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Developmental Biology: Frontiers for Clinical Genetics

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Mechanisms regulating the development of the corpus callosum and its agenesis in mouse and human

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The development of the corpus callosum depends on a large number of different cellular and molecular mechanisms. These include the formation of midline glial populations, and the expression of specific molecules required to guide callosal axons as they cross the midline. An additional mechanism used by callosal axons from neurons in the neocortex is to grow within the pathway formed by pioneering axons derived from neurons in the cingulate cortex. Data in humans and in mice suggest the possibility that different mechanisms may regulate the development of the corpus callosum across its rostrocaudal and dorsoventral axes. The complex developmental processes required for formation of the corpus callosum may provide some insight into why such a large number of human congenital syndromes are associated with agenesis of this structure.

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The corpus callosum is the largest fiber tract in the brain and connects neurons in the left and right cerebral hemispheres. Its principle cognitive function is to coordinate and transfer information between the left and right brain. Agenesis of the corpus callosum (ACC) is a birth defect that occurs in over 50 different human congenital syndromes (Table 1) (86, 87, 88). Malformations of the corpus callosum can manifest as partial agenesis, for example in only the rostral or the caudal region, hypoplasia across the entire structure, or complete agenesis.

Some individuals with agenesis of the corpus callosum have intelligence quotients within the normal range. However, recent evidence suggests that some of these individuals are more susceptible to behavioral and neuropsychiatric problems (in children) and thus learning difficulties (89), sleep disorders (90), language and social communication disorders (91), and visuospatial attention deficits (92). Thus, ACC and disorders of the callosal projection can be prevalent and wide ranging in their effects. Recently, studies in mouse have elucidated some of the mechanisms underlying callosal formation during development. Here, we review these mechanisms as well as the genetic mutations that cause defects in callosal formation in both mice and humans in order to provide a comparative approach to understanding the underlying causes of ACC in human development.

Early patterning of the nervous system affects midline-commissure formation

Early in development, the nervous system begins as a homogeneous sheet of ectoderm that folds to

Table 1. Human congential syndromes associated with agenesis of the corpus callosum

Disorder/OMIM number	Phenotype	Region	Gene	Reference
Autosomal dominant				
Apert syndrome/101200	ACC, Hypoplastic	10q26	*FGFR2*	1, 2
Basal cell nevus/109400	ACC	9q31	*PTCH*	5
		9q22.3		3, 4
Greig cephalopolysyndactly Syndrome/175700	ACC	7p13	*GLI3*	6, 7
Kallmann syndrome 2/147950	ACC	8p11.2-p11.1	*FGFR1*	8, 9
Lissencephaly type I/247200	ACC, Hypoplastic	17p13.3	*LIS1,* 14-3-3, ABR, *CRK, MYO1C, SKIP, PITPNA, RILP, SERPINF1*	10, 11
Rubinstein-Taybi syndrome/180849	ACC	16p13.3	*CREBBP*	12
				13, 14
SOD (Septo-Optic dysplasia)/182230	ACC	3p21.2-p21.1	*HESX1*	15
Sotos syndrome/117550	ACC, Hypoplastic, Hypoplastic (Caudal only)	5q35	*NSD1*	16, 17
Autosomal recessive				
Andermann syndrome/218000	ACC, Hypoplastic	15q13q14	*SLC12A6*	18, 19, 20, 21
Aniridia type II/106210	ACC (homozygotes only), Agenesis of the Anterior Commissure	11p13	*PAX6*	22, 23, 24
Desmosterolosis/602398	ACC, Hypoplastic	1p33-p31.1	*DHCR24*	25, 26
Fukuyama muscular dystrophy/253800	Partial ACC	9q31	*FCMD*	27, 28
Hemifacial microsomia/164210	Partial ACC (Rostral)	14q32		29
Joubert syndrome 1/213300	Hypoplastic, and occasional ACC	9q34.3, 2q13	*NPHP1*	30, 31, 32
Lyon syndrome (Encephalopathy, axonal, with necrotizing myopathy, cardiomyopathy, and cataracts)/225740	ACC likely due to axonal atrophy, Hypoplastic, Other midline defects			33
Macrocephaly with multiple epiphyseal dysplasia and distinctive facies/607131	ACC	15q26.1		34, 35
Meckel syndrome/249000	ACC, Partial ACC	17q21q23		36, 37
Microcephalic osteodysplasia dwarfism I/210710	ACC			38
Mowat-Wilson syndrome (Hirschprung disease Syndrome)/235730	Hypoplastic, partial ACC (rostral), agenesis of anterior commissure	2q22	*ZFHX1B*	39, 40
Toriello-Carey syndrome/217980	ACC, partial ACC, Hypoplastic			41
Vici syndrome/242840	ACC			42
Walker-Warburg syndrome/236670	ACC	9q34.1	*POMT1*	43, 44

