in the septum. Perturbed development of these subdomains results in disruption of the corresponding commissural projections passing through the domains, suggesting that correct patterning of the commissural plate is a prerequisite for commissure formation (Moldrich *et al.*, 2010).

The specification of neurons in the cortical plate as callosally projecting neurons, rather than corticofugally or intracortically projecting neurons (Fame *et al.*, 2011), is an essential process in callosal development. There are many genes involved in this specification, as callosal neurons comprise a heterogeneous population (Molyneaux *et al.*, 2009). An important regulator of callosal neuron specification is the transcription factor SATB2 (Alcamo *et al.*, 2008; Britanova *et al.*, 2008). When *Satb2* is functionally deleted in mice, the corpus callosum fails to form, and instead the normally callosal neurons project into either the corticofugal tract or the anterior commissure. This latter result is particularly interesting from an evolutionary perspective as marsupials have no corpus callosum, but have a larger anterior commissure that serves the same purpose (Ashwell *et al.*, 1996). Some human patients with ACC also display a larger anterior commissure (Fischer *et al.*, 1992; Barr and Corballis, 2002; Hetts *et al.*, 2006) but neither the underlying cause nor the clinical consequences are yet known.

After callosal neuron specification, these neurons extend an axon into the intermediate zone, which will later become the white matter, and make an axon guidance decision to project medially rather than laterally. Little is known about how this process occurs, but it may be regulated by guidance molecules in the cortical environment. For example, SEMA3A, expressed at the lateral border of the neocortex, repels callosal axons toward the midline, through its receptor neuropilin 1 (Zhao *et al.*, 2011). A different family member, SEMA3C, attracts callosal neurons to the midline (Niquille *et al.*, 2009; Piper *et al.*, 2009). Once callosal neurons reach the midline they encounter glial and neuronal guidepost populations that are crucial for their crossing of the interhemispheric midline. Any perturbation to the development of these structures results in some degree of callosal agenesis. The glial wedge and indusium griseum glia surround the corpus callosum on its dorsal and ventral sides, and both populations secrete repulsive and attractive guidance cues to direct axons across

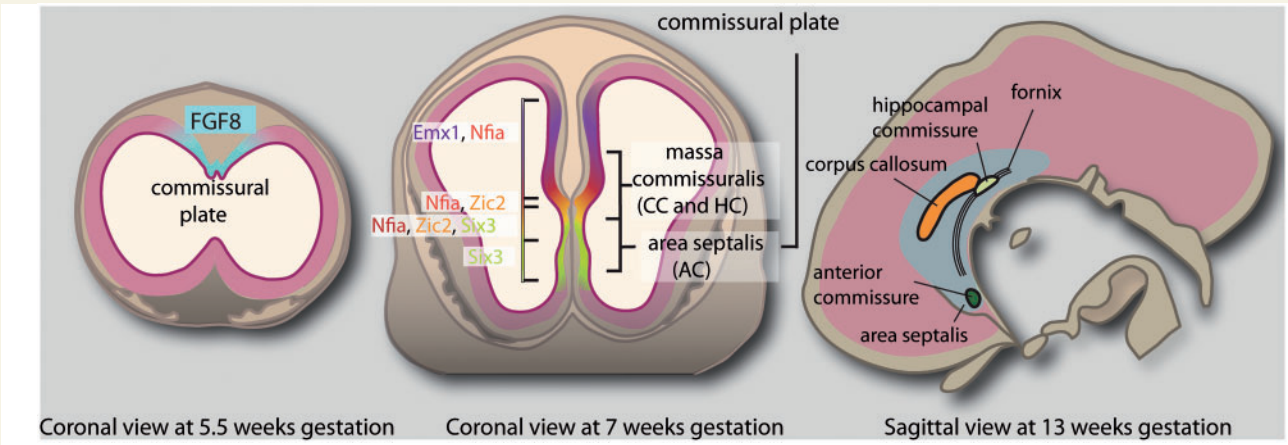

Figure 4 Processes underpinning midline patterning in the human foetal brain extrapolated from studies in mouse. Initial expression of the morphogen FGF8 at the midline is necessary for early forebrain patterning, and subsequent development of the commissural plate through which all forebrain commissures pass. The commissural plate can be divided molecularly into four distinct subdomains, each specified by midline patterning molecules that likely act downstream of FGF8. Each forebrain commissure correlates anatomically with a specific subdomain. The corpus callosum (CC) passes through a domain of *EMX1* and *NFIA* expression; the hippocampal commissure (HC) passes through domains expressing *NFIA*, *ZIC2* and *SIX3*, and the anterior commissure (AC) passes through a *SIX3*-expressing domain in the septum. Sagittal section at 13 weeks gestation adapted from Rakic and Yakovlev (1968).

the midline. Current research is focused on how growth cones modulate responsiveness to guidance molecules as they traverse the midline. As axons cross the midline, they must decrease responsiveness to attractive cues at the corticoseptal boundary, and gain responsiveness to repulsive cues in the same region to project dorsally in the contralateral hemisphere. Initial investigations in *Xenopus* identified the importance of DCC-Robo interactions in silencing axonal attraction at the midline (Stein and Tessier-Lavigne, 2001). Recent research in mice has shown that netrin 1 acts as a chemoattractant for pioneering axons originating in the cingulate cortex, but that it does not attract neocortical axons. Instead, netrin-DCC interactions inhibit Slit2-mediated repulsion until axons have crossed the midline (Fothergill *et al.*, 2013; for a review of axon guidance mechanisms involving interactions between multiple molecular pathways, see Dudanova and Klein, 2013).

Midline zipper glia develop at the medial pial surface of the corticoseptal region, and are thought to have an important role in midline fusion (Silver, 1993; Shu *et al.*, 2003*a*). Failure of the two hemispheres to fuse is often correlated with ACC, presumably as axons lack the proper substrate to cross the midline (Silver and Ogawa, 1983; Silver, 1993), but experimental evidence for how midline fusion occurs is currently lacking. The subcallosal sling was originally thought to be another midline glial population (Silver *et al.*, 1982), but was later shown to largely comprise neurons (Shu *et al.*, 2003*b*). Additional populations of glutamatergic and GABAergic neurons exist within and dorsal to the corpus callosum, and together they form a permissive SEMA3C-expressing corridor through which midline-projecting axons pass (Niquille *et al.*, 2009, 2013). This corridor appears particularly crucial for guiding the first axons to cross the midline, which arise from the cingulate cortex. These pioneering cingulate neurons are hypothesized to be necessary for later crossing of axons originating from the neocortex, as supported by a rostral ACC phenotype in *Emx2*$^{-/-}$ mice. In these mice, the cingulate cortex is not specified and pioneer axons are missing rostrally but not caudally (Piper *et al.*, 2009).

The reliance of neocortical-originating axons on pioneering cingulate axons in both mice and humans points to the importance of axon-axon interactions in callosal development. Before they encounter pioneering cingulate axons, callosally projecting axons fasciculate in part through neuropilin 1-mediated interactions (Hatanaka *et al.*, 2009). The importance of axons from the cingulate cortex appears to be conserved in humans. Decreased size and connectivity of the cingulum bundles has been documented in patients with ACC, and this appears to be correlated with the severity of callosal agenesis (Nakata *et al.*, 2009). However, how this relates to ACC remains to be determined.

Human corpus callosum development

The human commissural plate can be anatomically subdivided into the massa commissuralis through which the corpus callosum and hippocampal commissure pass, and the area septalis through which the anterior commissure crosses (Rakic and Yakovlev, 1968; Fig. 4). For many years, the prevailing theory held that human corpus callosum development occurred in an anterior-to-posterior fashion, with the first callosal axons crossing the midline at the anterior genu, with those in the rostrum added last (Byrd *et al.*, 1978; Barkovich and Kjos, 1988). More recently, neuroimaging studies have suggested that the first axons cross the commissural plate in the hippocampal primordium, with subsequent connections being made bidirectionally (Barkovich *et al.*, 1992; Kier and Truwit, 1996; Huang *et al.*, 2006, 2009; Paul, 2011). Callosal neurons originate from layers II/III, V and VI of the neocortex (Fame *et al.*, 2011), although midline crossing of neocortical neurons in both mouse and human is preceded by crossing of pioneering axons originating from the cingulate cortex (Koester and O'Leary, 1994; Rash and Richards, 2001).

Around Weeks 13 and 14 post-conception, pioneering axons begin to cross the midline; the anterior sections begin to grow by Weeks 14 and 15, whereas growth of the posterior sections occurs during Weeks 18 and 19 (Hewitt, 1962; Rakic and Yakovlev, 1968; Ren *et al.*, 2006). The apparently delayed development of the posterior and most anterior callosal sections led to the assumption that early perturbation of callosal development results in complete ACC, and later developmental disturbances result in partial agenesis confined to the posterior corpus callosum and rostrum. However, current data indicate that connections are first made in two separate loci: the anterior commissure and the hippocampal commissure (for a review see Paul, 2011). The early expansion of the frontal cortex results in the posterior displacement of the hippocampal commissure together with the associated callosal splenium, while the anterior section of the corpus callosum expands. It has therefore been suggested that the absence of the posterior part of the corpus callosum in partial ACC most commonly results from failed dorsoventral expansion of the splenium (Paul, 2011). The two-locus origin of the corpus callosum is to some degree consistent with the anatomic diversity of homotopic and heterotopic connections in the partial ACC brain (Tovar-Moll *et al.*, 2007; Wahl *et al.*, 2009). However, it still fails to account for the great diversity of connectivity seen in structurally similar callosal fragments.

By 20 weeks post-conception, the final shape of the corpus callosum is complete, although exuberant axonal growth continues until 2 months after birth; this is then followed by molecular- and activity-dependent axonal pruning (Innocenti and Price, 2005). Although the number of callosal fibres is more or less determined at birth, structural changes continue throughout post-natal development, and are most marked during childhood and adolescence (Luo and O'Leary, 2005; Luders *et al.*, 2010; Garel *et al.*, 2011).

Single gene syndromes with agenesis of the corpus callosum

Of the 30–45% of cases with ACC with an identifiable genetic cause, 20–35% are caused by a mutation affecting a single gene (Bedeschi *et al.*, 2006; Schell-Apacik *et al.*, 2008). Although some Mendelian syndromes show complete or near complete ACC

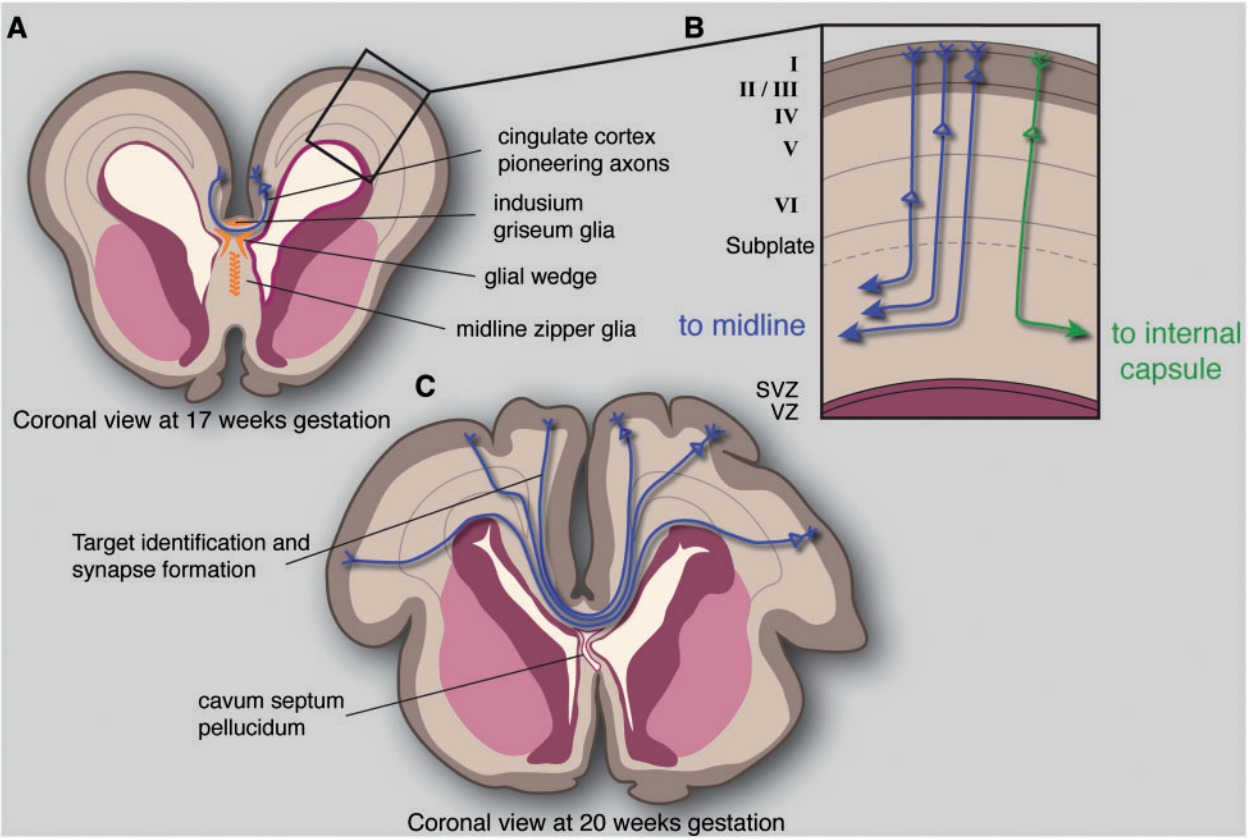

Figure 5 Processes extrapolated from mouse studies necessary for specification of callosal neurons, correct guidance of axons across the midline, and target identification in the contralateral cortex. Midline zipper glia develop in the septum and may play a role in fusion of the midline, which is correlated with corpus callosum development. As axons reach the midline, they encounter and must correctly interpret multiple attractive and repulsive guidance cues expressed by the glial wedge and indusium griseum. The first axons to cross the midline arise from the cingulate cortex, and these pioneering neurons appear to be necessary for the subsequent crossing of the majority of callosal axons, arising from the neocortex (**A**). Callosal neurons originate from layers I, II/III, V and VI of the cortex. However, the layer that a neuron resides in is not sufficient for specification as a callosally projecting neuron, and callosal neuron identity seems to coincide with expression of the transcription factor *SATB2*. These neurons project an axon radially towards the intermediate zone, which must then decide to turn medially rather than laterally (**B**). Once axons reach the contralateral hemisphere, they must recognize their target area and synapse with target neurons, presumably through molecular-recognition and activity-dependent mechanisms (**C**). Exuberant axonal growth continues after birth and is accompanied by axonal pruning which continues throughout childhood and adolescence.
SVZ = subventricular zone; VZ = ventricular zone.

penetrance, the majority display ACC with incomplete penetrance (Table 3), which suggests that modifying genetic influences are often at play. Autosomal dominant, autosomal recessive, and X-linked causes of ACC have been described; however, no inheritance pattern is found in a significant proportion of cases and it is possible that many arise from *de novo* mutations. This is consistent with current data from the California Birth Defects Monitoring Programme showing that the risk of giving birth to a child with ACC is 3-fold higher for mothers aged 40 and above (Glass *et al.*, 2008). It is also possible that oligogenic models of inheritance account for a proportion of apparently 'sporadic' cases of ACC.

