lar resolution capability. The next generation of such instruments will eventually lead to the direct detection of less and less massive planets.

During the 1980s, exozodiacal dust disks were found around a variety of stars. In the 1990s, the presence of planets around stars was found to be relatively common. A consistent strategy is now in place to understand and characterize the formation and evolution of these planetary systems. Eventually, we should be able to investigate nearby individual cases, and ultimately, terrestrial planets.

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NEUROSCIENCE

Genetic Control of Cortical Convolutions

Pasko Rakic

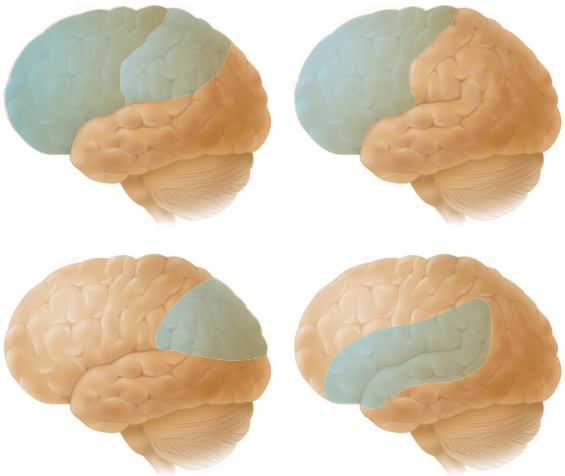
The cerebral cortex is composed of a sheet of neurons that during evolution has increased by three orders of magnitude in surface area. In humans, the cerebral cortex has assumed a highly convoluted (gyrencephalic) shape. A remarkable aspect of cortical development is that none of the constituent neurons, even in the large primate cerebrum, are generated within the cortex itself. Rather, cortical neurons originate in the proliferative ventricular and subventricular zones lining the cerebral cavity and then migrate to their proper laminar and areal positions (*1*). In all mammals, but particularly in the gyrencephalic primate cerebrum, this migration to appropriate positions critically depends on the transient scaffolding formed by shafts of elongated radial glial cells that span the fetal cerebral wall (*2*).

Elucidation of the cellular and molecular events underlying cortical development has come primarily from investigating the smooth (lysencephalic) mouse cerebrum, which is amenable to experimental approaches including the induction of genetic mutations (*3*–*6*). In contrast, spontaneous mutations in humans are nature's unique experiments that enable deciphering of developmental mechanisms, such as the formation of cortical convolutions, that cannot be studied in lysencephalic rodents. On page 2033 of this issue, Piao *et al.* (*7*) provide a state-of-the-art genetic analysis of a human disorder called bilateral frontoparietal polymicrogyria. Patients with this syndrome have an enlarged number of smaller convolutions in the cerebral cortex associated with profound cognitive abnormalities. The authors report that abnormal development in the same cortical location in these patients is caused by eight separate mutations in the human *GPR56* gene encoding an orphan G protein–coupled receptor. This finding implicates G protein–coupled receptor signaling in the development of specific areas of the human cerebral cortex.

Bilateral frontoparietal polymicrogyria is an autosomal recessive syndrome that has been mapped to a locus on chromosome 16q12-21 (*8*). In the new study, Piao *et al.* convincingly show that in each of 12 pedigrees the *GPR56* mutations segregate with polymicrogyria, and only affected patients carry homozygous *GPR56* mutations. They diagnosed the disease according to characteristic cranial magnetic resonance imaging and clinical manifestations. No mutations were observed in the *GPR56* gene in 260 control chromosomes. In addition, the authors demonstrated that the mouse *Gpr56* gene preferentially affects neuronal progenitors in the embryonic mouse proliferative zones. This indicates that the regional patterning of the cerebral cortex occurs at early stages of development, during production and migration of neurons, rather than later in response to abnormal axonal inputs.

The type of polymicrogyria studied by Piao *et al.* arises bilaterally in the sensory and association motor cortical areas of the frontal and parietal cerebral lobes. There are other types of bilateral polymicrogyria that selectively affect different cortical areas (see the figure). This suggests that mutations in specific genes affect cell proliferation only in the regions of the embryonic ventricular zone subjacent to these cortical areas. This, in turn, indicates that the proliferative zone consists of a heterogeneous population of progenitor cells that form a "protomap" (*2*) rather than a uniform sheet of totally equipotent stem cells. Because different regions of the ventricular zone have become separate targets for mutation in congenital malformations, one can speculate that a random mutation during human evolution could be the underlying cause of regional cortical enlargement (*2*).

The other intriguing feature of polymicrogyria is that the affected cortex, although thinner than normal, forms a larger number of convolutions with a net increase in cortical surface. It is instructive that during evolution, cerebral convolutions are formed concomitantly with an increase in cortical surface due to the addition of radial units (minicolumns), but without a comparable increase in cortical thickness (*2*). Why does an increase in the number of neurons result in surface expansion, rather than in a thicker cortex or amorphous cell mass? According to the radial unit model of cortical evolution (*2*), the cortical surface



Types of polymicrogyria syndromes. In the congenital malformation bilateral frontoparietal polymicrogyria, affected individuals have an enlarged number of smaller convolutions in the cerebral cortex that are associated with profound cognitive abnormalities. There are several region-specific types of bilateral symmetric polymicrogyria that are caused by mutations in different genes and can be distinguished by where they are localized in the human cerebral cortex (blue shading). This family of syndromes includes (clockwise from top left) bilateral frontal polymicrogyria, bilateral frontoparietal polymicrogyria described in the Piao *et al.* study (*7*), bilateral parieto-occipital polymicrogyria, and bilateral perisylvian polymicrogyria.