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Table 1. Continued

Disorder/OMIM number	Phenotype	Region	Gene	Reference
X-linked				
Aicardi syndrome/304050	ACC, Hypoplastic	Xp22		45, 46
ACC with mental retardation, ocular coloboma, and micrognathia/300472	ACC	Xq13.1–13.3	*IGBP1*	47
CFND (Craniofrontonasal syndrome)/304110	Partial ACC	Xq12, Xp22	*EFNB1*	48, 49, 50
HSAS (Hydrocephalus due to congenital stenosis of aqueduct of Sylvius)/307000	ACC	Xq28	*L1CAM*	51, 52
Lenz micropthalmia syndrome/309800	ACC	Xq27-q28		55, 56
MASA syndrome (Mental retardation, aphasia, shuffling gait, and adducted thumbs)/303350	ACC, Hypoplastic	Xq28	*L1CAM*	57, 58
MLS (Microphthalmia with linear skin defects)/309801	ACC	Xp22.31		59, 60
Opitz syndrome/300000 (Autosomal forms also exist)	ACC, Hypoplastic	Xp22	*MID1*	61, 62, 63
OFD1 (Oro–Facio–Digital syndrome Type 1)/311200	ACC	Xp22.3-p22.2	*CXORF5*	64, 65
Periventricular heterotopia/300049	Partial ACC	Xq28	*FLNA*	53, 54
Proud syndrome/300004 XLAG (X-linked lissencephaly with ambiguous genitalia)/300215	ACC	Xp11.3 q21.3 Xp22.13	*ARX*	66, 67 68, 69
XLIS (X-linked lissencephaly)/300067	ACC	Xq22.3-q23	*DCX*	70, 71
Metabolic disorders				
Fumarase deficiency/606812	ACC, Hypoplastic	1q42.1	*FH*	72, 73
Glycine encephalopathy/605899	ACC	9p22	*GCSP*	74, 75
PDH deficiency/312170	Partial ACC	Xp22	*PDHA1*	76, 77
Smith-Lemli-Opitz syndrome/270400	ACC	11q12-q13	*DHCR7*	78, 79
Zellweger syndrome (Cerebro-Hepato-Renal syndrome)/214100	ACC, Hypoplastic, Lissencephaly	6q23-q24	*PEX3*	80, 81
Miscellaneous				
Wolf–Hirschhorn syndrome/194190	Hypoplastic, partial ACC (caudal)	4p16.3	*WHSC1*	82, 83
Delleman syndrome (Oculocerebrocutaneous syndrome)/164180	ACC, Hypoplastic			84, 85

ACC, Agenesis of corpus callosum.

Note: Table 1 includes disorders where three or more cases have been reported, thus more rare syndromes associated with ACC have not been included. Furthermore, syndromes in which the corpus callosum has been reported to be hypoplastic (but where agenesis does not occur) have also not been included.

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form a tube initially and then differentiates both in the rostro-caudal axis and in the dorso-ventral axis to form the brain and spinal cord. The expression of genes in restricted regions determines which regions of the tube will differentiate into specific structures and cell types within the nervous system. These so-called genetic patterning events also regulate the development of the midline of the nervous system. Proper midline formation is crucial to the later formation of all the midline commissures in the forebrain, including the corpus callosum. Initially, the forebrain consists of a single vesicle called the prosencephalon (Fig. 1a). Shortly after the formation of the prosencephalon, buldges form on either side of the single vesicle through cellular proliferation and migration to form two telencephalic hemispheres (Fig. 1b). One of the most common developmental neurological malformations, called holoprosencephly, occurs when the prosencephalon fails to split leaving a single cerebral hemisphere. This major neurological malformation is a midline patterning defect that has profound effects on the formation of commissures within the forebrain. Although important and often cited as resulting in ACC, these effects will not be discussed further here, because their underlying cause is primarily due to a failure to form the two cerebral hemispheres, either in part or in whole.

Once the telencephalic hemispheres are formed a number of other developmental processes, some related to midline patterning, must also occur before the corpus callosum can develop. In rostral regions of the forebrain, the two hemispheres are joined ventrally but a fusion of the midline must occur in more dorsal regions where the callosal axons will eventually cross the midline (Fig. 1c). Midline fusion occurs at approximately E14-E15 (embryonic day 14-embryonic day 15) in mice and is hypothesized to occur by molecules expressed by glia that arise in this region known as the midline zipper glia (MZG) (Fig. 1d) (93, 94). Midline fusion is critical to the formation of the corpus callosum as the axons cannot cross the midline if no substrate exists for them to grow and extend upon. The midline is also often the site of interhemispheric cysts, which when occur during development, prevent the fusion of the telencephalic hemispheres and are a common cause of ACC.