By taking into account the known function of the affected gene, associated mouse models, and neuroanatomical findings in human patients, it is possible to hypothesize a general pathogenic mechanism for callosal agenesis in syndromes commonly associated with ACC. In this review, single gene syndromes associated with ACC have been broadly divided into categories based on abnormalities of important steps in cerebral development: neuronal and glial proliferation, midline patterning, neuronal migration and specification, axon guidance, and post-guidance development.

Abnormal neuronal and glial proliferation

Early cerebral development is associated with cortical patterning, driven by a combination of morphogenetic gradients that together with developing thalamocortical circuits, influence the molecular identity of neuronal progenitors (O'Leary *et al.*, 2007; Kanold and Luhmann, 2010). These influences give rise to spatio-temporal-specific signalling domains called patterning centres, which specify populations of neurons by regulating transcription factor expression. Many molecules involved in neurogenesis have multiple roles in development (Fig. 6), and callosal abnormalities as a

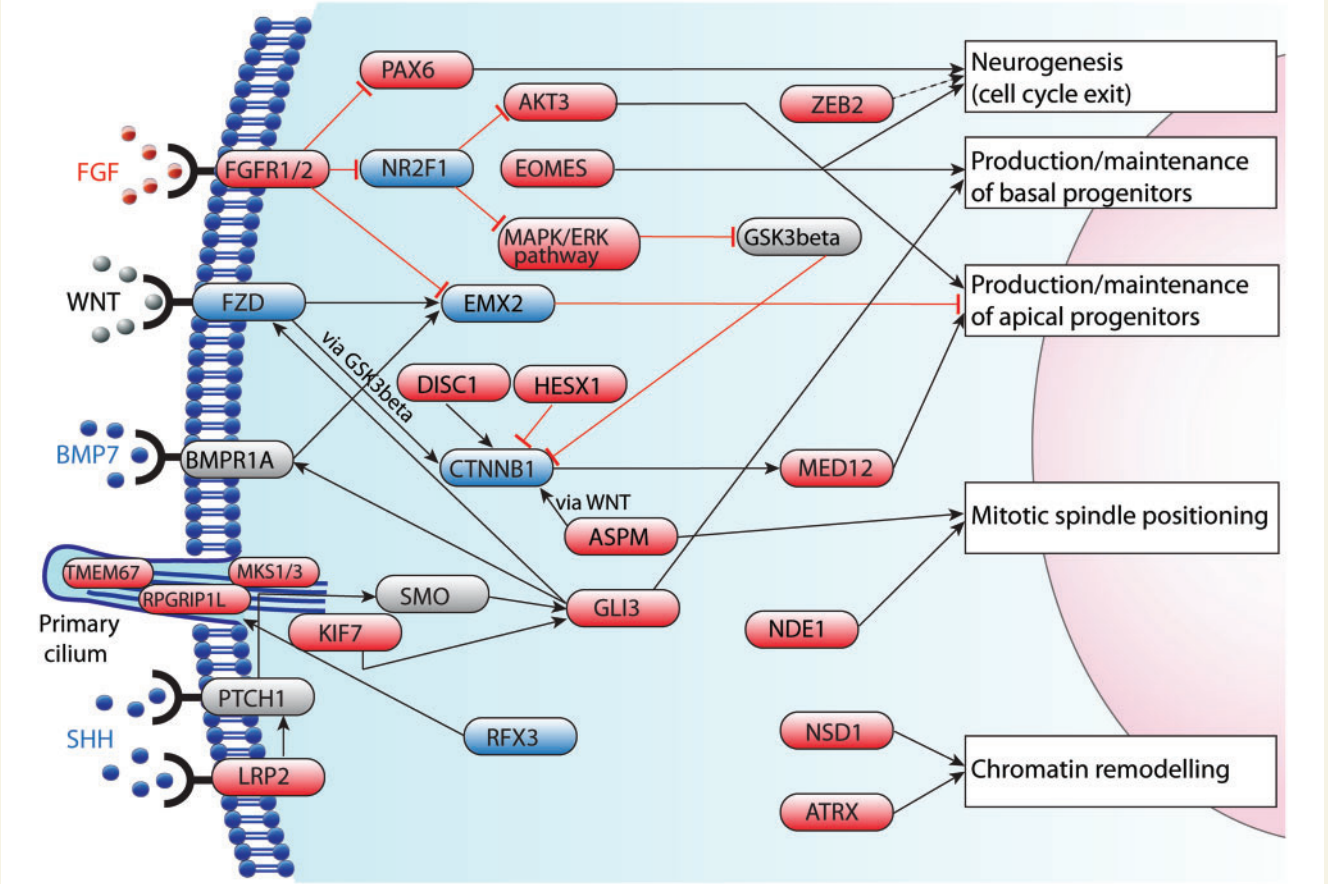

Figure 6 Major mechanisms underlying neurogenesis in the telencephalon relevant to ACC in humans. Many molecules involved in neurogenesis have multiple functions, and genetic mutations can therefore result in complex neurodevelopmental disorders. Many midline patterning genes functionally interact with primary cilia, and mutations in these genes give rise to a group of overlapping syndromes termed 'ciliopathies', which can feature ACC. Genes in red are associated with a human syndrome; genes in blue have a mouse model with ACC but have not yet been associated with a human ACC syndrome, and genes in grey (ligands in black) have not been implicated in either human or mouse ACC.

result of abnormal neuronal and glial development are never diagnosed in isolation. In these cases, ACC should not be considered a diagnosis in itself, but should rather be cause for detection of additional congenital defects. Glutamatergic cortical neurons are born in the subventricular zone from intermediate progenitor cells, and from radial glia in the ventricular zone (Noctor *et al.*, 2004; Kowalczyk *et al.*, 2009). Multiple transcription factors are necessary for specification of cells in the subventricular zone and ventricular zone, but these are beyond the scope of this review. Intermediate progenitor cells are themselves born from asymmetrical division of radial glia within the ventricular zone (Noctor *et al.*, 2004). To maintain progenitor cell numbers, radial glia may less frequently undergo symmetrical cell division to expand the pool of neuronal precursors (Tamamaki *et al.*, 2001). Whether radial glia produce proliferative or differentiating cells is highly dependent on the orientation of the mitotic spindle relative to the ventricular surface (Shioi *et al.*, 2009), and loss of control over this process results in prenatal microcephaly.

Autosomal recessive primary microcephaly (MCPH) results from decreased or ineffective proliferation of neurons, generally without disturbance of cortical organization (for a review, see Mahmood *et al.*, 2011). Callosal development is usually not impaired in this group of prenatal microcephalies, so abnormal neuronal proliferation alone cannot always account for ACC. Syndromes that do encompass both ACC and microcephaly represent a broad group, but differ from MCPH in the degree of associated cortical disorganization.

G-protein signalling modulator 2 (GPSM2) is necessary for the planar orientation of the mitotic spindle in symmetrical division, and mutations in *GPSM2* result in the autosomal recessive Chudley-McCullough syndrome, which can display complete ACC (Diaz-Horta *et al.*, 2012; Doherty *et al.*, 2012). Cortical malformations in Chudley-McCullough syndrome seem to be principally because of disrupted cortical architecture rather than decreased neuronal proliferation. Mouse models of homozygous *Gpsm2* mutations show that vertically aligned divisions of radial glia that would normally produce identical apical progenitor cells instead produce aberrant progenitors that migrate into the cortex (Konno *et al.*, 2008; Shioi *et al.*, 2009). It is possible that a similar disruption to the spatial organization of neurogenesis underlies the

two primary microcephaly syndromes in which abnormal cortical architecture and ACC have been well characterized: MCPH5 and MCPH2, caused by mutations in the abnormal spindle-like, microcephaly-associated gene (*ASPM*) and WD-repeat domain 62 gene (*WDR62*), respectively. Mutations in *ASPM* and *WDR62* genes together account for at least 55% of MCPH families, and are directly involved in mitotic spindle orientation of neural precursors within the ventricular zone (Mahmood *et al.*, 2011). Along similar lines, homozygous mutations in nudE nuclear distribution E homolog 1 *(A. nidulans)* (*NDE1*), which localizes to the centrosome and mitotic spindle poles, results in a severe microlissencephaly syndrome encompassing cortical disorganization and ACC. These patients present with marked architectural defects in the cortex, which is consistent with a combined disorder of neurogenesis and neuronal migration (Feng and Walsh, 2004; Alkuraya *et al*., 2011; Paciorkowski *et al*., 2013).

The balance between symmetric and asymmetric division of radial glia is influenced by a series of transcription factors expressed by neuronal precursors and post-mitotic migrating neurons. Mowat-Wilson syndrome results from heterozygous, mostly *de novo* mutations in the *ZEB2* gene encoding SMAD interacting protein 1 (SIP1) (Cacheux *et al.*, 2001; Garavelli and Mainardi, 2007). In neurogenesis, SIP1 is one of several transcription factors expressed specifically in post-mitotic neocortical neurons, and non-cell autonomously controls differentiation of neuronal progenitor cells. Loss of SIP1 function in mice leads to increased superficial layer neuron production and gliogenesis, all at the expense of deep layer neurons (Seuntjens *et al.*, 2009). Callosal agenesis is present in just over 40% of Mowat-Wilson cases (Mowat *et al.*, 2003; Dastot-Le Moal *et al.*, 2007); however, even patients from within the same family show an inconsistent callosal phenotype, suggesting that modifier genes interact with SIP1 to influence callosal development. In addition, SIP1 appears to have earlier roles in telencephalic patterning (Verschueren *et al.*, 1999; Verstappen *et al.*, 2008) and neural crest cell migration, and better genotype-phenotype correlations will improve the accuracy of prognosis in neonates and infants.

The change in expression of a series of transcription factors signals the transition from radial glia to intermediate progenitors to neurons. Expression of the transcription factor eomesodermin (T-box brain protein 2 in mice) in radial glia is sufficient to induce intermediate progenitor cell identity (Sessa *et al.*, 2008). Conversely, expression of PAX6, EMX2 and SOX2 transcription factors maintains radial glia populations (Graham *et al.*, 2003; Englund *et al.*, 2005; Sansom *et al.*, 2009). With the exception of one report of a microcephalic patient with a disruption of the Eomesdermin gene (Baala *et al.*, 2007), no human mutations in these genes have been associated with cortical dysgeneses that recapitulate the severe neurological phenotypes of mouse models. Indeed, for patients with *PAX6* or *SOX2* mutations, mild callosal hypoplasia is a more common finding than partial or complete ACC (Kelberman *et al.*, 2006).

In syndromes where diffuse thinning of the corpus callosum (callosal hypoplasia) is a frequent finding and ACC occurs occasionally, it is likely that agenesis lies on a spectrum of pathogenic mechanisms underlying hypoplasia. Sotos syndrome is an overgrowth syndrome caused by haploinsufficiency in the *NSD1* and *NFIX* genes (Kurotaki *et al.*, 2002; Malan *et al.*, 2010). Diffuse callosal hypoplasia or thinning of the posterior body is a common finding, whereas callosal agenesis has been reported in only a small proportion of patients (Schaefer *et al.*, 1997; Melo *et al.*, 2002; Horikoshi *et al.*, 2006). It is difficult to tease apart the mechanisms underlying hypoplasia and agenesis; however, it is likely that the underlying mechanisms are similar, and that genetic modifiers influence the severity of the callosal phenotype.

Modifying genetic influences also play an important role in neuropsychiatric disorders such as autism and schizophrenia, in which variable decreases in callosal size and fractional anisotropy suggest underlying abnormalities of white matter microstructure (Woodruff *et al.*, 1995; Downhill *et al.*, 2000; Innocenti *et al.*, 2003). In general, neuropsychiatric disorders such as schizophrenia can be considered polygenic disorders, the inheritance of which is influenced by the combined effect of many genetic modifiers. One possible exception to this rule, however, is mutations in the disrupted in schizophrenia 1 gene (*DISC1*), which have been implicated in both ACC and a small percentage of schizophrenia cases (Osbun *et al.*, 2011). DISC1 inhibits neuronal progenitor proliferation by inhibiting phosphorylation of β-catenin, which causes cell cycle exit and differentiation (Mao *et al.*, 2009). Following this, DISC1 acts as a molecular switch that, when phosphorylated in post-mitotic neurons, recruits Bardet-Biedl syndrome (BBS) proteins BBS1 and BBS4 to the centrosome and interacts with NDE1-like 1 to promote neuronal migration and neurite outgrowth, respectively (Kamiya *et al.*, 2006; Ishizuka *et al.*, 2011). A mouse model of *Disc1* mutation shows high penetrance of partial ACC (Shen *et al.*, 2008), and several rare, potentially pathogenic mutations in *DISC1* have been identified in patients with ACC. The number of schizophrenia patients with *DISC1* mutations and ACC has not been as widely studied. Given the likelihood that developmental pathways exist that are common to both ACC and schizophrenia, however, it is possible that the link between schizophrenia and callosal development is more widespread than currently thought, and further study may uncover genetic modifiers involved in these disorders (Walterfang *et al*., 2008; Osbun *et al.*, 2011).

Abnormal midline patterning

Early disruptions in patterning of the prosencephalic vesicle can result in ACC, but this is secondary to more severe pathologies. Failure of invagination of the dorsal prosencephalon to produce two hemispheres results in a single hollow vesicle being formed (holoprosencephaly) and subsequent loss of all midline structures including the corpus callosum. This condition can affect the entire telencephalon, or can be restricted to either rostral or caudal regions, in which case parts of the corpus callosum may still form provided there is a bridge of white matter across which axons can traverse the midline (for a review see Marcorelles and Laquerriere, 2010). Likewise, failure of an established telencephalic midline to fuse invariably results in callosal agenesis because of loss of a substrate through which callosal axons can pass (Silver and Ogawa, 1983; Demyanenko *et al.*, 1999; Brouns *et al.*, 2000; Wahlsten *et al.*, 2006). The BALB/c and 129 mouse strains, for example, display severe retardation of midline fusion in the septal

region, but guidance of putative callosal axons is normal to the midline, at which point the axons stall (Wahlsten *et al.*, 2006). Correct patterning of the commissural plate and midline glial populations is essential for commissural axons to cross the midline (Moldrich *et al.*, 2010). Midline glia function primarily as guideposts for callosal axons, and secrete guidance molecules to define migratory boundaries, while each telencephalic commissure must pass through a molecularly distinct region of the commissural plate.

Sonic hedgehog (SHH) is a secreted morphogen that bestows ventral cell identity in the early telencephalon in a concentration-dependent manner. Human mutations in *SHH* or its receptor patched 1 (*PTCH1*) cause holoprosencephaly, as a result of disturbances too early in dorsal-ventral patterning to fall within the scope of this review (for a review of the hedgehog signalling network, see Robbins *et al*., 2012). SHH signalling through PTCH1 is mediated by low density lipoprotein-related protein 2 (LRP2) (Willnow *et al.*, 1996; Spoelgen *et al.*, 2005; Christ *et al.*, 2012), which when mutated, results in the autosomal recessive Donnai-Barrow syndrome (Kantarci *et al.*, 2007). In *Lrp2*$^{-/-}$ mice, loss of Shh signalling almost always results in holoprosencephaly (Spoelgen *et al.*, 2005), although human cases present with milder ventral patterning defects including ACC (Kantarci *et al.*, 2007), suggesting that there is greater redundancy for the role of LRP2 in SHH signalling in humans.