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expands as a result of changes in proliferation kinetics in the ventricular zone in which cohorts of postmitotic neurons generated at the same site follow transient radial glial scaffolding to form the arrays of minicolumns. The larger the number of columns, the larger the cortical surface. This hypothesis gained support from studies in mice in which an experimentally induced increase in neuronal production in the ventricular zone resulted in a larger number of radial columns and an increase in the cortical surface (*9*, *10*). Thus, overproduction of neurons due to the *GPR56* mutations described by Piao *et al*. (*7*) probably affects neurons that use a radial, rather than a tangential, mode of migration. Interestingly, unlike in rodents (*11*), the majority of interneurons in the human fetal cerebrum originate from the subventricular zone and migrate radially to the overlying cortex (*12*). The phylogenetically newest subtypes of stem cells in the subventricular zone may be selectively vulnerable to mutation in the human cerebrum.

The Piao *et al.* study indicates that some genes in the human forebrain may underlie species-specific programs for the generation of cortical neurons that are destined for particular regions of the cerebral cortex. Although the differences among mammalian genomes are remarkably small, they can produce functionally important changes in the brain's neuronal organization. In this case, nature has generated a random experiment from which we can learn not only about causes of (and, possibly, ways to prevent) frontoparietal polymicrogyria, but also about the mechanisms of normal human brain development. It has been calculated that all mutations in the human genome that could occur have already occurred, and thus the main problem remains to detect these mutations and their associated abnormal phenotypes. The polymicrogyria families in the Piao *et al*. study came from across the world, from Canada and the Middle East to the India-Pakistan border, where they probably originated from a consanguineous Afghan family. If we want to learn more about the development of unique traits of the human brain, large studies such as the Piao *et al*. study discussed here are essential, as there may be no better alternative.

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PARASITOLOGY

New Ways to Control Malaria

Janet Hemingway and Alister Craig

The *Plasmodium* parasite that causes malaria is transferred to its human host by a mosquito vector. Over centuries this relationship between insect, parasite, and mammalian host has been finely tuned, enabling the parasite to partially evade both human and insect immune systems, thus ensuring its own survival. Control of malaria in developing countries remains a major public health issue. A principal strategy has been to reduce mortality by rapid treatment with antimalarial drugs, but drug resistance in many malaria-endemic countries has made this approach unsustainable. The emergence of drug-resistant parasites means that control of the insect vector is again the most cost-effective and practical way to reduce the burden of malaria. Numerous control trials of both indoor residual spraying with insecticides and the use of pyrethroid-impregnated bednets have demonstrated that human morbidity and mortality can be dramatically reduced when these measures are applied effectively. But in endemic countries, where the poorest rural sectors of society are hardest hit by malaria, these control methods are rarely applied effectively and problems with insecticide resistance now outpace the introduction of new insecticides onto the market. The report by Osta *et al*. on page 2030 of this issue (*1*) advances the quest for new methods to control the mosquito vector, an imperative if we are to sustain our position, let alone win the war, against malaria. These authors identify three mosquito genes that control the immune response of *Anopheles gambiae*, the principal vector of the malaria parasite in Africa. They show that these three genes directly affect development of the rodent malaria parasite, *Plasmodium berghei*, within the insect gut.

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This is an exciting time for the malaria research community. The genomes of both mosquito and parasite have been sequenced (*2*, *3*), insect vectors can be transformed in culture, and the power of RNA interference (RNAi) can be applied to silence the expression of single mosquito genes. Initial analysis of important insect gene families that are targets for parasite or vector control, and their comparison between *Drosophila* and *A. gambiae*, suggest that many of these gene families have undergone recent expansions (*1*, *4*). For example, *CYP12*, a member of the P450 gene family that detoxifies insecticides, has expanded independently in *Drosophila* and *A. gambiae*, giving rise to six and four genes, respectively, that have no obvious equivalent in the other species. The availability of the *A. gambiae* genome sequence allows detailed transcriptional analysis of the mosquito gut epithelium during development of the parasite's sexual stages, the ookinete and oocyst (see the figure) (*5*, *6*). The three mosquito immune genes identified by Osta *et al*. as having a direct effect on the malaria parasite do not have orthologs in *Drosophila*. This makes them ideal candidates for specifically blocking mosquito-parasite interactions without negatively impacting nontarget organisms.

Most research on the human malaria parasite has been targeted toward blocking *Plasmodium* invasion of erythrocytes and hepatocytes, and preventing development of the erythrocytic forms of the parasite. For decades, transmission-blocking therapies, preventing transmission from insect vector to human host and vice versa, have been a major topic of malaria research (*7*). Recent advances include raising antibodies against two related *P. vivax* proteins, Pv25 and Pv28, that block oocyst development in the mosquito gut (see the figure) (*8*). In addition, deletion of Pb25 and Pb28 from the surface of the *P. berghei* ookinete demonstrates that these parasite genes are important for oocyst development (*9*).

The path of the malaria parasite through the insect is a complex one. Not only must the parasite travel from the gut of the insect (where it is first ingested in an infected blood meal) to the insect salivary glands (to be transferred to its next human host), but en route it must also pass through the various stages of its sexual reproductive cycle (see the figure). To achieve this, the parasite must evoke or evade insect vector pathways involved in proteolytic digestion, cell-cell recognition, cell motility, signal transduction, and melanization (the killing and darkening of the malaria parasite in the mosquito gut).

The three mosquito immune genes identified by Osta and colleagues as affecting the parasite life cycle—at the point where the *Plasmodium* ookinete becomes transformed into an oocyst in the mosquito gut—exert their effects differently.When the investiga-

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