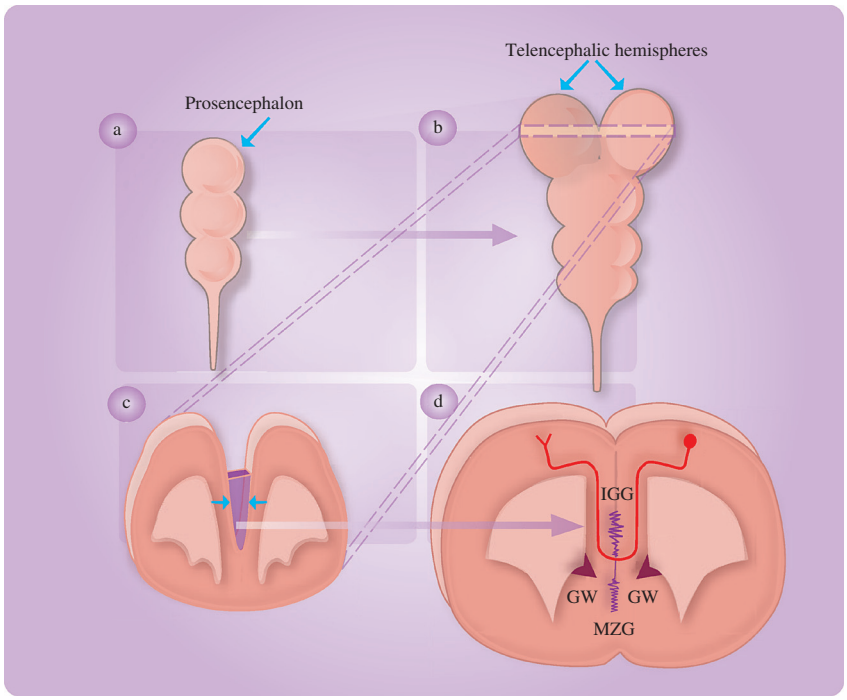

Fig. 1. Development of the telencephalic hemispheres and fusion of the rostral cortical midline. The brain begins as a three-vesicle structure (shown in a). The rostral-most vesicle, called the prosencephalon, will form the entire forebrain. Slightly later in development two large buldges form on either side of the prosencephalon to form two telencephalic hemispheres (b). A cross section through the brain at a slightly later stage of development [embryonic day (E)14 in mouse] shows that although the ventral region of the brain is connected the hemispheres are still separate in more dorsal regions of the rostral forebrain (c). Midline glia known as the midline zipper glia (MZG) are thought to play an active role in fusing the hemispheres together (blue arrows in C show direction of fusion). By E17 the two hemispheres are fused and the glial are split into two populations by the formation of the corpus callosum (d). The glia within the indusium griseum (IGG) reside above the corpus callosum, while the MZG and the bilaterally symmetrical glial wedge (GW) reside below the corpus callosum. The red axon depicts the callosal projection of a neuron within the neocortex.

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Within the developing cortex are cellular processes that produce the six layers of the mature cortex. These include, proliferation within the ventricular zone, migration to the correct position, and differentiation of the cells into neurons and glia. It goes without saying that each of these processes are also critical to the formation of the corpus callosum, because the majority of axons making up the corpus callosum arise from neurons within the neocortex. These cellular processes are mentioned here however, because defects, particularly in cellular migration such as lissencephaly, are often grouped with syndromes that cause ACC, and some have been included in our table of human disorders associated with ACC. It should be noted, however, that the ACC observed in these syndromes is likely to be secondary to the primary defects in cellular migration that cause these malformations.