In recent years, the association between disorders involving primary cilia (ciliopathies) and ACC has been increasingly studied. Primary cilia cooperate with SHH signalling by interacting with the downstream signalling molecules kinesin family member 7 (KIF7) and GLI family zinc finger 3 (GLI3) (Liem *et al.*, 2009; Besse *et al.*, 2011). There are multiple, diverse genetic causes of ciliopathies, but all of the implicated genes are necessary for the normal function of primary cilia (Lee and Gleeson, 2011; Novarino *et al.*, 2011). A summary of the major ciliopathies associated with ACC is given in Table 1. Mice lacking the ciliogenic transcription factor RFX3 display altered patterning of the corticoseptal boundary and abnormal positioning of guidepost neurons associated with expanded FGF8 expression (Benadiba *et al.*, 2012). This is of particular importance because of the well-established role of FGF8 in establishing the commissural plate (Moldrich *et al.*, 2010). However, neurodevelopmental abnormalities are not confined to the corpus callosum. Failure of decussation of superior cerebellar peduncles and absence of the pyramidal decussation (Quisling *et al.*, 1999), in addition to distinctive malformations of the cerebellum (Juric-Sekhar *et al*., 2012), are consistent with multiple roles for primary cilia throughout brain development.

GLI3 mutations result in multiple overlapping syndromes including acrocallosal syndrome, Greig cephalopolysyndactyly and metopic craniosynostosis, and some of these affected patients present with callosal anomalies (Vortkamp *et al.*, 1991; Elson *et al.*, 2002; McDonald-McGinn *et al.*, 2010). Specific mutations in different regions of *GLI3* have helped to delineate the way in which it transduces SHH signalling, and genotype–phenotype correlations have been made previously (Kang *et al.*, 1997; Johnston *et al.*, 2005; Naruse *et al.*, 2010). The severity of these disorders ranges from polydactyly and hypothalamic hamartoma to holoprosencephaly or neonatal lethality, and neuroanatomical abnormalities appear to correlate with the degree of disruption to the normal dorsal midline patterning function of GLI3. Abnormalities in midline patterning in GLI3 hypomorphic mice are similar to those observed in *Rfx3*$^{-/-}$ mice, whereby ACC is associated with increased *Slit2* and *Fgf8* expression (Magnani *et al.*, 2012). Interestingly, FGF signalling has been implicated in Apert syndrome (Wilkie *et al.*, 1995; Slaney *et al.*, 1996; Quintero-Rivera *et al.*, 2006) and a proportion of patients with Kallmann syndrome for whom ACC has occasionally been described (Dode *et al.*, 2003; Falardeau *et al.*, 2008; McCabe *et al.*, 2011). Together, these syndromes represent disruptions of a common developmental pathway (Vaaralahti *et al*., 2012), and corresponding mouse models all show common midline patterning defects with aberrant positioning of midline glial guideposts.

Abnormal callosal neuron migration and specification

Once born from the subventricular or ventricular zones, postmitotic neurons migrate outwards along radial glial processes to form six distinct cortical layers in a birth date-dependent inside-out manner (Noctor *et al*., 2001; Huang, 2009). Early born neurons populate the deeper zones, whereas later born neurons migrate past them to populate more superficial cortical layers. Radial migration from the subventricular and ventricular zones towards

Table 1 Major syndromes associated with ACC that are part of the extended ciliopathy spectrum

	Joubert syndrome	Meckel syndrome	Hydrolethalus syndrome	Acrocallosal syndrome	Bardet-Biedl syndrome (JSRD)
Selected genes affected	TMEM67, TMEM216, RPGRIP1L, KIF7	MKS1, MKS3, TMEM67, RPGRIP1L	HYLS1, KIF7, ACLS	GLI3, KIF7, HLS2	BBS1–12, TMEM67, MKS1
Major neuroanatomical abnormalities	Molar tooth sign (cerebellar vermis hypoplasia/absence, deep interpeduncular fossa, thick elongated superior cerebellar peduncles)	Occipital encephalocele, absence of olfactory bulbs, complete or partial ACC	Severe hydrocephalus, absence of midline structures (ACC)	Exencephaly, hydrocephalus, ACC	Molar tooth sign
ACC common/ occasional finding?	Uncommon	Common	Common	Common	Occasional

the cortical plate is achieved by a recurring cycle of leading process extension, nucleokinesis, and trailing process retraction (Kanatani *et al.*, 2005). Several human ACC syndromes have been associated with the intracellular molecules that underpin neuronal migration. Not surprisingly, mutations in genes known to be involved in microtubule structure (e.g. *TUBA1A*) and stabilization (e.g. *DCX* and *DCLK1*) severely affect early radial migration and post-migrational development of cortical neurons (Gleeson *et al.*, 1998; Deuel *et al.*, 2006; Koizumi *et al.*, 2006*a*, *b*; Poirier *et al.*, 2007). The resulting group of human syndromes are often severe, characterized by lissencephaly and periventricular nodular heterotopias, but can also present as disorders mainly of axon guidance (O'Driscoll *et al.*, 2010; Tischfield *et al.*, 2010; Chew *et al.*, 2013).

Mutations in the *ARX* gene cause a nearly continuous series of syndromes ranging from severe hydranencephaly, lissencephaly and ACC, to syndromes with no brain malformations visible on MRI scans (Kitamura *et al.*, 2002; Weaving *et al.*, 2004; Suri, 2005). ARX comprises an aristaless domain and a prd-like homeodomain (Stromme *et al.*, 2002). In general, non-conservative mutations in either functional domain result in X-linked lissencephaly with an absent corpus callosum and ambiguous genitalia (XLAG), whereas a more severe syndrome is observed when both domains are disrupted (Kato *et al.*, 2004). XLAG is typified by a posterior-to-anterior gradient of lissencephaly, ambiguous genitalia, hypoplastic basal ganglia/hypothalamus, and a slightly thickened cortex comprising three pyramidal neuron layers, epilepsy and complete ACC (Bonneau *et al.*, 2002; Miyata *et al.*, 2009). Abnormal cortical layering is consistent with a radial migration defect of cortical neurons; however, murine *Arx* is expressed in GABAergic interneurons arising from the ganglionic eminences and the subventricular zone (Friocourt *et al.*, 2008). XLAG is a combined disorder of tangential and radial neuronal migration, and it is likely that defects in neurogenesis also exist (Friocourt *et al.*, 2008). Interestingly, the female XLAG syndrome is less severe than that of the male, suggesting gene dosage effects of *ARX* mutations; carrier females can exhibit isolated ACC with Probst bundles, variably impaired cognitive function and epilepsy (Bonneau *et al.*, 2002).

The cortical layer that a neuron will inhabit is primarily determined by the time of its birth (Desai and McConnell, 2000; Shen *et al.*, 2006). Once a neuron has migrated to this layer, however, it must continue to be specified by its layer and target area. Callosal neuron identity appears to coincide with expression of the chromatin-remodelling factor *Satb2*, which has been proposed to specify rostral callosal projecting neurons at the expense of corticofugal projection neurons (Alcamo *et al.*, 2008; Britanova *et al.*, 2008), which are specified by the transcription factors FEZF2 and CTIP2 (Arlotta *et al.*, 2005; Chen *et al.*, 2005; Molyneaux *et al.*, 2005; Chen *et al.*, 2008). SATB2 has recently been shown to functionally interact with the proto-oncogene *Ski* to specify callosal neurons (Baranek *et al.*, 2012), as discussed later in relation to 1p36 deletion syndrome.

In ACC, the neurons that would have crossed the corpus callosum must be re-specified such that they may project subcortically, intracortically in Probst bundles, or they may preserve some interhemispheric connectivity by projecting to the contralateral cortex through the anterior or hippocampal commissures. In the majority of patients with ACC, the anterior and hippocampal commissures are absent or small, which is consistent with common processes of commissure development (Hetts *et al.*, 2006). In a smaller subset of patients with ACC, but in all cases with ACC with an identified *ARX* mutation (Hetts *et al.*, 2006; Kara *et al.*, 2010), the anterior commissure is enlarged, and limited evidence suggests that this may represent a compensatory mechanism to maintain inter-cerebral transfer of information (Fischer *et al.*, 1992; Barr and Corballis, 2002). A similar increase in anterior commissure size has been well established in multiple inbred mouse strains, and is accounted for by an increase in unmyelinated axons (Livy *et al.*, 1997). Whether the apparent use of the anterior commissure as a surrogate corpus callosum is compensatory in some patients will depend largely on whether it can transmit information from origins normally exclusive to the corpus callosum (Guenot, 1998), and this is not yet clearly established.

Abnormal axon guidance

Correct callosal axon guidance is a tightly regulated process that relies on two distinct levels of guidance cue response. First, growth cones must respond to guidance cues specifically and with high fidelity, and this is dependent on correct temporal and spatial expression of receptors. Second, underlying axon migration and the guidance response is a complex network of intracellular actin and microtubule dynamics, and intercellular recognition and fasciculation. Molecules that modulate these processes can be influenced by activation of guidance cue receptors (Fig. 7). The directionality of growth cones can be influenced by long-range attractive or repulsive cues, short-range attractive or repulsive cues, factors affecting axon fasciculation, growth substrate and cellular influences (Lindwall *et al.*, 2007).

Although understanding the mechanisms of axonal guidance has elucidated important aspects of normal corpus callosum development, few patients with ACC syndromes have been identified with mutations in axon guidance genes. This may be because of the fact that broad syndromes as a result of neuronal proliferative or maturational defects display clear neurological disorders, whereas guidance defects could manifest as isolated and less detectable callosal dysgeneses. Indeed, the correct guidance of callosal axons is dependent on a large body of signalling molecules and transcription factors that must be correctly expressed before and during axon guidance. Guidance cues can also act in parallel and compensate for one another, and may therefore exhibit significant redundancy and reduced ACC penetrance. Conversely, homozygous null mice for guidance genes such as netrin 1 (Serafini *et al.*, 1996), *Robo1* (Andrews *et al.*, 2006) and *Dcc* (Fazeli *et al.*, 1997) die as embryos or shortly after birth, and thus human mutations in these genes might be lethal and not actually result in clinically evident syndromes. Interestingly, mutations in *DCC* have been associated with congenital mirror movements, which is somewhat reminiscent of the hopping gait and mirror movements seen in the $Dcc^{Kanga/Kanga}$ mouse model (Finger *et al.*, 2002; Srour *et al.*, 2010; Djarmati-Westenberger *et al.*, 2011). In addition, a weakly expressing haplotype of *ROBO1* has been associated with dyslexia and impaired interhemispheric

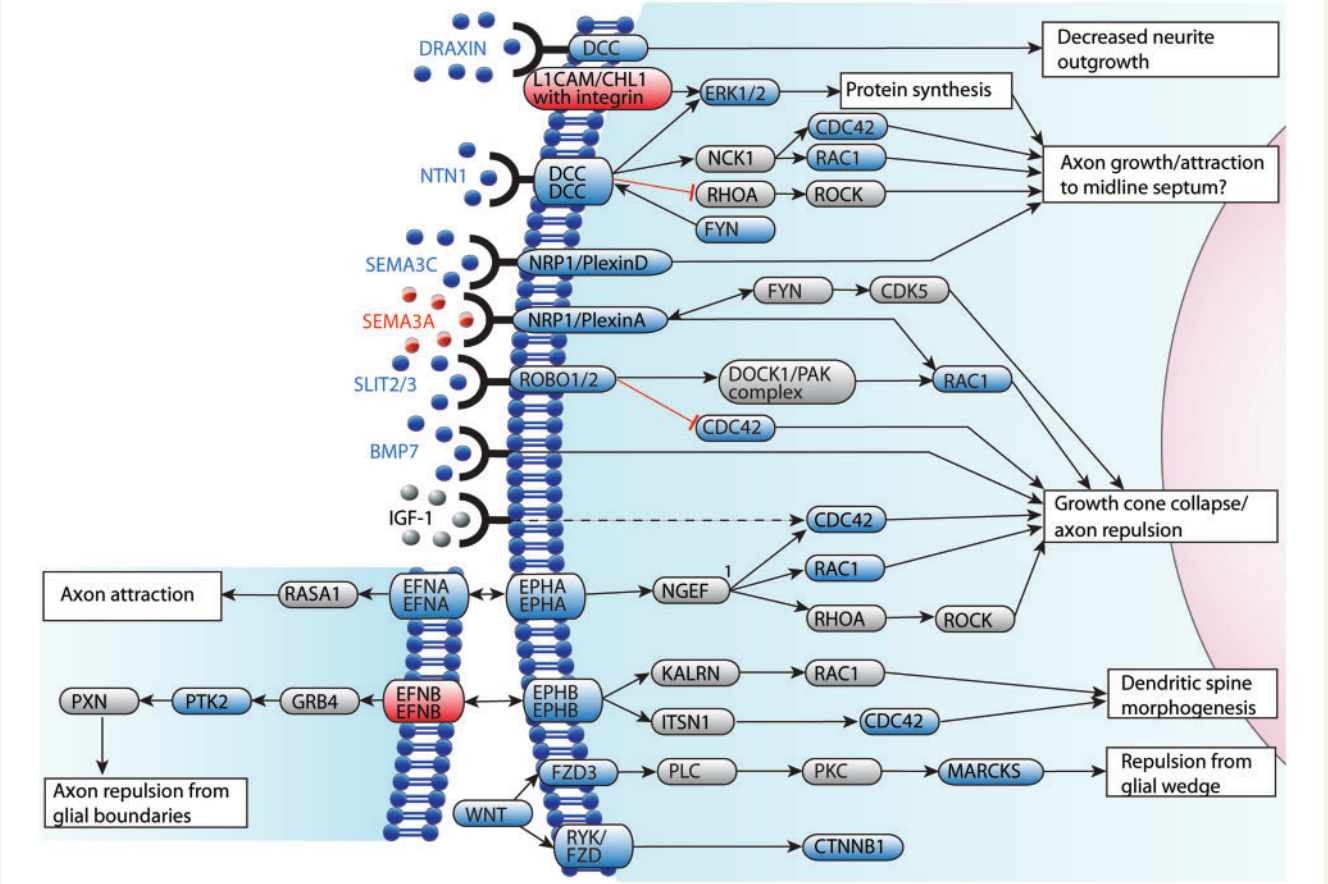

Figure 7 Major mechanisms that potentially underlie guidance of callosal axons in humans. Guidance receptors are expressed on the growth cone of commissural axons, and when bound to their ligand/s, influence microtubule and actin dynamics through second messengers including RHOA, RAC1 and CDC42. Some guidance receptors, such as DCC, have multiple ligands, and the effects of receptor activation depend on the bound ligand. Whereas most ligands are secreted from midline glial populations into the surrounding extracellular matrix, ephrin ligands are membrane-bound and can initiate reverse signalling. The effects of ephrin receptors vary depending on the subtype of receptor activated, and ligands expressed. Genes in red are associated with a human syndrome; genes in blue have a mouse model with ACC but are not associated with a human ACC syndrome, and genes in grey (ligands in black) have not been implicated in human or mouse ACC. 1, based on overexpression studies, NGEF increases RHOA activity relative to RAC1 and CDC42.

transfer of auditory signals (Hannula-Jouppi *et al.*, 2005; Lamminmaki *et al.*, 2012).

