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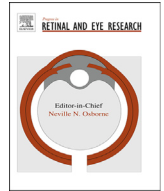

Genomic control of neuronal demographics in the retina

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ABSTRACT

The mature retinal architecture is composed of various types of neuron, each population differing in size and constrained to particular layers, wherein the cells achieve a characteristic patterning in their local organization. These demographic features of retinal nerve cell populations are each complex traits controlled by multiple genes affecting different processes during development, and their genetic determinants can be dissected by correlating variation in these traits with their genomic architecture across recombinant-inbred mouse strains. Using such a resource, we consider how the variation in the numbers of twelve different types of retinal neuron are independent of one another, including those sharing transcriptional regulation as well as those that are synaptically-connected, each mapping to distinct genomic loci. Using the populations of two retinal interneurons, the horizontal cells and the cholinergic amacrine cells, we present in further detail examples where the variation in neuronal number, as well as the variation in mosaic patterning or in laminar positioning, each maps to discrete genomic loci where allelic variants modulating these features must be present. At those loci, we identify candidate genes which, when rendered non-functional, alter those very demographic properties, and in turn, we identify candidate coding or regulatory variants that alter protein structure or gene expression, respectively, being prospective contributors to the variation in phenotype. This forward-genetic approach provides an alternative means for dissecting the molecular genetic control of neuronal population dynamics, with each genomic locus serving as a causal anchor from which we may ultimately understand the developmental principles responsible for the control of those traits.

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1. Introduction

The nervous system is assembled during development through various processes that control the size, the distribution, and the connectivity of different populations of neurons. Neuronal function, in turn, depends upon the effective outcome of these various developmental events, leading to the common presumption that there is an optimal number of neurons in each population in order to establish the proper ratio of afferent and target cells in a neuronal circuit. Indeed, different species exhibit conspicuous variation in both neuronal number and in the ratios of their pre-to post-synaptic populations, suggesting that such developmental processes are precisely controlled to ensure the neuronal wiring and connectivity that is unique to each species.

For instance, numerous studies have shown how manipulating the expression of a particular gene can yield conspicuous alterations in the proportions of different neuronal populations, for instance, increasing the numbers of some cell types at the expense of others. This approach has been most fruitfully employed in the study of fate assignment within the retina, where a hierarchical transcription factor code has been shown to modulate neuronal competence, determination and differentiation (Bassett and Wallace, 2012; Ohsawa and Kageyama, 2008; Xiang, 2013), and where the associated gene regulatory networks mediating these events are being dissected in increasing detail (Kwasnieski et al., 2012; Mu and Klein, 2008; Wang et al., 2014). Others studies have demonstrated how modifying the size of a target population of neurons during development can yield corresponding changes in the number of their afferents. Such target-dependency, best illustrated within the peripheral nervous system, has been shown to depend upon trophic factors that control cell survival (Cowan, 2001; Davies, 1996). “Quantitative (or numerical) matching” of pre- and post-synaptic populations was said to be achieved by such a mechanism, placing the critical control of neuronal number upon a target-dependent modulation of programmed cell death (Buss et al., 2006). Within the central nervous system, the retinal ganglion cell population has been one of the most thoroughly studied populations, having been shown to undergo substantial programmed cell death during development (Linden and Reese, 2006), where the amount of cell loss is modulated by the size of the target tissue (as well as by afferent innervation) and factors secreted therein (Spalding et al., 2004; Voyatzis et al., 2012). Together, these studies would suggest that the precision in neuronal number within the retina is regulated with exquisite cell-intrinsic transcriptional control but also modulated by target-dependent trophic support to establish the characteristic neuronal architecture and associated cellular ratios that underlie visual performance unique to each species (Fig. 1). We begin by considering the evidence for this presumption using the mouse retina.

2. Neuron number is precisely specified in the mouse retina

In order to examine the generality of these conclusions, we recently quantified the sizes of twelve different neuronal populations in the retina across a collection of 26 genetically distinct recombinant inbred mouse strains (Keeley et al., 2014a). Specifically, we sought to assess the extent to which the population size of retinal neurons is tightly controlled, and whether such specification serves to ensure consistent species-typical afferent-to-target cell ratios. These strains, the AXB/BXA strain-set, were originally derived from two parental inbred laboratory strains (C57BL/6J, called B6/J hereafter, and A/J), each one of them being a unique mix, due to recombination during meiosis, of their respective haplotypes (abbreviated *B* versus *A*, respectively) throughout the genome (Williams et al., 2001) (Fig. 2). We sampled the populations of rod and cone photoreceptors, horizontal cells, four types of bipolar cells, and five different populations of amacrine cells (Fig. 3A), populations that can be reliably determined and discriminated from other cells of the same class. These different populations exhibit a massive range in their absolute numbers, from millions of rod photoreceptors to as few as hundreds of dopaminergic amacrine cells (Fig. 3B). Despite this enormous variation in number between the cell types, we found the range of variation for any particular cell type in a strain to be limited, and fairly consistent, across the twelve cell types. For example, the coefficient of variation (CoV), averaged across the 26 strains, ranged from a low of 0.030 for the VGluT3+ amacrine cell population, to a high of 0.065 for the Type 4 cone bipolar cell population (Fig. 3C).

We expected to find that estimating the size of larger populations through sampling only a small proportion of total retinal area would lead to greater variability across individuals, yet we found no such correlation between population size and CoV: for instance, we found a comparably low average CoV for the largest neuronal population (the rod photoreceptors, being 0.036), for which we had sampled only ~0.1% of total retinal area, as we did for the sparsest neuronal population (the dopaminergic amacrine cells, having an average CoV of 0.045), for which we sampled the entirety of the retina (Keeley et al., 2014a). As every individual mouse within each strain should be genetically identical, this variation observed within any strain should arise from some combination of technical or sampling variance plus that due to any intrinsic variability in biological processes governing the determination of cell number (see Keeley et al., 2016, for a fuller consideration of this point). That these non-genetic contributions yielded relatively meager variation would indicate an impressive degree of precision in the control of neuronal number. Indeed, one may marvel as much at the fidelity by which the developing retina produces a precise if tiny number of cells (the dopaminergic amacrine cells, totaling ~0.01% of all retinal neurons) as when it consistently produces a precise if enormous number (the rod photoreceptors, totaling about three-quarters of all retinal neurons; Jeon et al., 1998; Macosko et al., 2015).

3. Different strains of mice show considerable variation in neuron number

This degree of control over neuronal number within a strain is the more remarkable when considering the terrific variation in number *between* the strains, for every cell type. For instance, the population of rod photoreceptors increases, from the strain with the lowest number (having 6,051,100 cells) to the strain with the highest number (with 8,227,260 cells), by 36%. The population of Type 3b cone bipolar cells shows a 60% increase, and that for the horizontal cells shows a 92% increase, while the population of dopaminergic amacrine cells increases by 298% (Keeley et al., 2014a) (Fig. 3C). For every one of these different cell types, the variation in cell number (from the strain with the lowest number to the strain with the highest number) is graded, rather than conspicuously step-like with discrete phenotypic groupings of the strains (histograms in Fig. 3B), indicating that cell number must be a complex trait controlled by multiple genes for which variants discriminate the two parental genomes. Nerve cell number, therefore, varies substantially across these different mouse strains, due to the actions of allelic variants in many genes. Imagine how many more variants would be brought into play on a mixed genetic background like our own.

4. Variation in neuron number is largely uncorrelated between different cell types

We can use this dataset on neuronal number, derived from

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