Development of the callosal projection

The cerebral cortex is made up of six cellular layers. The major projection across the corpus callosum is derived from neurons in layers 2/3 and 5. We have arbitrarily divided the projection pathway of callosal axons into six distinct decision points in order to better describe and characterize the entire pathway (Fig. 2). Neurons within each layer send an axon ventrally toward the intermediate zone possibly under the influence of guidance factors such as Sema3A (95) which repels axons away from the marginal zone (layer 1 of the neocortex) (decision number 1 in Fig. 2) is thus to send an axon ventrally toward the intermediate zone. Once these axons reach the intermediate zone they turn toward the midline rather than projecting laterally (decision number 2 in Fig. 2). This decision is where callosal axons are distinguished from subcortically projecting axons which turn laterally to project through the internal capsule (green axons in Fig. 2). At present nothing is known about how this differential decision is made, however, there is some evidence that axons may hedge their bets at this decision point by dividing and projecting a process both medially and laterally (96). This appears to be a transient decision however, because by the time the axons have projected across the midline and down into the internal capsule there are few, if any, bifurcating projection neurons found (97). Callosal axons then approach the midline by growing through the cingulate cortex (Fig. 2). The axons approach the midline in a steep ventral trajectory and then abruptly turn to cross the midline at the corticoseptal boundary (decision number 3 in Fig. 2). At the corticoseptal boundary, the axons encounter midline glial structures known as the glial wedge and indusium griseum glia (how these glia are involved in regulating callosal axon guidance at the midline is discussed in more detail below). As the axons turn to cross the midline they encounter another glial wedge in the opposite hemisphere, where the axons must make another turn dorsally (decision number 4 in Fig. 2) to enter the contralateral cingulate cortex and then the contralateral neocortex. Growing within the contralateral neocortex, the axons must locate their target neocortical area for innervation (decision number 5 in Fig. 2). Little is known about how callosal axons locate the contralateral cortical area, but it is likely that they use similar cues to those that thalamic axons use to find their cortical target areas. Thalamic axons are regionally sorted as they leave the ventral forebrain both by virtue of the rostro-caudal location of the specific thalamic nuclei from which they arise, and by molecules expressed in the ventral forebrain that help maintain this rostro-caudal pattern of projections (98, 99, 100). However, once thalamic axons enter the cortex they need to locate their final target region and do so probably by identifying regionally expressed molecules within the cortex. Current research shows that cortical areas are defined by both growth factors such as FGF8 (101, 102) and transcription factors such as Emx2 and Pax6 (103, 104, 105). However, this research is looking at the master control genes for cortical arealization and has not yet identified the downstream molecules that tell thalamic axons where to innervate. Once callosal axons decide where to innervate

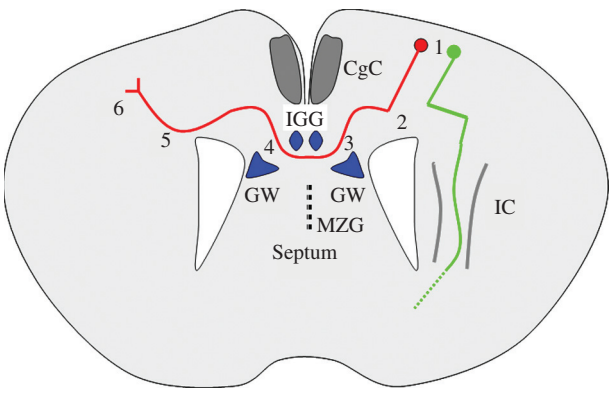

Fig. 2. Developmental stages in the formation of the corpus callosum. The callosal tract can be divided into six different axonal decision points. These points (labeled 1–6) are described in detail in the text. A representative callosal axon is shown in red while a laterally projecting cortical axon is shown in green projecting through the internal capsule (IC). CgC, cingulate cortex; IGG, indusium griseum glia; GW, glial wedge; MZG, midline zipper glia.

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they then use radial glial fibers to grow dorsally into the cortical plate (106) where they make their final targeting decision to locate the correct cortical layer and target neurons to innervate (decision number 6 in Fig. 2), with the final pattern and maintenance of projections likely sculpted by activity dependent mechanisms (107).

Mechanisms regulating the development of the corpus callosum

In the developing brain axons use a number of different mechanisms in order to find their correct path of growth. The specialized tip at the end of the axon, called a growth cone is exquisitely sensitive (108) and able to detect subtle changes in the concentration of molecules within the environment. A number of axonal guidance molecules have been identified, and these can be divided into secreted/diffusible factors and factors bound to cellular membranes or to the extracellular matrix (109). Within both groups there are chemoattractive and chemorepulsive molecules as well as molecules that are permissive or suppressive (suppressing growth but not repelling the axons). Axons often have to grow over very large distances to reach their final target, and callosal axons are a good example of this. It is, therefore, impractical for the final target to be the sole source of guidance molecules for these axons. One way that the nervous system copes with this is to employ intermediate targets along the way to the final target to essentially break down the path into smaller, more manageable segments. These intermediate targets express guidance factors that guide axons to a given point and then possibly repel them on to the next intermediate target. The midline is an intermediate target and has been shown to be critical for the formation of commissures throughout the nervous system, particularly through the expression of molecules by midline glial populations (110).

Glial development and midline commissure formation

Midline glia have been shown to regulate the formation of midline commissures from fruit flies to mammals. Even within the mammalian nervous system, midline glial (or glial-like) structures are essential for formation of commissures. Particularly, the floorplate, a glial-like structure, secretes guidance cues for the formation of commissural axons of the dorsal sensory neurons in the spinal cord (111); the glial palisade which guides retinal ganglion cell axons of the optic chiasm (112), and the glial tunnel which is associated with the anterior commissure (113) are all important midline glial structures for the formation of commissural projections in the nervous system. Moreover, not only are these midline glial structures conserved in humans (114) but also the molecules they express that guide commissural axons are also highly conserved throughout evolution.