Craniofrontonasal syndrome, caused by mutations in the *EFNB1* gene encoding ephrin-B1, is an exception to the lack of human ACC syndromes associated with axon guidance (Wieland *et al.*, 2004, 2005). Craniofrontonasal syndrome is an atypical X-linked recessive disorder as females are severely affected whereas males show mild or no abnormalities; it typically presents with craniofacial and skeletal abnormalities, and less commonly, ACC (Saavedra *et al.*, 1996; Wieacker and Wieland, 2005). The reason for low ACC penetrance (a review of the literature found ACC in 10% of cases) is likely because of the redundant nature of the ephrin family, which has been verified by mouse models of single and double gene knockouts (Table 2) (Wieacker and Wieland, 2005; Mendes *et al.*, 2006). Ephrins define migratory boundaries in multiple developmental contexts; in callosal development, they are expressed in the glial wedge and redundantly direct axons toward the midline (Mendes *et al.*, 2006). Heterozygous *EFNB1* mutations in females seem to have a dominant negative effect owing to the multiple interactions possible between ephrin ligands and receptors of different subclasses. In females, random X-inactivation produces two types of cell, those expressing functional ephrin-B1 and those expressing the mutant ephrin-B1. Mutant ephrin-B1 expressing cells may present alternative ephrin ligands with different receptor affinity, resulting in abnormal cellular cross-talk within these mosaic compartments and unclear migratory boundaries (Twigg *et al.*, 2004; Wieland *et al.*, 2004; Wieacker and Wieland, 2005; Davy *et al.*, 2006).

Axonal growth and fasciculation are dependent on cell adhesion molecules (CAMs), and mutations in a member of the immunoglobulin family of CAMs, *L1CAM*, cause a broad range of X-linked disorders collectively termed L1 syndrome (Fransen *et al.*, 1995). The phenotypic spectrum of the X-linked L1 syndrome comprises partial ACC, CRASH syndrome (corpus callosum hypoplasia, retardation, adducted thumbs, spasticity and hydrocephalus), MASA syndrome (mental retardation, aphasia, shuffling gait and adducted thumbs), X-linked complicated ACC, X-linked complicated spastic paraplegia type 1, and various

Table 2 Genes with ACC mouse models and no human ACC syndrome

Gene #	OMIM Number	HGNC ID	Location (human)	Mouse phenotype					References[a]
				Callosal phenotype		Associated midline defects			
				cACC[b]	pACC[b]	Midline glia	Hippocampal commissure	Anterior commissure	
GROUP I - Abnormal neuronal and/or glial proliferation									
Achaete-scute complex homolog 1 (Drosophila) (ASCL1)	100790	738	12q22-q23	Y	Y	N	Y	N	Niquille *et al.*, 2009
Catenin (cadherin-associated protein), beta 1, 88 kDa (CTNNB1)	116806	2514	3p22.1	Y					Machon *et al.*, 2003
Eomesodermin (EOMES)	604615	3372	3p24.1	Y	Y		Y	Y	Arnold *et al.*, 2008; Sessa *et al.*, 2008
Mitogen-activated protein kinase 1 (MAPK1)	176948	6871	22q11.2	N	Y				Newbern *et al.*, 2008; Satoh *et al.*, 2011
Mitogen-activated protein kinase 3 (MAPK3)/Mitogen-activated protein kinase 1 (MAPK1)	601795/ 176948	6877/ 6871	16p11.2/ 22q11.2	N	Y				Satoh *et al.*, 2011
Mitogen-activated protein kinase kinase kinase 4 (MAP3K4)	602425	6856	6q26	Y	Y				Chi *et al.*, 2005
N-ethylmaleimide-sensitive factor attachment protein, alpha (NAPA)	603215	7641	19q13.33	Y			Y	N	Chae *et al.*, 2004
Nuclear receptor subfamily 2, group E, member 1 (NR2E1)	603849	7973	6q21	N	Y		Y	Y	Monaghan *et al.*, 1997; Land and Monaghan, 2003
Zinc finger and BTB domain containing 18 (ZBTB18)	608433	13030	1q44	Y					Xiang *et al.*, 2011
Zinc finger protein 423 (ZNF423)	604557	16762	16q12	Y		Y	Y	Y	Cheng *et al.*, 2007
GROUP II – Abnormal midline patterning									
Bone morphogenetic protein 7 (BMP7)	112267	1074	20q13	Y (50%)	Y (50%)	Y			Choe *et al.*, 2012; Sanchez-Camacho *et al.*, 2011
Empty spiracles homeobox 1 (EMX1)	600034	3340	2p13.2	Y	Y	Y	N	Y	Qiu *et al.*, 1996; Yoshida *et al.*, 1997
Empty spiracles homeobox 2 (EMX2)	600035	3341	10q26.11	N	Y		Y	Y	Pellegrini *et al.*, 1996; Yoshida *et al.*, 1997
Nuclear factor I/A (NFIA)	600727	7784	1p31.3-p31.2	Y (100%)		Y	Y	Y	das Neves *et al.*, 1999; Shu *et al.*, 2003*a*
Nuclear factor I/B (NFIB)	600728	7785	9p24.1	Y	Y	Y			Steele-Perkins *et al.*, 2005; Piper *et al.*, 2009
Regulatory factor X, 3 (influences HLA class II expression) (RFX3)	601337	9984	9p24.2	Y (36%)	Y (36%)	Y	N	Y	Benadiba *et al.*, 2012

(continued)

Table 2 Continued

Gene #	OMIM Number	HGNC ID	Location (human)	Mouse phenotype					References[a]
				Callosal phenotype		Associated midline defects			
				cACC[b]	pACC[b]	Midline glia	Hippocampal commissure	Anterior commissure	
GROUP III- Abnormal callosal neuron migration and/or specification									
Amyloid Beta A4 precursor protein-binding, family B, member 1 (APBB1)	602709	581/582	11p15/4p13	Y (100%)					Guenette *et al.*, 2006
Amyloid beta (A4) precursor protein (APP)	104760	620	21q21.2	Y	Y		Y	Y	Muller *et al.*, 1996; Magara *et al.*, 1999
Ankyrin 2, neuronal (ANK2)	106410	493	4q25	N	Y				Scotland *et al.*, 1998
Cell adhesion molecule with homology to L1CAM (close homolog of L1) (CHL1)	607416	1939	3p26.3		Y				Demyanenko *et al.*, 1999
Cell division cycle 42 (CDC42)	116952	1736	1p36.12	N	Y				Yokota *et al.*, 2010
Cytoplasmic protein tyrosine kinase 2 (PTK2)	600758	9611	8q24.3	N	Y				Beggs *et al.*, 2003
Doublecortin-like kinase 1 (DCLK1)	604742	2700	13q13.3	Y			Y	N	Deuel *et al.*, 2006; Koizumi *et al.*, 2006*b*
Laminin, gamma 1 (formerly LAMB2) (LAMC1)	150290	6492	1q31.1	N	Y				Chen *et al.*, 2009
Myristoylated alanine-rich protein kinase C substrate (MARCKS)	177061	6759	6q21	Y (93%)	Y (7%)		Y	Y	Stumpo *et al.*, 1995
MARCKS-like 1 (MARCKSL1)	602940	7142	1p35.1	Y (100%)			N	N	Wu *et al.*, 1996; Bjorkblom *et al.*, 2012
Mitogen-activated protein kinase 8-interacting protein 3 (MAPK8IP3)	605431	6884	16p13.3	Y (100%)			N	Y	Kelkar *et al.*, 2003; Ha *et al.*, 2005; Cho *et al.*, 2011
Rap guanine nucleotide exchange factor (GEF) 1 (RAPGEF1)	600303	4568	9q34.13	N	Y (100%)	Y	Y	Y (100%)	Bilasy *et al.*, 2009; 2011
Rho GTPase-activating protein 5 (ARHGAP5)	602680	675	14q12	N	Y (100%)		Hypoplasia	Y	Matheson *et al.*, 2006
Rho GTPase activating protein 35 (ARHGAP35)	605277	4591	19q13.32	Y (100%)			Y	Y	Brouns *et al.*, 2000; Matheson *et al.*, 2006
Special AT-rich sequence-binding protein-2 (SATB2)	608148	21637	2q33.1	Y (100%)	N	N	N	N	Alcamo *et al.*, 2008; Britanova *et al.*, 2008
V-SKI Avian sarcoma viral oncogene homolog (SKI)	164780	10896	1p36.33	Y	Y	N			Baranek *et al.*, 2012

(continued)

Table 2 Continued

Gene #	OMIM Number	HGNC ID	Location (human)	Mouse phenotype					References[a]
				Callosal phenotype		Associated midline defects			
				cACC[b]	pACC[b]	Midline glia	Hippocampal commissure	Anterior commissure	
GROUP IV- Abnormal axon growth and/or guidance									
Cyclin-dependent kinase 5, regulatory subunit 1 (p35) (CDK5R1)	603460	1775	17q12		Y		N	Y	Kwon *et al.*, 1999
Deleted in colorectal cancer (DCC)	120470	2701	18q21.2	Y (100%)			Y	Y	Fazeli *et al.*, 1997; Ren *et al.*, 2007
Dorsal repuslive axon guidance protein (DRAXIN)	612682	25054	1p36.22	Y (42%)	Y (58%)	Y	Y	Y	Islam *et al.*, 2009; Ahmed *et al.*, 2011
Enabled homolog (Drosophila) (ENAH)	609061	18271	1q32.2	Y (55%)[c]			Y	N	Lanier *et al.*, 1999
EFNB3/EPH receptor B1	602297/600600	3228/3392	17p13.1/3q22.2	Y (87%)	Y (13%)				Mendes *et al.*, 2006
EFNB3/EPH receptor B2	602297/600997	3228/3393	17p13.1/1p36.12	y (45%)	Y (44%)				Mendes *et al.*, 2006
EFNB3/EPH receptor A4	602297/602188	3228/3388	17p13.1/2q36.3	Y (29%)	Y (35%)				Mendes *et al.*, 2006
EPH receptor A5 (EPHA5)	600004	3389	4q13.1	N	Y (100%)	N	Y (46%)		Yue *et al.*, 2002; Hu *et al.*, 2003
EPH receptor B1 (EPH B1)	600600	3392	3q22.2	Y (43%)	Y (44%)				Mendes *et al.*, 2006
EPH receptor B2 (EPH B2)	600997	3393	1p36.12	Y (13%)[c]	Y (48%)[c]			Y	Orioli *et al.*, 1996; Mendes *et al.*, 2006; Ho *et al.*, 2009
EPH receptor B2 (Nuk)	600997	3393	1p36.12	N	Y (20%)			Y (100%)	Henkemeyer *et al.*, 1996; Orioli *et al.*, 1996
EPH receptor B3 (EPH B3) (Sek)	601839	3394	3q27.1	Y (37.5%)				N	Orioli *et al.*, 1996
Ephrin B3 (EFNB3)	602297	3228	17p13.1	Y (64%)	Y (20%)				Orioli *et al.*, 1996; Mendes *et al.*, 2006
EPH receptor B1/EPH receptor B2	600600/600997	3392/3393	3q22.2/1p36.12	Y (60%)	Y (28%)				Mendes *et al.*, 2006
EPH receptor B1/EPH receptor B3	600600/601839	3392/3394	3q22.2/3q27.1	Y (18%)	Y (90%)				Mendes *et al.*, 2006
EPH receptor B1/EPH receptor A4	600600/602188	3392/3388	3q22.2/2q36.3	Y (12%)	Y (14%)				Mendes *et al.*, 2006
EPH receptor B2/EPH receptor B3	600997/601839	3393/3394	1p36.12/3q27.1	Y (67%)	Y (33%)				Mendes *et al.*, 2006
EPH receptor B2/EPH receptor B3 (Nuk/Sek)	600997/601839	3393/3394	1p36.12/3q27.1	Y (89%)			N	Y (100%)	Orioli *et al.*, 1996
Exostosin 1 (EXT1)	608177	3512	8q24.11	Y			Y	Y	Inatani *et al.*, 2003
FEZ family zinc finger 2 (FEZF2)	607414	13506	3p14.2	Y	Y		N		Chen *et al.*, 2005; Molyneaux *et al.*, 2005
Frizzled family receptor 3 (FZD3)	4041	4041	8p21.1	Y	Y		Y	Y	Wang *et al.*, 2002; 2006
Growth associated protein 43 (GAP43)	162060	4140	3q13.31	Y (100%)		Y	Y (100%)	Y (100%)	Shen *et al.*, 2002; 2004
Heparan sulphate 6-O-sulfotransferase 1 (HS6ST1)	604846	5201	2q21	Y (100%)		Y			Merry *et al.*, 2001; Conway *et al.*, 2011
Microtubule-associated protein 1B (MAP1B)	157129	6836	15q13.2	Y (80%)	Y (20%)		Y	N	Meixner *et al.*, 2000

(continued)

Table 2 Continued

Gene #	OMIM Number	HGNC ID	Location (human)	Mouse phenotype					References[a]
				Callosal phenotype		Associated midline defects			
				cACC[b]	pACC[b]	Midline glia	Hippocampal commissure	Anterior commissure	
Netrin 1 (NTN1)	601614	8029	17p13.1	Y (100%)			Y (100%)	Y	Serafini *et al.*, 1996; Ren *et al.*, 2007
Neuropilin 1 (NRP1)	602069	8004	10p12	Y	Y		Y		Piper *et al.*, 2009
Nuclear receptor subfamily 2, group F, member 1 (NR2F1)	132890	7975	5q15	Y (63%)	Y (16%)		Y	Y	Armentano *et al.*, 2006
Pleckstrin homology domain containing, family B (evectins) member 1 (PLEKHB1)	607651	19079	11q13.5-q14.1	N	Y		N	Y	Bloom *et al.*, 2007; Lewcock *et al.*, 2007; Hendricks and Jesuthasan, 2009
Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1) (RAC1)	602048	9801	7p22	Y (100%)	N		Y	Y	Kassai *et al.*, 2008
Receptor-like tyrosine kinase (RYK)	600524	10481	3q22.2	N	Y (25%)	N	N	N	Keeble *et al.*, 2006
Roundabout, axon guidance receptor, homolog 1 (Drosophila)	602430	10249	3p12.3	N	Y	Y	Y	N	Andrews *et al.*, 2006; Unni *et al.*, 2012
Roundabout, axon guidance receptor, homolog 1 (Drosophila)/roundabout, axon guidance receptor, homolog 2 (Drosophila)	602430/ 602431	10249/ 10250	3p12.3/ 3p12.3	N	Y (100%)			N	Lopez-Bendito *et al.*, 2007
Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	602645	10725	7q21-q31	Y	Y	N		N	Niquille *et al.*, 2009
Serum response factor (c-fos serum response element-binding transcription factor) (SRF)	600589	11291	6p	N	Y		Y	Y	Lu and Ramanan, 2011
Slit homolog 2 (Drosophila)	603746	11086	4p15.2	N	Y (100%)	Y	N	N	Bagri *et al.*, 2002; Unni *et al.*, 2012
Slit homolog 3 (Drosophila)	603745	11087	5q35	N	Y (33%)	Y			Unni *et al.*, 2012
ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2 (ST8SIA2)	602546	10870	15q26	N	Y			N	Hildebrandt *et al.*, 2009
ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2 (ST8SIA2)/ST8 alpha-N-acetyl-neuraminide alpha-2, 8-sialyltransferase 4 (ST8SIA4)	602546/ 602547	10870/ 10871	15q26/ 15q21	N	Y			Y	Hildebrandt *et al.*, 2009
Trio Rho guanine nucleotide exchange factor (TRIO)	601893	12303	5p15.2	N	Y (100%)			Y (100%)	Briancon-Marjollet *et al.*, 2008
Uronyl-2-sulfotransferase (UST)	610752	17223	6q25.1	Y (50%)	Y (12.5%)	Y			Merry *et al.*, 2001; Conway *et al.*, 2011
Vasodilator-stimulated phosphoprotein (VASP)	601703	12652	19q13.32	Y (100%)		Y	Y (100%)	Y (100%)	Menzies *et al.*, 2004

