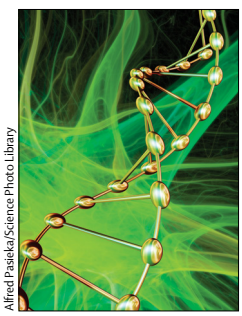
Progress in autism research and postgenomic studies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In their Comment,[1] Berg and Dobyns call for the identification of more genetic mutations to better define the phenotype of developmental disorders. Here, I argue that this static view of brain development, which directly links genotype and phenotype, does not take into account the cascade of deleterious events triggered by mutations.

The developing brain is not a small adult brain. Voltage-gated and transmitter-mediated ionic currents have unique features and, like the brain oscillations they generate, follow developmental sequences that progressively change to adult features. Slow kinetic, immature currents enable heterogeneous neurons to activate, connect together, and build neuronal assemblies. Developmental processes such as proliferation, migration, neuronal growth, or synapse formation are heavily dependent on activity and environmental cues.[2,3,4] Errors or injury during this process will have long-term deleterious effects that depend on the type of neuron affected and timing. Mutations that affect early born hub neurons,[3] which orchestrate the activity of large neuronal populations, will not have the same effects as those mutations that alter later born neurons. Genetic mutations implicated in autism spectrum disorders notably code for cytoskeletal or synaptic proteins that, when invalidated, will lead to a vicious cycle of events deviating developmental sequences and the formation of misplaced or misconnected neuronal ensembles, with deleterious consequences. From a therapeutic perspective, reintroduction of the correct gene in an animal model at best attenuates the effects of mutations during a small window of opportunity that corresponds to late gestation in human beings,[5] which is a strategy very unlikely to be used for obvious ethical and efficiency reasons.

I have proposed the notion of neuroarcheology—the idea that immature neurons affected by a mutation remain in an immature state and generate currents that perturb the function of adjacent networks and hamper their integrative properties.[6] Therefore, specific antagonists of immature currents generated in the adult brain by misplaced or misconnected neurons will prevent these perturbations, thus constituting a new therapeutic strategy. As an example, development is associated with a progressive reduction of intracellular chloride concentrations and a developmental GABA excitatory-to-inhibitory shift.[3] This shift is eliminated in animal models of autism and its restoration by the diuretic bumetanide, which re-establishes low concentrations of intracellular chloride, attenuates the severity of the disorder.[7] In clinical trials, bumetanide attenuated the severity of the disorder in children with autism.[8] Collectively, these findings call for more efforts and investments to determine the dynamic alterations produced by genetic mutations in animal models. To understand, characterise, and possibly treat developmental disorders, we must identify developmental processes, establish how they are deviated by mutations of environmental insults, and the properties of misplaced and misconnected neurons. Identification of more mutations and linear linkage of genotype and phenotype will not be sufficient to understand and treat autism and related developmental disorders.

YB-A is the chief executive officer of and reports grants and personal fees from Neurochlore, and has a patent for the use of NKCC1 antagonists to treat autism.

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