Midline glia are also required for formation of the corpus callosum. Figure 2 shows where specific glial populations arise at the cortical midline. One population, called the glial wedge has been isolated and shown *in vitro* to express molecules such as Slit2, required for callosal axons to cross the midline (94, 115). The glial wedge is part of the radial-glial scaffold of the cerebral cortex and expresses markers of radial-glial cells such as RC2, BLBP, and GLAST (116). However, the glial wedge has three distinguishing features; (i) they are the first cells within the rostral cortex to express glial fibrillary acidic protein (GFAP), the prototypical glial marker; (ii) they express guidance molecules such as Slit2, and (iii) they retract their pial endfeet prior to retracting their ventricular endfeet (116) (this may be how this structure achieves its wedge shape). Two other populations of glia that arise at the midline and are not part of the radial-glial scaffold, are glia within the indusium griseum (IGG) and the MZG. The MZG and their proposed function in midline fusion have been described above. The IGG also express the guidance molecule Slit2 and reside directly above the corpus callosum. At present we hypothesize their function in callosal development to be in channeling the axons across the midline, and defining dorsoventrally where the axons cross the midline.

Pioneering axons – evidence of a role for pioneering axons in growth cone guidance

In many other systems, both in invertebrates and in the mammalian cortex, pioneering axons have been shown to be important for the guidance of later-arriving axons (117, 118, 119). Pioneering axons are defined as the first axons to grow down a specific pathway, probably under the influence of guidance molecules expressed in the environment. Later arriving axons then use the pioneers, perhaps by even direct fasciculation with the pioneers, to find their correct path of growth. Logically, this would mean that the later-arriving axons would not need to express the myriad of receptors required for gross guidance as they could merely follow the pioneers. Thus, one possibility could be that molecules expressed within the environment could then be used for more subtle wiring decisions involving axons leaving the main

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tract at defined stopping points to specifically innervate targets along the main trajectory.

The corpus callosum is pioneered by axons from neurons that reside within the cingulate cortex, the most medial region of the cerebral cortex (120, 121, 122). The cingulate pioneers cross the midline at E15.5 in mice, followed by neocortical axons that cross as early as E16.5 (122). Evidence that the cingulate pioneers may be important for callosal formation is that the neocortical axons appear to fasciculate with the cingulate pioneers, crossing the midline within the tract formed by the pioneering axons. The cingulate pioneering axons express the guidance receptor Neuropilin1 (Plachez and Richards, unpublished observation), and preliminary evidence demonstrates a role for Neuropilin1 in guiding callosal axons across the midline (123).

In summary, a number of guidance events are critical to callosal formation. These include the formation of midline glial structures and the pioneering axon population, and the expression of molecules by these structures and axons for neocortical-callosal axon guidance. In Table 2, we have reviewed the current literature to present a table of genes and molecules that in mice have been shown to cause defects in callosal development. This large number of genes is comprised of molecules as diverse as transcription factors, guidance molecules and their receptors, intracellular signaling molecules, growth factors, and patterning molecules (Table 2). It is likely that this wide array of genes involved in callosal development is due in part to some of these genes regulating the large number of developmental steps required to form a corpus callosum and in part because

Table 2. Genes shown to cause malformations in development of the corpus callosum in mice

Gene	Mouse loci	Human loci	Reference
Guidance molecules/receptors			
DCC	18 45.0 cM	18q21.3	124
EphA5	5 43.0 cM	4q13.2	125
EphB2 (Sek4)	4 65.7 cM	1p36.1–36.5	126
EphB3 (Nuk)	16 B1-B4	3q21–qter	127
fzd3	14 27.0 cM	8p21	128
Netrin1	11 B3	17p13–p12	129
Npn1	8 73.0 cM	10p12	123
Slit2	5 B3	4p15.2	130
Transcription factors			
Emx1	6 35.5 cM	2p14–p13	131, 132
Emx2	19 53.5 cM	10q26.1	132, 133
Hesx1	14 A3-B	3p21.2–p21.1	134
Nfia	4 45.8 cM	1p31.3–p31.2	135, 136
Pax6	2 58.0 cM	11p13	137
Vax1	19 53.5 cM	10q26.1	138
Tlx	10 25.5 cM	6q21	139
Extracellular matrix molecules			
$Ankyrin_B$ (ankyrin2)	3 62.5 cM	4q25–q27	140
L1 CAM	X 29.51 cM	Xq28	141
Signaling/Cytoplasmic molecules			
βAPP	16 56.0 cM	21q21.2	142, 143
CREB1	1 31.0 cM	2q34	144
GAP43	16 29.5 cM	3q13.1–q13.2	145
MAP1B	13 51.0 cM	5q13	146
MARCKS	10 22.0 cM	6q22.2	147
macMARCKS (MLP)	4 59.0 cM	1p34.3	148
Mena (Enah)	1 98.7 cM	1q42.13	149
p35 (cdk5R1)	11 46.5 cM	17q12	150
cdk5	5 12.0 cM	7q36	
p190-A RhoGAP	unknown	19q13.3	151
PTPó	17 33.8 cM	19p13.3	152
Arx	X C1	Xp22.1–21.3	69
Jip3	17 A3.3	16p13.3	153
FE65	7 46.6 cM	11p15	154
FE65L1	5 C3.1	4p14	
Growth factors			
FGF8	19 45.0 cM	10q24	155
IGFBP-1	11 1.3 cM	7p13–p12	156
ACC mouse strains			
BTBR T/+*tf/tf*			157
Ckr			158
BALB/cWah1 9XCA/Wah			159