(continued)

Table 2 Continued

Gene #	OMIM Number	HGNC ID	Location (human)	Mouse phenotype					References[a]
				Callosal phenotype		Associated midline defects			
				cACC[b]	pACC[b]	Midline glia	Hippocampal commissure	Anterior commissure	
GROUP V – Abnormal post-guidance development									
cAMP responsive element binding protein 1 (CREB1)	123810	2345	2q33.3	N	Y		N	Y	Rudolph *et al.*, 1998
Forkhead box C1 (FOXC1)	601090	3800	6p25.3	Y					Zarbalis *et al.*, 2007
Unclear function in corpus callosum development									
Protein tyrosine phosphatase, receptor type, S (PTPRS)	601576	9681	19p13.3	N	Y (100%)				Meathrel *et al.*, 2002
Insulin-like growth factor binding protein 1 (IGFBP1)	146730	5469	7p12.3	N	Y (100%)				Doublier *et al.*, 2000

[a]References in the table that are not included in the reference list can be found in the Supplementary material.
[b]For the purposes of this review, complete ACC (cACC) is defined as a complete absence of all callosal axons, or failure of all callosal axons to cross the midline. Partial ACC (pACC) has therefore been defined to encompass incomplete agenesis, where at least part of the corpus callosum can be identified.
[c]Phenotype varies with mouse strain.
Y = yes; N = no.
Blank cells signify that the given abnormality was not mentioned by the reference/s.

hydrocephalus-associated syndromes (Rosenthal *et al.*, 1992; Jouet *et al.*, 1994; Vos *et al.*, 2010). In general, males with L1 syndrome display a phenotype at the severe end of the disorder spectrum, which includes macrocephaly, mental retardation and spastic paraparesis. Other individuals can have ACC with Probst bundles and subcortically projecting tracts in the absence of cortical dysplasia, which is consistent with a role for L1CAM in axonal guidance and growth (Chow *et al.*, 1985; Halliday *et al.*, 1986; Graf *et al.*, 2000). The genotype-phenotype correlations for neurological abnormalities in L1 syndrome are well characterized (Vos *et al.*, 2010), and generally depend on whether homophilic L1CAM interactions or heterophilic interactions are disrupted (De Angelis *et al.*, 1999, 2002; Itoh *et al.*, 2011).

In addition to genetic causes, it is likely that a significant proportion of cases with ACC are caused by environmental insults. One example of this is foetal alcohol spectrum disorders, which can present with either complete or partial ACC, or callosal hypoplasia (Riley *et al.*, 1995). Early exposure to alcohol has been proposed to result in an overall decrease in white matter volume and organization, and structural abnormalities including ACC (Spadoni *et al.*, 2007). Alcohol exposure silences growth cone responses to guidance cues such as SEMA3A and netrin 1, which are involved in corpus callosum development (Sepulveda *et al.*, 2011). These features are similar to the L1 syndrome spectrum; ethanol inhibits L1CAM-mediated cell–cell adhesion (Charness *et al.*, 1994; Ramanathan *et al.*, 1996) and neurite outgrowth (Bearer *et al.*, 1999), suggesting that a comparable axon growth/guidance defect is common to both syndromes.

Abnormal post-guidance development

Synaptogenesis and synaptic specificity are usually achieved by a combination of molecular recognition and activity-dependent signals that prune initially formed synapses. The mechanisms by which callosal axons make specific synaptic connections are likely to be dependent on the origin and target of callosal axons and the functional information that will be transmitted. Andermann syndrome is one of a small group of neurodevelopmental disorders known to result from an ion transporter defect, namely homozygous mutations in *SLC12A6* encoding the K–Cl transporter KCC3 (Howard *et al.*, 2002). It is also a member of an interesting group of ACC-associated syndromes that feature nervous system degeneration post-natally. Andermann syndrome has presented in neuroimaging studies as a primary defect in axonal growth/guidance (Dupre *et al.*, 2003). It has been suggested that loss of KCC3 in migrating callosal neurons increases their susceptibility to damage early in development. In support of this hypothesis, homozygous SLC12A6 loss of function mice display callosal hypoplasia, but no specific abnormality in callosal development has been identified (Shekarabi *et al.*, 2012). It may also be the case that activity-dependent mechanisms are one aspect of callosal development in which humans and mice differ.

ACC has been noted in several enzyme deficiencies affecting cellular metabolism, including pyruvate dehydrogenase deficiency (Patel *et al.*, 2012), fumarase deficiency (Coughlin *et al.*, 1998; Mroch *et al.*, 2012), desmosterolosis (Zolotushko *et al.*, 2011) and Smith-Lemli-Opitz syndrome (Garcia *et al.*, 1973; Fierro *et al.*,

1977). The causative link between cellular metabolism disorders and callosal agenesis is unclear, although the majority of callosal abnormalities are hypoplastic, and may be secondary to post-natal CNS development or white matter injury (Bamforth *et al.*, 1988; Weinstein *et al*., 2003). Deficient cholesterol synthesis, in particular, has been linked with abnormal neurological development. Desmosterolosis results from homozygous or compound heterozygous mutations in *DHCR24*, and ACC has been reported in all cases where imaging has been performed (Zolotushko *et al.*, 2011). Desmosterolosis shares midline neurological defects with Smith-Lemli-Opitz syndrome, which results from homozygous mutations in *DHCR7* (Fitzky *et al.*, 1998; Jira *et al.*, 2003). In addition to its role in myelination, cholesterol is required for post-translational modification of the ventral morphogen SHH (Grover *et al.*, 2011), and therefore has a direct role in neural patterning.

Agenesis of the corpus callosum as a result of copy number variations

Despite the progress made in identifying and characterizing single-gene Mendelian disorders associated with ACC, a clear genetic cause will not be identified in the majority of patients (Bedeschi *et al.*, 2006; Schell-Apacik *et al.*, 2008). Improved and increased use of microarray comparative genomic hybridization has resulted in the identification of multiple rare copy number variants associated with ACC, and this genotype-to-phenotype diagnostic approach has resulted in a series of new recognizable disorder spectrums (Table 4 and Supplementary Table 1). A recent analysis of cytogenic, fluorescence *in situ* hybridization and microarray studies of 374 patients with reported or confirmed ACC identified many new loci associated with ACC and demonstrated the power of this approach (O'Driscoll *et al.*, 2010).

One of the most notable copy number variants associated with callosal agenesis is 1q42-q44 deletion syndrome, which is strongly associated with ACC of variable severity and post-natal microcephaly (O'Driscoll *et al.*, 2010). The major locus within this region appears to be 1q44, which contains the *AKT3* gene. Over 90% of patients with ACC and microcephaly were found to have a disrupted *AKT3*, a gene shown to promote neuronal survival in mouse models (Tschopp *et al.*, 2005; Boland *et al.*, 2007; Hill *et al.*, 2007; Merritt *et al.*, 2007). Although dysregulation of the PI3K/AKT-signalling pathway may explain the apparent proliferative/apoptotic abnormality, some patients have presented with 1q42-44 deletions outside the *AKT3* gene (Poot *et al.*, 2007; van Bon *et al.*, 2008; Malan *et al.*, 2010), suggesting that at least one more neurodevelopmental gene exists within the locus. Haploinsufficiency of other genes, such as *DISP1* located in 1q41, has been suggested as a cause of midline developmental defects. In particular, *ZBTB18* is a promising candidate, as one patient with post-natal microcephaly and ACC was found to have a reciprocal translocation with a breakpoint between *AKT3* and *ZBTB18* (Boland *et al.*, 2007; Perlman *et al*., 2013). In reality, there are likely multiple genes involved, reflecting combined defects in both midline and lateral axis patterning (Filges *et al.*, 2010; O'Driscoll *et al.*, 2010).

In some cases, phenotypic effects of microdeletions or microduplications are likely to result from the disruption of the synergistic action of two or more genes. Miller-Dieker lissencephaly syndrome is a contiguous gene deletion syndrome involving genes within the chromosome 17p13.3 region (Cardoso *et al.*, 2003; Nagamani *et al.*, 2009; Bruno *et al.*, 2010; Mignon-Ravix *et al.*, 2010). Miller-Dieker syndrome is characterized by a combination of classic lissencephaly, microcephaly, seizures and facial dysmorphisms, and is more severe than isolated lissencephaly. In both isolated lissencephaly and Miller-Dieker syndrome, the *LIS1* gene is affected, and the more severe phenotype in Miller-Dieker syndrome has been attributed to deletion of the *YWHAE* gene distal to *LIS1* (Bruno *et al.*, 2010). Both genes are involved in neuronal migration, and interact indirectly through the CDK5 substrate NDEL1 (Niethammer *et al.*, 2000; Toyo-oka *et al.*, 2003). Interestingly, patients with 17p13.3 microduplications present within the autistic spectrum, which is more severe when *LIS1*, but not *YWHAE*, is duplicated, suggesting that interactions between the proteins are related to the pathogenesis of the syndrome (Bruno *et al.*, 2010).

8p rearrangements are frequently associated with brain malformations (Robinow *et al.*, 1989; Newton *et al.*, 1993; Schrander-Stumpel *et al.*, 1994; Winters *et al.*, 1995; O'Driscoll *et al.*, 2010). The 8p inverted duplication/deletion is one of the most common and results in brain malformations including ACC and speech problems (O'Driscoll *et al.*, 2010). Fifteen cases of mosaic tetrasomy of 8p have also been described, of which ACC was identified in 10 (Wilson *et al.*, 2010). A recent review of the imaging literature confirmed ACC in 25% of published 8p rearrangements reported with callosal agenesis (O'Driscoll *et al.*, 2010), although variations in penetrance exist depending on the type of rearrangement. As ACC is apparently most common in inversion duplication/deletions (O'Driscoll *et al.*, 2010), it is likely that at least two loci exist, one that contributes to ACC when deleted, and another that contributes to ACC when duplicated. This explanation is supported by the recent description of ACC in two patients with 8p duplications only (Nieh *et al.*, 2012; Sajan *et al*., 2013).

1p36 deletion syndrome (monosomy 1p36) is one of the most common chromosome deletions (incidence is 1 in 5000), but has a relatively low penetrance of ACC (5.8%; Table 3) (Gajecka *et al.*, 2007; Bahi-Buisson *et al.*, 2008; Battaglia *et al.*, 2008). The phenotypic diversity of this syndrome and apparent lack of genotype-phenotype correlations illustrate the complexity of contiguous gene syndromes. Common neurological features include pachygyria, polymicrogyria, hydrocephalus and ACC (Gajecka *et al.*, 2007; Battaglia *et al.*, 2008). It has been suggested that haploinsufficiency of functionally unrelated but contiguous genes is responsible for some phenotypic variability (Redon *et al.*, 2005; Rosenfeld *et al.*, 2010); however, the expression of long-distance genes may also be affected through a positional effect of the deletion (Giannikou *et al.*, 2012). Epigenetic and modifier factors may contribute to the phenotype, and herein lies a major difficulty in pinpointing causative genes in contiguous deletions. The haploinsufficiency of one gene in 1p36 deletions, *SKI*, is of particular interest for ACC (Colmenares *et al.*, 2002; Rosenfeld *et al.*, 2010)

Table 3 Genes associated with human ACC syndromes

Syndrome	Gene (HGNC approved symbol)	OMIM number	HGNC ID	Cytogenic Location (human)	Human phenotype		Mouse phenotype				References[a]
					ACC penetrance	Salient features	Callosal phenotype		Associated midline defects		
							Complete ACC	Partial ACC	Midline glia	Hippocampal commissure	Anterior commissure	
GROUP I - Abnormal neuronal and/or glial proliferation												
ACC with mental retardation, ocular coloboma, and micrognathia	Immunoglobulin binding protein 1 (IGBP1)	300139	5461	Xq13.1	Defining feature	ACC, iris/optic nerve coloboma, mental retardation			n.d			Graham *et al.*, 2003
Alpha thalassemia/mental retardation syndrome X-linked	Alpha thalassemia/mental retardation syndrome X-linked (ATRX)	300032	886	Xq21.1	Uncommon	Developmental delay, α-thalassemia, cerebral atrophy			n.d			Gibbons *et al.*, 1995*a*, *b*; Villard *et al.*, 1996; Gibbons and Higgs, 2000; Berube *et al.*, 2005
Aniridia	Paired box 6 (PAX6)	607108	8620	11p13	2/20 (10%)	Aniridia, cataract, glaucoma, anterior commissure agenesis	N	Y		Y		Jones *et al.*, 2002; Bamiou *et al.*, 2007; Abouzeid *et al.*, 2009
Chudley-McCullough syndrome	G protein signalling modulator 2 (GPSM2)	609245	29501	1p13.3	Defining feature	Sensorineural deafness, ACC, interhemispheric cyst, cerebral/cerebellar dysplasias			n.d			Nadkarni *et al.*, 2008; Alrashdi *et al.*, 2011; Diaz-Horta *et al.*, 2012; Doherty *et al.*, 2012
Coffin Siris syndrome	AT-rich interaction domain-containing protein 1B (ARID1B)	614556	18040	6q25.3	9/42 (21%)	Developmental delay, coarse facial appearance, hirsutism, hypoplastic or absent fifth distal phalanges, and microcephaly			n.d			Reversade *et al.*, 2009; Mohamed *et al.*, 2011 Santen *et al.*, 2012; Schrier *et al.*, 2012; Tsurusaki *et al.*, 2012
Cutis laxa, autosomal recessive, type IIB/IIIB	Pyrroline-5-carboxylate reductase 1 (PYCR1)	179035	9721	17q25.3	Common	Microcephaly, failure to thrive			n.d			Reversade *et al.*, 2009; Mohamed *et al.*, 2011
Growth retardation with deafness and mental retardation due to IGF1 deficiency	Insulin-like growth factor I (IGF1)	147440	5464	12q23.2	Uncommon	Poor growth, microcephaly, micrognathia, sensorineural deafness, mental retardation	N	Y			Y	Beck *et al.*, 1995; Ye *et al.*, 2002
Lujan-Fryns syndrome	Mediator complex subunit 12 (MED12)	300188	11957	Xq13.1	Unknown	Marfanoid habitus, mental retardation, ACC			n.d			Jeret *et al.*, 1987; Lerma-Carrillo *et al.*, 2006
Marshall-Smith syndrome	Nuclear factor I/X (NFIX)	164005	11957	19p13.3	8/39 (21%)	Macrogyria, cerebral atrophy, ACC	N	Y	N			Driller *et al.*, 2007; Campbell *et al.*, 2008; Malan *et al.*, 2010; Shaw *et al.*, 2010
Meckel syndrome	RPGRIP1-Like (RPGRIP1L) TMEM67 MKS1, TMEM216, CEP290, CC2D2A, NPHP3, TCTN2, B9D1, B9D2	610937 609884	29168 28396	16q12.2 8q22.1	4/7 (57%)	Chiari malformation, Dandy-Walker malformation, hydrocephalus, cerebral hypoplasia	Y Y (wpk rat)	Y Y (wpk rat)	n.d			Paetau *et al.*, 1985; Smith *et al.*, 2006*a*; Delous *et al.*, 2007
Microcephalic osteodysplastic primordial dwarfism, type I/III	RNA, U4atac small nuclear (U12-dependent splicing) (RNU4ATAC)	601428	34016	2q14.2	5/9 (56%)	Failure to thrive, short stature, microcephaly, pachygyria, heterotopias, ACC			n.d			Abdel-Salam *et al.*, 2011; Juric-Sekhar *et al.*, 2011