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some of these molecules may turn out to be involved in similar processes either through direct interactions or by being within the same molecular pathways.

Development of the rostro-caudal extent of the corpus callosum

The corpus callosum can be partitioned into regions known as the rostrum (which includes a beaked segment and the lamina rostralis), genu, body, and splenium from rostral to caudal (Fig. 3). It was once thought that the body of the corpus callosum formed first, followed by expansion in both anterior and posterior directions (160). However, detailed MRI studies have provided new insights into how the corpus callosum forms in the rostral-caudal axis during human development (161, 162). These studies provide convincing evidence that the corpus callosum is anchored early in development rostrally by the lamina rostralis region of the rostrum and caudally by the fornix. The first regions to form then are the lamina rostralis and the anterior region of the body of the corpus callosum which crosses directly over the fornix/hippocampal commissure (162). Recent developmental studies in rodents suggest that axons cross the midline in rostral regions very early. The axons arise from neurons in the cingulate cortex which are closely followed by axons from neurons in the neocortex (120, 122, 163). In caudal regions (the future body of the corpus callosum) callosal axons grow in close proximity to the axons of the hippocampal commissure. In mouse the hippocampal commissure forms around one day earlier [at embryonic day (E)14] than the corpus callosum (at E15.5). This suggests a correlation between where callosal axons cross the midline in more caudal regions and the formation of the hippocampal commissure (164) suggesting the callosal axons may use the axons of the hippocampal commissure to cross the midline. In order to investigate this further and to determine the developmental sequence of events in mouse, we injected mouse brains between embryonic day 15.5 and birth with different colored carbocyanine dyes from rostral to caudal. Figure 4 presents evidence that axons in the rostral region and in the region of the future body of the corpus callosum cross simultaneously. That is, cingulate pioneering axons cross the midline at both the most rostral extent (which probably correlates with the lamina rostralis in humans) and caudally (in the future body of the corpus callosum) above the hippocampal commissure at the same stage of development. More caudal regions of the corpus callosum that will form the splenium are added approximately one day later (Fig. 4). These data confirm and extend those of Ozaki and Wahlsten (165) and provide evidence that the callosal axons are not added in a rostral to caudal manner and therefore we propose that callosal axons in more caudal regions (the future body and the spenium) may not require the presence of the cingulate pioneering axons in order to cross the midline. Further experiments are required to define medio-laterally which regions of the cortex (cingulate *vs* neocortex) cross first in more caudal regions. However, the presence of the hippocampal commissure in these regions may obviate the need for the cingulate pioneering axons in this region with callosal axons (in the future body of the corpus callosum) instead using the axons of the hippocampal commissure to cross the midline, and axons of the splenium being added to these in a rostro-caudal manner.

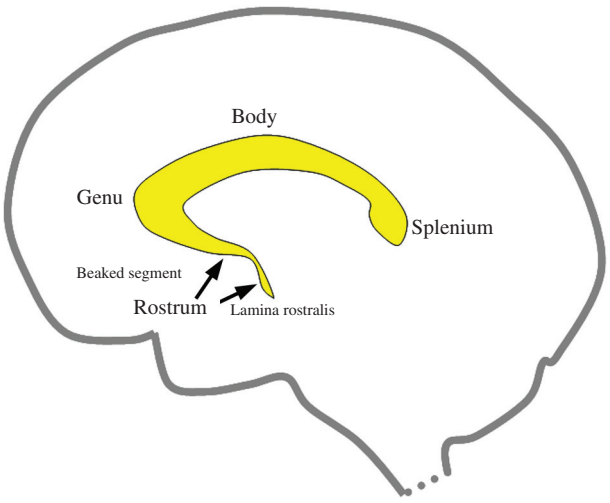

Fig. 3. Regions of the corpus callosum. Schematic depiction of a sagittal section showing the different regions of the corpus callosum from rostral to caudal. The rostrum is made up of the lamina rostralis and a beaked segment, followed by the genu, body, and splenium of the corpus callosum. The lamina rostralis and the rostral part of the body are reported to be the sites of where the first callosal axons cross the midline in humans.