(continued)

Table 3 Continued

Syndrome	Gene (HGNC approved symbol)	OMIM number	HGNC ID	Cytogenic Location (human)	Human phenotype		Mouse phenotype				References[a]
					ACC penetrance	Salient features	Callosal phenotype		Associated midline defects		
							Complete ACC	Partial ACC	Midline glia	Hippocampal commissure	Anterior commissure	
Microcephaly 2, primary, autosomal recessive, with or without cortical malformations	WD repeat domain 62 (WDR62)	604317	24502	19q13.12	Uncommon	Microcephaly, pachygyria, callosal hypoplasia			n.d			Bilguvar *et al.*, 2010; Yu *et al.*, 2010
Microcephaly 5, primary, autosomal recessive	Asp (abnormal spindle) homolog, microcephaly associated (Drosophila) (ASPM)	605481	19048	1q31.3	3/12 (25%)	Simplified gyral pattern, ventriculomegaly, partial ACC			n.d			Bond *et al.*, 2002; Passemard *et al.*, 2009
Mowat-Wilson syndrome	Zinc finger E-box binding homeobox 2 (ZEB2)	605802	14881	2q22.3	67/155 (43%)	Mental retardation, seizures, microephaly Hypoplasia of the corpus callosum, ACC, microcephaly	Y	N				Amiel *et al.*, 2001; Cacheux *et al.*, 2001; Mowat *et al.*, 2003; Dastot-Le Moal *et al.*, 2007; Miquelajauregui *et al.*, 2007
Opitz–Kaveggia syndrome	Mediator complex subunit 12 (MED12)	300188	11957	Xq13.1	14/28 (50%); 13/13 (100%) for p.R961W mutation	Seizures, hydrocephalus, agenesis of corpus callosum, heterotopia, dysmorphic facies			n.d			Graham *et al.*, 1999; Risheg *et al.*, 2007; Graham *et al.*, 2008; Rump *et al.*, 2011
Perlman syndrome	DIS3 mitotic control homolog (S. cerevisiae)-like 2 (DIS3L2)	614184	267000	2q37.1	Unknown	Polyhydramnios, neonatal macrosomia, visceromegaly, renal dysplasia, Wilms tumour			n.d			Alessandri *et al.*, 2008; Astuti *et al.*, 2012
Rubinstein-Taybi syndrome	CREB-binding protein (CREBBP)	600140	2348	16p13.3	Uncommon	Mental retardation, ACC, post-natal growth deficiency, dysmorphic facies			n.d			Petrij *et al.*, 1995; Tsai *et al.*, 2001; Roelfsema *et al.*, 2005; Wojcik *et al.*, 2010
	E1A binding protein p300 (EP300)	602700	3373	22q13.2					n.d			
Seckel syndrome	Ataxia telangiectasia and Rad3 related (ATR)	601215	882	3q23	Common	Microcephaly, cerebellar vermis hypoplasia, dwarfism	Y (100%)					Shanske *et al.*, 1997; Capovilla *et al.*, 2001; Murga *et al.*, 2009; Thapa and Mukherjee, 2010; Juric-Sekhar *et al.*, 2011
	RBBP8, SCKL3, CENPJ, CEP152, CEP63, NIN						n.d					
Septo-optic dysplasia	HESX homeobox 1 (HESX1)	601802	4877	3p14.3	Common	Absent septum pellucidum, ACC, pituitary dysplasia, optic nerve hypoplasia	Y (75%)	Y (25%)		Y (50%)	Y (75%)	Dattani *et al.*, 1998; Kelberman and Dattani, 2008
Sotos syndrome 1	Nuclear receptor binding SET domain protein 1 (NSD1)	606681	14234	5q35	1/51 (2%)	Macrocephaly, mental retardation, seizures, corpus callosum hypoplasia, ventriculomegaly			n.d			Schaefer *et al.*, 1997; Bedeschi *et al.*, 2006; Driller *et al.*, 2007; Campbell *et al.*, 2008; Malan *et al.*, 2010
Sotos syndrome 2	Nuclear factor I/X (NFIX)	164005	7788	19p13.3			N	Y	N			

(continued)

Table 3 Continued

Syndrome	Gene (HGNC approved symbol)	OMIM number	HGNC ID	Cytogenic Location (human)	Human phenotype		Mouse phenotype					References[a]
					ACC penetrance	Salient features	Callosal phenotype		Associated midline defects			
							Complete ACC	Partial ACC	Midline glia	Hippocampal commissure	Anterior commissure	
GROUP II - Abnormal midline patterning												
Acrocallosal syndrome	GLI family zinc finger 3 (GLI3)	165240	4319	7p13	Defining feature	ACC and/or Dandy-Walker malformation	N	Y				Elson *et al.*, 2002; Putoux *et al.*, 2011; 2012; Wang *et al.*, 2011
	Kinesin family member 7 (KIF 7)	611254	30497	15q26.1					n.d			
Apert syndrome	Fibroblast growth factor receptor 2 (FGFR2)	176943	3689	10q26.13	23%	ACC, ventriculomegaly, no septum pellucidum, Chiari I malformation	Y (66%)			Y		Wilkie *et al.*, 1995; Slaney *et al.*, 1996; Quintero-Rivera *et al.*, 2006; Stevens *et al.*, 2010
COACH syndrome	Transmembrane protein 67 (TMEM67)	609884	28396	8q22.1	6/71 (8.5%)	Cerebellar vermis dysplasia, mental retardation, ocular coloboma, hepatic fibrosis	Y (wpk rat)	Y (wpk rat)				Smith *et al.*, 2006*a*; Arts *et al.*, 2007; Delous *et al.*, 2007; Brancati *et al.*, 2009; Doherty *et al.*, 2010
	RPGRIP1-like (RPGRIP1L)	610937	29168	16q12.2			Y	Y				
	Coiled-coil and C2 domain containing 2A (CC2D2A)	612013	29253	4p15.33					n.d			
Donnai-Barrow Syndrome	Low density lipoprotein receptor-related protein 2 (LRP2)	600073	6694	2q31.1	Common	Sensorineural deafness, ACC, congenital diaphragmatic hernia	Y (90%)					Willnow *et al.*, 1996; Kantarci *et al.*, 2007
Greig cephalopolysyndactyly syndrome	GLI family zinc finger 3 (GLI3)	165240	4319	7p13	Uncommon	Hydrocephalus, ACC, polydactyly	N	Y				Hootnick and Holmes, 1972; Marafie *et al.*, 1996; Wild *et al.*, 1997; Kalff-Suske *et al.*, 1999; Wang *et al.*, 2011
Hydrolethalus syndrome (HLS)	Kinesin family member 7 (KIF 7)	611254	30497	15q26.1	Defining feature	Hydrocephalus, olfactory aplasia, fused thalami, hypothalamic hamartoma, polymicrogyria, lissencephaly II, ACC			n.d			Mee *et al.*, 2005; Paetau *et al.*, 2008; Putoux *et al.*, 2011
	Hydrolethalus syndrome 1 (HYLS1)	610693	26558	11q24					n.d			
Hypogonadotropic hypogonadism with or without anosmia	Heparan sulfate 6-O-sulfotransferase 1 (HS6ST1)	604846	5201	2q21	Uncommon; potentially more common in Kallmann syndrome type 2	Hypogonadotropic hypogonadism, olfactory lobe agenesis, hyposmia or anosmia, mirror hand movements (bimanual synkinesia), ataxia	Y (100%)		Y			Huffman *et al.*, 2004; Dode *et al.*, 2006; Smith *et al.*, 2006*b*; Tole *et al.*, 2006; Conway *et al.*, 2011
	Fibroblast growth factor receptor 1 (FGFR1)	136350	3688	8p11.23-p11.22			Y		Y	Y	Y	
	Fibroblast growth factor 8 (FGF8)	600483	3686	10q24.32			Y					
	KAL1, GNRHR, KISS1R, NSMF, TAC3, TACR3,GNRH1, KISS1, WDR11, SEMA3A											
Joubert syndrome	Kinesin family member 7 (KIF7)	611254	30497	15q26.1	6/71 (8.5%)	Dysplasia of brainstem, cerebellar vermis hypoplasia, molar tooth sign, distinctive facies, hypotonia/ataxia			n.d			Smith *et al.*, 2006*a*; Baala *et al.*, 2007; Doherty *et al.*, 2010; Dafinger *et al.*, 2011; Poretti *et al.*, 2011
	RPGRIP1-Like (RPGRIP1L)	610937	29168	16q12.2			Y	Y				
	Transmembrane protein 67 (TMEM67)	609884	28396	8q22.1			Y (wpk rat)	Y (wpk rat)				
	INPP5E, TMEM216, AHI1, NPHP1, CEP290, ARL13B, CC2D2A, OFD1, TECT1, TMEM237, CEP41, TMEM138, CTBP1-AS1, TCTN3								n.d			

(continued)

Table 3 Continued

Syndrome	Gene (HGNC approved symbol)	OMIM number	HGNC ID	Cytogenic Location (human)	Human phenotype		Mouse phenotype				References[a]
					ACC penetrance	Salient features	Callosal phenotype		Associated midline defects		
							Complete ACC	Partial ACC	Midline glia	Hippocampal commissure	Anterior commissure
GROUP III- Abnormal callosal neuron migration and/or specification											
Complex cortical dysplasia with other brain malformations	Tubulin, beta 3 class III (TUBB3)	602661	20772	16q24	2/9 (22.2%)	Polymicrogyria, gyral simplification, dysplastic cerebellar vermis, hypoplastic brainstem, ACC, fusion of basal ganglia			n.d			Poirier *et al.*, 2010
Congenital fibrosis of extraocular muscles 3A with extraocular involvement	Tubulin, beta 3 class III (TUBB3)	602661	20772	16q24	2/8 (25%)	Congenital fibrosis of the extraocular muscles, ACC, peripheral neuropathy			n.d			Tischfield *et al.*, 2010
FG syndrome	Filamin A, aplha (FLNA) Calcium/calmodulin-dependent serine protein kinase (MAGUK family) (CASK)	300017 300172	3754 1497	Xq28 Xp11.4	50% (14/28)	See Opitz-Kaveggia syndrome			n.d n.d			Graham *et al.*, 1999; Unger *et al.*, 2007
Lissencephaly 2	Reelin (RELN)	600514	9957	7q22	33%	Microcephaly, inversion of cortical layers, thick cerebral cortex	N	N				Kara *et al.*, 2010
Lissencephaly 3	Tubulin alpha 1A (TUBA1A)	602529	20766	21q13.2	50% (4/8)	Cerebellar and hippocampal dysplasia, ACC, seizures			n.d			Poirier *et al.*, 2007
Lissencephaly 4	NudE nuclear distribution E homolog 1 (A. nidulans) (NDE1)	609449	17619	16p13.11	4/6 (67%)	Extreme microcephaly, lissencephaly, brain atrophy	N	N				Alkuraya *et al.*, 2011; Bakircioglu *et al.*, 2011
Muscular dystrophy-dystroglycanopathy type A	POMT1, POMGNT1, POMT2, GTDC2, ISPD, FKTN, FKRP, LARGE				Unknown	Eye defects, ACC, cobblestone lissencephaly type 2			n.d			Dobyns *et al.*, 1989; Villanova *et al.*, 1998; van Reeuwijk *et al.*, 2005; Judas *et al.*, 2009
Polymicrogyria, symmetric or asymmetric	TUBB2B	612850	30829	6p25.2	100% (6/6)	Asymmetric polymicrogyria, ACC, cerebellar hypoplasia, brainstem abnormalities			n.d			Jaglin *et al.*, 2009; Romaniello *et al.*, 2012
Proud syndrome	Aristaless related homeobox (ARX)	300382	18060	Xp21.3	Defining feature	Mental retardation with ACC, microcephaly, limb contractures, scoliosis, coarse facies, tapered digits, and urogenital abnormalities	N	Y		Y		Kitamura *et al.*, 2002; Kato *et al.*, 2004
Schizophrenia	Disrupted in schizophrenia 1 (DISC1)	605210	2888	1q42.1	Uncommon	Multiple loci involved, hallucinations/delusions	N	Y (100%)			N	Shen *et al.*, 2008; Osbun *et al.*, 2011
X-linked dominant periventricular heterotopia	Filamin A, alpha (FLNA)	300017	3754	Xq28	Uncommon	Mild mental retardation, seizures, subependymal periventricular heterotopic nodules, cardiovascular abnormalities			n.d			Fox *et al.*, 1998; Poussaint *et al.*, 2000; Sheen *et al.*, 2001
X-linked lissencephaly 1	Doublecortin (DCX)	300121	2714	Xq22.3-23	Uncommon	Lissencephaly, subcortical band or laminar heterotopia (in female carriers), malformation of the insula, ACC	Y[b]	Y[b]		Y[b]	Y[b]	Gleeson *et al.*, 1998; Koizumi *et al.*, 2006*a*; Chou *et al.*, 2009

(continued)