These data, coupled with the MRI evidence showing that the human corpus callosum forms simultaneously in the lamina rostralis and more caudally, in the region of the future body, above the fornix indicate a model in which different mechanisms operate in the development of the rostral *vs* the caudal region of the corpus callosum. One way in which this may occur is that in rostral regions callosal axons may require the presence of pioneering axons from the cingulate cortex, and in caudal regions callosal axons could use the presence of the hippocampal commissure to cross the midline (Fig. 5). Axons of the genu and splenium would then be added to these two

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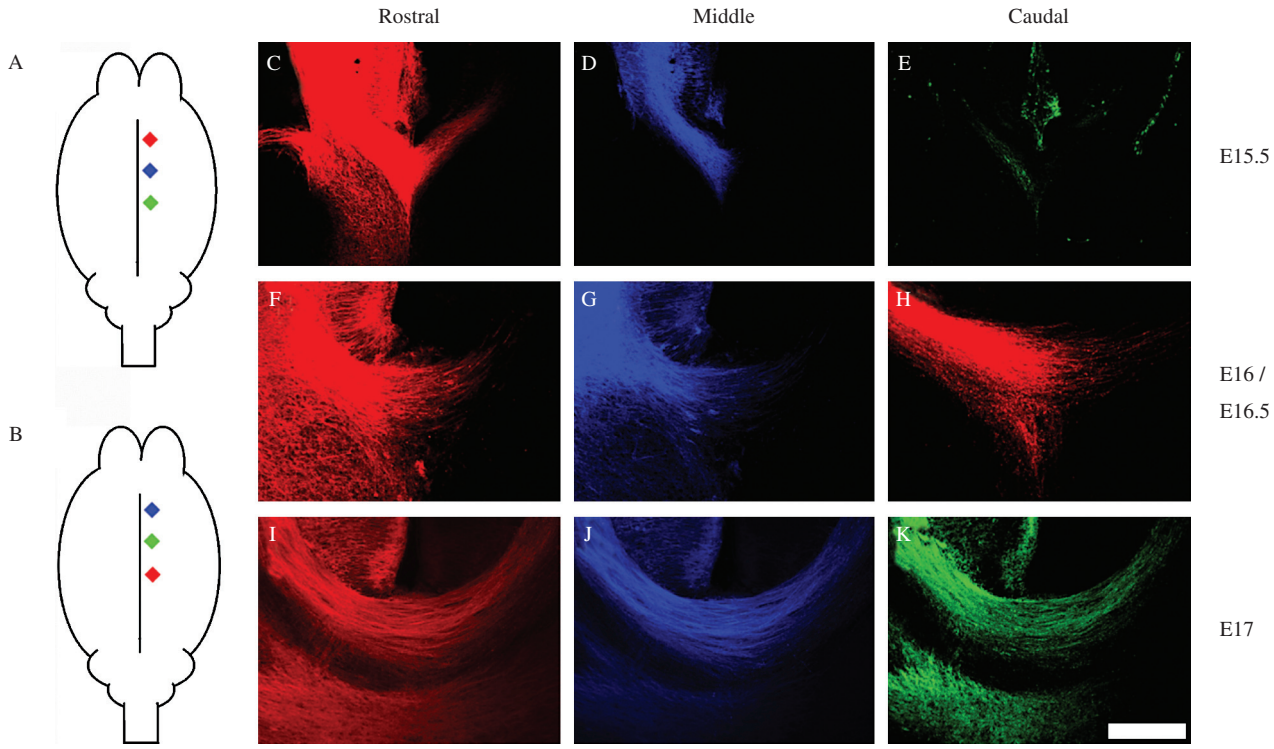

Fig. 4. Development of the corpus callosum in the rostro-caudal axis in mice. Brains between E15 and post-natal day 0 were injected with three different colored carbocyanine dyes using methods previously described (37) to determine the order of development of the corpus callosum in the rostro-caudal axis. Brains were injected from rostro-caudal with either a sequence of red, blue, green or blue, green, red dyes as shown in panels A and B respectively. The order of the dyes was changed for some brains at each age to control for any possible differences in transport time or efficiency between the three different dyes. No axons were found to cross the midline at E15 (data not shown). At E15.5 axons crossed in the rostral region (C) slightly ahead of axons in the middle region (D; which were nevertheless also crossing the midline). Axons in the caudal region were not crossing the midline (E). Axons also crossed the midline at E16 in rostral (F) and middle (G) regions but not in caudal regions (not shown). By E16.5, however, axons did cross in the caudal region (H). Panels I–K show axons crossing in all rostro-caudal regions of the corpus callosum in the same brain at E17. Thus, the first axons to cross the corpus callosum in mice cross in the rostral and middle regions simultaneously followed approximately 1-day later by axons forming the caudal corpus callosum. Scale bar = 200 μm.

initial populations, respectively, in a rostro-caudal manner. This model is supported by the existence of some human congenital syndromes in which either the rostral or caudal region of the corpus callosum is most affected (Table 1).