Table 3 Continued

Syndrome	Gene (HGNC approved symbol)	OMIM number	HGNC ID	Cytogenic Location (human)	Human phenotype		Mouse phenotype				References[a]
					ACC penetrance	Salient features	Callosal phenotype		Associated midline defects		
							Complete ACC	Partial ACC	Midline glia	Hippocampal commissure	Anterior commissure	
X-linked lissencephaly 2 (XLAG)	Aristaless related homeobox (ARX)	300382	18060	Xp21.3	Defining feature	Ambiguous genitalia, mental retardation, neonatal seizures, lissencephaly, pachygyria/agyria, ACC	N	Y		Y		Kitamura *et al.*, 2002; Stromme *et al.*, 2002; Kato *et al.*, 2004; Friocourt *et al.*, 2008; Kara *et al.*, 2010
X-linked subcortical laminar heteropia	Doublecortin (DCX)	300121	2714	Xq22.3-23	Common	See X-linked lissencephaly 1	Y[b]	Y[b]		Y[b]	Y[b]	des Portes *et al.*, 1998*a*, *b*; Gleeson *et al.*, 1998; Koizumi *et al.*, 2006*b*
GROUP IV- Abnormal axon growth and/or guidance												
Craniofrontonasal syndrome	Ephrin B1 (EFNB1)	300035	3226	Xq13.1	6/58 (10%)	Developmental delay, corpus callosum hypoplasia, diaphragmiatic and umbilical hernias; more severe phenotype in females	Y		Y		N	Twigg *et al.*, 2004; Wieland *et al.*, 2004; 2005; Wieacker and Wieland, 2005
L1 Syndrome spectrum (HSAS/MASA)	L1 cell adhesion molecule (L1CAM)	308840	6470	Xq28	Common	Phenotypic spectrum ranging from partial ACC to hydrocephalus and complete ACC	Y (17%)	Y (83%)			N	Demyanenko *et al.*, 1999
Syndromic micropthalmia	Ventral anterior homeobox 1 (VAX1) BCOR, SOX2, ANOP1, OTX2, BMP4, HCCS, STRA6	604294	12660	10q26.11	Unknown	Hypothalamic hamartoma, generalized white matter reduction, ACC, anterior pituitary hypoplasia, cardiovascular abnormalities	Y	N	n.d	Y	Y	Bertuzzi *et al.*, 1999; Slavotinek *et al.*, 2012
GROUP V - Abnormal post-guidance development												
Andermann syndrome	Solute carrier family 12 (potassium/chloride transporters), member 6 (KCC3)	604878	10914	15q13	Defining feature	Peripheral neuropathy and ACC, ventriculomegaly, axonal neuropathy (PNS), dysmorphic facies	N	N				Larbrisseau *et al.*, 1984; Howard *et al.*, 2002; Dupre *et al.*, 2003; Shekarabi *et al.*, 2012
Autosomal recessive spastic paraplegia 11	Spastic paraplegia 11 (autosomal recessive) (SPG11)	610844	11226	15q13-q15	Uncommon	Progressive weakness/ spasticity of lower limbs, mental retardation, corpus callosum hypoplasia			n.d			Stevanin *et al.*, 2007, 2008; Southgate *et al.*, 2010
Desmosterolosis	24-dehydrocholesterol reductase (DHCR24)	606418	2859	1p32.3	100% (5/5)	Seizures, ventriculomegaly, hydrocephalus, decreased white matter, partial or complete ACC			n.d			FitzPatrick *et al.*, 1998; Schaaf *et al.*, 2011; Zolotushko *et al.*, 2011
Micropthalmia with linear skin defects (MLS) syndrome	Holocytochrome C synthase (HCCS)	300056	4837	Xp22.2	14/40 (35%)	Bilateral microphthalmia, linear skin defects			n.d			Prakash *et al.*, 2002; Sharma *et al.*, 2008
Pontocerebellar hypoplasia 9	Adenosine monophosphate deaminase 2 (AMPD2)	102771	469	1p13.3	100%	Cerehellar and pontin hypoplasia, progressive microcephaly, limb spasticity, ACC			n.d			Akizu *et al.*, 2013*a*
Pyruvate dehydrogenase deficiency	Pyruvate dehydrogenase (lipoamide) alpha 1 (PDHA1)			Xp22.1	31%	Lactic acidosis, cerebral atrophy, ventricular dilatation, ACC			n.d			Patel *et al.*, 2012
	Pyruvate dehydrogenase (lipoamide) beta (PDHB)	179060	8808	3p21.1-p14.2					n.d			

(continued)

Table 3 Continued

Syndrome	Gene (HGNC approved symbol)	OMIM number	HGNC ID	Cytogenic Location (human)	Human phenotype		Mouse phenotype				References[a]
					ACC penetrance	Salient features	Callosal phenotype		Associated midline defects		
							Complete ACC	Partial ACC	Midline glia	Hippocampal commissure	Anterior commissure
Unclear function in corpus callosum development											
Coffin-Lowry syndrome	Ribosomal protein S6 kinase, 90 kDa, polypeptide 3 (RPS6KA3)	300075	10432	Xp22	Unknown	Sensorineural hearing loss, skeletal malformations, cognitive impairment			n.d		Soekarman and Fryns, 1993
Fumarase deficiency	Fumarate hydratase (FH)	136850	3700	1q42.1	Uncommon	Polymicrogyria, ACC, relative macrocephaly, fumaric aciduria			n.d		Bourgeron *et al.*, 1994; Kerrigan *et al.*, 2000
Genitopatellar syndrome	K(lysine) acetyltransferase 6B (KAT6B)	605880	17582	10q22	11/14 (77%)	Absent/hypoplastic patellae, lower extremity contractures, urogenital anomalies			n.d		Goldblatt *et al.*, 1988; Cormier-Daire *et al.*, 2000; Penttinen *et al.*, 2009; Brugha *et al.*, 2011; Campeau *et al.*, 2012
Opitz G/BBB syndrome type I (X-linked)	Midline 1 (Opitz/BBB syndrome) (MID1)	300552	7095	Xp22	Unknown	Developmental delay, ACC, dysmorphic facies			n.d		Fontanella *et al.*, 2008
Oro–facio–digital syndrome type 1	Oral-facial-digital syndrome 1 (OFD1)	300170	2567	Xp22	Unknown	Oral, facial and digital malformations, polycystic kidney disease			n.d		Towfighi *et al.*, 1985; Connacher *et al.*, 1987
Pitt-Hopkins syndrome	Transcription factor 4 (TCF4)	602272	11634	18q21.1	Unknown	Severe mental retardation, hyperventilation episodes,			n.d		Amiel *et al.*, 2001; Whalen *et al.*, 2012
Smith-Lemli-Opitz syndrome	7-dehydrocholesterol reductase (DHCR7)	602858	2860	11q13.4	Uncommon	Mental retardation, autistic features, microcephaly, periventricular heterotopia			n.d		Garcia *et al.*, 1973; Fierro *et al.*, 1977; Fitzky *et al.*, 1998
TARP syndrome	RNA-binding motif protein 10 (RBM10)	300080	9896	Xp11.23	Uncommon	Congenital heart defect, clubfoot, cleft palate, glossoptosis, micrognathia		Y			Johnston *et al.*, 2010; Gripp *et al.*, 2011
Temtamy syndrome	Chromosome 12 open reading frame 57 (C12ORF57)	615140	29521	12p13.31	Common	Craniofacial dysmorphism, absent corpus callosum, and iris coloboma			n.d		Temtamy and Sinbawy, 1991; Temtamy *et al.*, 1996; Chan *et al.*, 2000; Talisetti *et al.*, 2003; Li *et al.*, 2007; Akizu *et al.*, 2013*b*
Vici syndrome	Ectopic P-granules autophagy protein 5 homolog (C. elegans) (EPG5)	615068	29331	18q12.3	100%	Combined immunodeficiency, poor post-natal growth, cleft lip and palate, hypopigmentation of skin and hair, ACC			n.d		Vici *et al.*, 1988; del Campo *et al.*, 1999; Chiyonobu *et al.*, 2002; Miyata *et al.*, 2007; Al-Owain *et al.*, 2010; McClelland *et al.*, 2010; Rogers *et al.*, 2011; Callup *et al.*, 2013
Warburg micro syndrome	RAB3GAP1, RAB3GAP2, RAB18				Unknown	Microcephaly, mental retardation, hypogenitalism			n.d		Aligianis *et al.*, 2005

[a]References in the table that are not included in the reference list can be found in the Supplementary material.
[b]Only in DCX/DCLK double knockouts; n.d, no data.
[#]For syndromes to be considered, the following criteria had to be met: at least three patients with the syndrome had been documented, of whom at least two displayed complete or partial ACC. Syndromes in which callosal abnormalities were secondary to more severe neural defects such as holoprosencephaly were excluded. ACC penetrance was determined by considering case reports and previous imaging studies.

Table 4 Major copy number variants associated with ACC in humans

	Candidate genes for ACC	MIM Phenotype number	Callosal abnormality penetrance	Salient features	References[a]
1p36 deletion	TMEM52, C1ORF222, KIAA1751, GABRD, PRKCZ, SKI	607872	5.8%	Corpus callosum hypoplasia, diffuse white matter reduction, periventricular nodular heterotopia	Neal *et al.*, 2006; Gajecka *et al.*, 2007; Bahi-Buisson *et al.*, 2008; Battaglia *et al.*, 2008; O'Driscoll *et al.*, 2010; Rosenfeld *et al.*, 2010
1p32-p31 deletion	NFIA	613735	2/6 (33%)	Hypoplasia or agenesis of the corpus callosum, tethered spinal cord, urinary tract defects	Lu *et al.*, 2007; Koehler *et al.*, 2010
1q42-q44 deletion	AKT3, DISP1, HNRNPU, FAM36A, ZBTB18, NCRNA00201	612337	12/15 (80%)	Micrognathia, post-natal microcephaly, ACC	De Vries *et al.*, 2001; Tschopp *et al.*, 2005; Boland *et al.*, 2007; Hill *et al.*, 2007; Merritt *et al.*, 2007; van Bon *et al.*, 2008; Thierry *et al.*, 2012; Zaki *et al.*, 2012
3q24-q25.3 deletion	ZIC1, GSK3B	N/A	Unknown	Not common enough to have a clear cluster of features	O'Driscoll *et al.*, 2010
4p16.3 deletion (Wolf-Hirschhorn syndrome)	WHSC1, LETM1, TACC3, SLBP, HSPX153, WHSC2, YOL027, MSR7, FGFR3 CPLX1, DGKQ, FGFRL1, CTBP1	194190	17/24 (71%)	Prenatal and post-natal growth deficiency, developmental disability, characteristic craniofacial features and seizures, microcephaly, dysgenic corpus callosum	Battaglia *et al.*, 1999; Tutunculer *et al.*, 2004; Bergemann *et al.*, 2005; Balci *et al.*, 2006; Righini *et al.*, 2007
6pter-p24 deletion (6p25 deletion included)	FOXC1, FOXF2, FOXQ1, TUBB2A, TUBB2B	612582	Unknown	Hydrocephalus, hypoplasia of the cerebellum, brainstem, and corpus callosum, Dandy-Walker malformation	Nishimura *et al.*, 1998; Maclean *et al.*, 2005; Aldinger *et al.*, 2009; O'Driscoll *et al.*, 2010
6q2 deletion	MARCKS, MAP3K4, NRE1, ARID1B, UST, TIAM2, SYNJ2	612863	5/20 (25%); 6q25.2–q25.3 microdeletion: 5/11 (45%)	Periventricular nodular heterotopia, polymicrogyria, cerebellar malformations, hydrocephalus, and ACC	Hopkin *et al.*, 1997; Eash *et al.*, 2005; Sherr *et al.*, 2005; Nagamani *et al.*, 2009
8p rearrangements	ARHGEF10, FZD3, FGFR1, FGF17, FGF20, NRG1	N/A	25%; 66% for mosaic tetrasomy 8p	Varies with rearrangement type; ACC appears commonly, with hydrocephaly	O'Driscoll *et al.*, 2010; Wilson *et al.*, 2010
9q34.3 deletion (Kleefstra syndrome)	EHMT1	610253	Uncommon (hypoplasia more common)	Ventriculomegaly, microcephaly, abnormal myelination	Schimmenti *et al.*, 1994; Knight *et al.*, 1999; Anderlid *et al.*, 2002; Dawson *et al.*, 2002; Cormier-Daire *et al.*, 2003; Font-Montgomery *et al.*, 2004; Harada *et al.*, 2004; Iwakoshi *et al.*, 2004; Stewart *et al.*, 2004; Yatsenko *et al.*, 2005
11q23-q25 duplication	NCAM1, ANKK1	N/A	Unknown	ACC, microcephaly and cerebellar malformations	Pihko *et al.*, 1981; O'Driscoll *et al.*, 2010
13q14 deletion syndrome	NUFIP1, HTR2A, PCDH8, PCDH17	613884	1/3	Hypoplasia of the corpus callosum, retinoblastoma, mental impairment	Caselli *et al.*, 2007; O'Driscoll *et al.*, 2010
13q32.3-q33.1 deletion	ZIC2, ZIC5, FGF14, TMTC4	N/A	Unknown	ACC, holoprosencephaly, cerebellum abnormalities	Brown *et al.*, 1993, 1995; Ballarati *et al.*, 2007; O'Driscoll *et al.*, 2010

(continued)

Table 4 Continued

	Candidate genes for ACC	MIM Phenotype number	Callosal abnormality penetrance	Salient features	References[a]
13q34 duplication	COL4A1, COL4A2, ARHGEF7, SOX1, ATP11A, MCF2L	N/A	Unknown	ACC, unspecified brain malformations	Witters *et al.*, 2009; O'Driscoll *et al.*, 2010
14q11-q22 deletion	FOXG1B, ARHGAP5	613457	Unknown	Corpus callosum hypoplasia and abnormal myelination	Schwarzbraun *et al.*, 2004; Ariani *et al.*, 2008; O'Driscoll *et al.*, 2010; Kortum *et al.*, 2011; Torgyekes *et al.*, 2011
14qter deletion	GARNL1	N/A	Unknown (hypoplasia more common)	Corpus callosum hypoplasia, polymicrogyria, heterotopia, and microcephaly	Schwarzbraun *et al.*, 2004; Schneider *et al.*, 2008; O'Driscoll *et al.*, 2010; Engels *et al.*, 2012
17p13.3 deletion (Miller-Dieker lissencephaly syndrome)	LIS1, YWHAE	613457	74% (27 patients)	Lissencephaly, microcephaly, micrognathia, bitemporal narrowing, short nose with up-turned nares, protuberant upper lip and a thin vermilion border, severe mental retardation and seizures	Dobyns *et al.*, 1991; Cardoso *et al.*, 2003; Toyo-oka *et al.*, 2003; Nagamani *et al.*, 2009; Bruno *et al.*, 2010
21q22.3 deletion	DYRK1A	145410	Unknown	Microcephaly, pachygyria, polymicrogyria, colpocephaly, corpus callosum hypoplasia and generalized white matter reduction	Moller *et al.*, 2008; O'Driscoll *et al.*, 2010
DiGeorge syndrome (22q11.2 deletion)	TBX1, COMT, UFD1L, RANBP1	188400	Uncommon	Delayed development, tetany, seizures	Kraynack *et al.*, 1999; Maynard *et al.*, 2003
Opitz G/BBB syndrome, autosomal dominant (22q11.2 deletion; Opitz phenotype)	TBX1, COMT, UFDL1, RANBP1	145410	Uncommon	Cerebellar vermal hypoplasia, cortical atrophy, ventriculomegaly, widened cavum septum pellucidum	Robin *et al.*, 1995; 1996; Maynard *et al.*, 2003
Xp21 deletion (Complex glycerol kinase deficiency)	GK, DMD, NR0B1	300679	2/10 (20%)	Mental retardation, severe developmental delay, hypotonia, seizures and progressive microcephaly	Stanczak *et al.*, 2007
Xq28 duplication syndrome	GDI1, MECP2	300815	Uncommon	Microcephaly, Dandy-Walker malformation, with agenesis of the cerebellar vermis and corpus callosum hypoplasia	Vandewalle *et al.*, 2009

[a]References in the table that are not included in the reference list can be found in the Supplementary material.