Toward an understanding of agenesis of the corpus callosum in humans

We propose that different mechanisms regulating callosal formation may operate in both the rostro-caudal axis as well as the dorso-ventral axis. It has been previously shown that there is a loose topography of the origin of axons within the corpus callosum, with more medially-situated neurons crossing more dorsally than more laterally-situated neurons (164). Thus the pioneering axons coming from the cingulate cortex, the most medial region of the cerebral cortex, cross within the dorsal region of the tract. Thus, any differences in guidance mechanisms specific for the pioneering axons *vs* neurons from the neocortex would also represent different mechanisms regulating callosal formation in the dorsal *vs* the ventral region of the tract.

How do these hypotheses relate to the genetic regulation of callosal development in humans? The most significant point is that the large number of defined genes and genetically uncharacterized syndromes associated with agenesis of the corpus callosum (summarized in Table 1) can be explained if these layers of complexity involved in regulating callosal formation are taken into account. As outlined here, these layers of complexity include the large number of defined points in the developmental sequence of events required for callosal formation, how these events are regulated by molecules and structures within the environment, and finally, that mechanisms regulating the development of the corpus callosum may not be uniform in either the rostro-caudal or dorso-ventral axes. By defining each of these aspects of callosal formation we may be able to arrive at a means for classifying known

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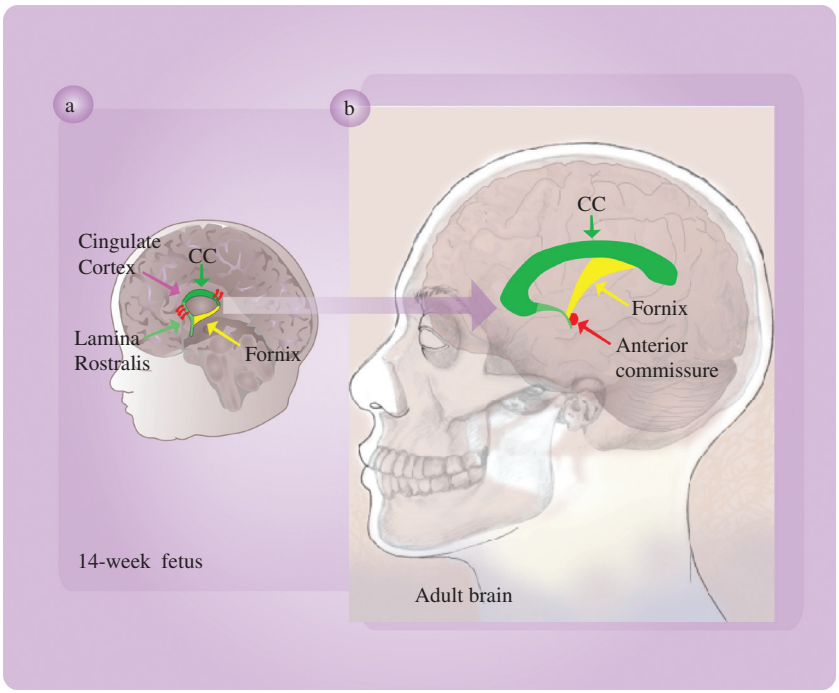

Fig. 5. Model of callosal development in humans. The data presented in Fig. 4 and MRI data previously described (126) show that the first regions of the corpus callosum to form are the lamina rostralis and the anterior region of the body of the corpus callosum. We propose that different mechanisms may be used by axons to cross the midline in these two regions. In rostral regions callosal axons use the pioneering axons derived from the cingulate cortex as well as midline glial structures that prevent them from entering the septum and repel them away from the midline once they have crossed. In caudal regions pioneering axons may follow the axons of the fornix and hippocampal commissure to cross the midline. Once these primary regions are established, more axons are then added to form the genu and finally the splenium of the corpus callosum. Shown are sagittal views of schematics of a 14-week-old fetal (a) and adult (b) human brains depicting where the first axons are proposed to cross during development (sites of red axons in a) and their corresponding regions in the adult brain.

genetic mutations as regulating one or more aspects of development and to pinpoint more accurately where development has been disrupted in genetically undefined syndromes associated with callosal agenesis. Usually, agenesis of the corpus callosum is not observed in isolation but in conjunction with other neurological deficits. Thus, it is also likely that the mechanisms and molecules being uncovered in the callosal system may also regulate the development of other commissures or other structures in the brain and spinal cord. The challenge now lies in sorting out which genes, if any, are part of the same molecular pathways and whether any of the genes known to cause defects in specific developmental events required for callosal formation in mouse are involved in similar events in humans.

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