Table 5 ACC syndromes for which a causative gene has not been identified

	Inheritance	MIM Phenotype number	ACC penetrance	Salient features	References[a]
Aicardi syndrome	X-linked dominant	304050	100%	Microcephaly, periventricular and subcortical heterotopia, ACC	Aicardi *et al.*, 1965; Donnenfeld *et al.*, 1989; Smith *et al.*, 1996; Yamagata *et al.*, 1990; Barkovich *et al.*, 2001; Palmer *et al.*, 2006; Hopkins *et al.*, 2008
Cerebrofrontofacial syndrome	Unknown	608578	Unknown (few clearly delineated cases)	Grey matter heterotopia, white matter cysts,	Guion-Almeida and Richieri-Costa, 1992, 2001; Masuno *et al.*, 2000; Winter, 2001
Craniosynostosis-mental retardation syndrome of Lin and Gettig	Unknown	218649	3/3 (100%)	ACC, Chiari malformation type I	Lin and Gettig, 1990; Hedera and Innis, 2002
Curry-Jones syndrome	Unknown	601707	5/9 (56%)	ACC, polysyndactyly, skin defects	Temple *et al.*, 1995; Mingarelli *et al.*, 1999; Thomas *et al.*, 2006; Grange *et al.*, 2008
Ectodermal dysplasia, hypohidrotic, with hypothyroidism and agenesis of the corpus callosum	X-linked recessive^	225040	3/3 (100%)	ACC, primary hypothyroidism, hypohidrotic ectodermal dysplasia	Fryns *et al.*, 1989; Soekarman and Fryns, 1993; Devriendt *et al.*, 1996
Fryns syndrome	Autosomal recessive	229850	13.5%	Congenital diaphragmatic hernia, distal limb hypoplasia, pulmonary hypoplasia	Pinar *et al.*, 1994; Neville *et al.*, 2002; Slavotinek, 2004; Ludmiła *et al.*, 2010
Hartsfield syndrome	X-linked inheritance	300571	3/11 (27%)	Holoprosencephaly, etrodactyly, cleft lip/palate, complete or partial ACC	Imaizumi *et al.*, 1998; Corona-Rivera *et al.*, 2000; Vilain *et al.*, 2009; Zechi-Ceide *et al.*, 2009
Ivemark syndrome	Autosomal recessive	208530	Unknown	Asplenia, cardiovascular anomalies, ACC, malposition and maldevelopment of the abdominal organs	Kiuchi *et al.*, 1988; Rodriguez *et al.*, 1991; Devriendt *et al.*, 1997; Noack *et al.*, 2002
Marden-Walker syndrome	Autosomal recessive^	248700	Unknown	Microcephaly, hydrocephaly, ACC, cerebellar vermis hypoplasia, enlarged cisterna magna	Begum and Nayek, 2002; Ozbek *et al.*, 2005; Theys *et al.*, 2011
Macrocephaly with multiple epiphyseal dysplasia and distinctive facies	Autosomal recessive^	607131	2/4 (50%)	Dysmorphic facies, genu valgum, and swelling of the joints	al-Gazali and Bakalinova, 1998
Neu-Laxova Syndrome	Autosomal recessive	256520	24/71 (34%)	Microcephaly, lissencephaly, cerebellar hypoplasia and ACC	Manning *et al.*, 2004; Ugras *et al.*, 2006; Coto-Puckett *et al.*, 2010
Oculocerebrocutaneous syndrome	Unclear	164180	10/10 (100%)	Orbital cyst, ACC, frontal polymicrogyria, periventricular nodular heterotopia, ventriculomegaly or hydrocephalus	Moog *et al.*, 2005
Pai syndrome	Autosomal dominant^	155145	8/16 (50%)	Nasal cleft, facial skin polyps and CNS lipomas; ACC	Pai *et al.*, 1987; Preece *et al.*, 1988; Morgan and Evans, 1990; Rudnik-Schoneborn and Zerres, 1994; Mishima *et al.*, 1999; Al-Mazrou *et al.*, 2001; Coban *et al.*, 2003; Castori *et al.*, 2007; Guion-Almeida *et al.*, 2007; Vaccarella *et al.*, 2008
Sakoda complex	Unknown (likely X-linked)	610871	24/24 (100%)	Sphenoethmoidal encephalomeningocele, complete or partial ACC	Sakoda *et al.*, 1979; Ehara *et al.*, 1998; Dempsey *et al.*, 2007
Shapiro syndrome	Unknown	N/A	Defining feature	Recurrent episodes of hypothermia, hyperhidrosis, ACC	Shapiro *et al.*, 1969; Tambasco *et al.*, 2005; Shenoy, 2008
Toriello-Carey syndrome	Autosomal recessive^	217980	100%	Mental retardation, ACC, post-natal growth delay, cardiac defects, distal limb defects, micrognathia, microcephaly, facial abnormalities,	Toriello *et al.*, 2003; McGoey *et al.*, 2010
Lissencephaly type III with bone dysplasia	Autosomal recessive^	601160	4/7 (57%)	ACC and vermis agenesis, lissencephaly, hypoplastic brainstem, cystic cerebellum, ventriculomegaly and multicystic periventricular lesions	Encha Razavi *et al.*, 1996; Plauchu *et al.*, 2001

[a]References in the table that are not included in the reference list can be found in the Supplementary material.

as it was recently reported to functionally interact with SATB2 to specify callosally projecting neuron identity (Baranek *et al*., 2012).

Agenesis of the corpus callosum syndromes of unknown aetiology

Several ACC syndromes are yet to have causative genetic mutations identified (Table 5). Confirming the underlying genetic cause of inheritable syndromes is complicated by the high incidence of *de novo* mutations, genetic heterogeneity and difficulties achieving consistent clinical diagnosis.

Many of these syndromes are of interest because of the diversity of organ systems affected, which may allude to their underlying genetic aetiology. Curry-Jones syndrome is a rare disorder associated with ACC and ventriculomegaly, polysyndactyly, eye defects and malformations of the skin and gastrointestinal tract (Temple *et al*., 1995). Importantly, the association of this syndrome with the development of skin and CNS neoplasias has implicated the SHH signalling pathway in its pathogenesis. In addition, the defects in limb development seen in patients with Curry-Jones syndrome are similar to those reported in patients with confirmed mutations in the SHH signalling pathway (Johnston *et al*., 2005). If nothing else, Curry-Jones syndrome illustrates the necessity of investigating multiple organ systems if ACC is identified, as it often serves as a relatively easily identifiable phenotypic marker for wider developmental disturbances.

Aicardi syndrome is another multisystem disorder with a complex neurological phenotype, and is only observed in females (and XXY males). Neurological features incorporate severely disordered neuronal migration, ACC, infantile spasms and chorioretinal lacunae (Aicardi *et al*., 1965; Hopkins *et al*., 2008; Fig. 8). The interhemispheric and intrahemispheric mis-wirings that result from aberrant neuronal migration are profound. Diffusion tensor imaging has shown widespread disruption of corticocortical tracts

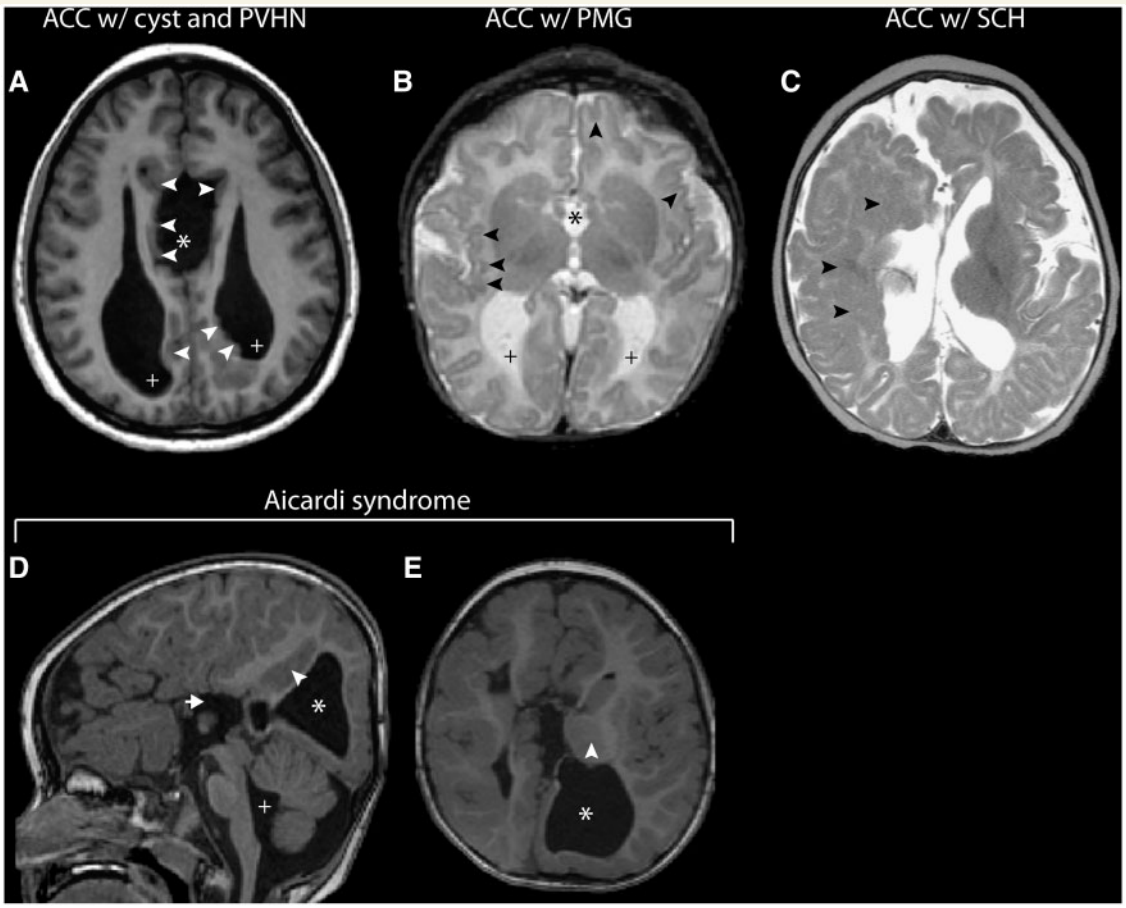

Figure 8 Associated malformations commonly seen in patients with ACC. (**A**) T_1-weighted axial MRI scan showing complete ACC associated with a third ventricle cyst (asterisk) and periventricular nodular heterotopia (arrowheads). (**B**) T_2-weighted axial MRI scan showing ACC (asterisk) associated with polymicrogyria (PMG) (arrowheads) and copolcephaly (+). (**C**) T_2-weighted axial MRI scan showing ACC with subcortical heterotopia (SCH) (arrowheads) and marked asymmetry of the cerebral hemispheres. Midsagittal (**D**) and axial (**E**) T_1-weighted MRI scan of a patient with Aicardi syndrome revealing a constellation of neuroradiological features, including complete ACC (arrow), grey matter heterotopia (white arrowhead), cystic dilation of the left lateral ventricle (asterisk) and enlarged fourth ventricle (+). In addition, there is marked asymmetry of the cerebral hemispheres.

not replicated in matched subjects with callosal agenesis and cortical malformations (Wahl *et al.*, 2010). Pachygria and periventricular and subcortical heterotopias are consistent with an interruption of radial neuronal migration, although the extent of corticocortical disorganization suggests that the neuronal migration defect is almost universal. The presence of type 2 interhemispheric cysts in some patients is intriguing, and may be secondary to failure of midline formation resulting from a related abnormality in migration and positioning of midline glial and neuronal populations. Given the widespread migration defects, it seems unlikely that the formation of Probst bundles in Aicardi syndrome is adaptive or compensatory, but rather suggests that they may represent multiple aetiologies and functions that differ depending on the developmental processes that are disturbed.

Increased use of array comparative genomic hybridization has highlighted the genetic heterogeneity of disorders such as Toriello-Carey syndrome, which has ACC as a defining feature. It is possible that several syndromes previously considered distinct are in fact a cluster of clinical features that are aetiologically unrelated. In Toriello-Carey syndrome, microdeletions at 22q12 (Hatchwell *et al.*, 2007; Said *et al.*, 2011) and 1q42 (Hatchwell *et al.*, 2007), an unbalanced translocation t(8;18)(p12;q22) (Martin-Denavit *et al.*, 2004), and a cryptic translocation t(10q;16p) (Martin *et al.*, 2002) have all been reported to produce a similar phenotype. These diverse findings may also be an artefact of the difficulties in diagnosing a complex syndrome based on clinical features alone.

Conclusion

ACC remains one of the most complicated neurological birth defects described, given the sheer number of developmental processes that may be disrupted. As a corollary, callosal agenesis rarely occurs in isolation, and is a specific and relatively easy-to-detect phenotypic marker for developmental disorders. Mouse models have vastly improved our understanding of the mechanisms of normal corpus callosum formation, and have paved the way for a developmental classification system based on the clinical and genetic features of human ACC syndromes.

Callosal development can be affected by the disruption of neurogenesis, telencephalic midline patterning, neuronal migration and specification, axon guidance and post-guidance development. Recent genetic studies have identified an abundance of copy number variations and single gene mutations in patients with ACC, but have also highlighted the underlying genetic complexity of many ACC syndromes. Meanwhile, continually improving neuroimaging data are allowing us to understand how genetic mutations affect brain connectivity, and in turn how the brain responds to developmental perturbations. These approaches have, in combination with animal models, improved our understanding of the mechanisms involved in callosal agenesis, and may pave the way for future therapies tailored towards individual patients.

Acknowledgements

We thank Ilse Buttiens for illustration and preparation of the figures and Rowan Tweedale for reading and editing the text.

Funding

This work was supported by the National Health and Medical Research Council (NHMRC) [grant numbers APP1048849 and APP1043045 and Principal Research Fellowship to L.J.R.]; Drs. Sherr and Barkovich were supported in part by a grant from the National Institutes of Health/National Institute of Neurological Disorders and Stroke R01NS058721 and the University of Queensland (Summer Research Scholarship) [T.J.E.]. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the NHMRC.

Supplementary material

Supplementary material is available at *Brain* online.

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