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Shared Cell Biological Functions May Underlie Pleiotropy of Molecular Interactions in the Germ Lines and Nervous Systems of Animals

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Evolutionary developmental biology focuses on understanding the origin and evolution of extant biological variation, and the genetic basis for this variation. The genetic toolkit appears largely finite across animals, such that a combination of regulatory evolution, gene recruitment (co-option) and genetic modularity often allow morphological and developmental diversity to arise. Here we summarize a number of observations from across animals, which together suggest that many genes and gene product interaction "modules" originally characterized for their role in the germ line also have neural roles. We explore potential explanations for this observation, noting that in the context of the germ line, these genes appear to have molecular and biochemical properties that make them well-suited to breaking symmetry within cells. The resulting asymmetry is often caused by gene products co-localizing asymmetrically to sub-cellular, non-membrane bound, electron dense compartments known as ribonucleoprotein (RNP) granules. RNP granules contain high concentrations of translationally quiescent messenger RNAs and proteins and are thought to act as hubs of localized translational control. We propose that the use of strict translational control, which may be achieved via molecular processes important for RNP granule formation and/or small RNA-related processes, is an important property of and a commonality between the germ line and nervous tissues, and helps explain, at least in part, the close relationship between these two tissue types.

Keywords: genetic toolkit, co-option, modularity, developmental function evolution, germ line, nervous system, RNP granules, pleiotropy

INTRODUCTION

Understanding the genomic basis of extant biological variation over evolutionary time scales has been the main focus of modern evolutionary developmental biology (evo-devo) research. In the pre-genomic era, it was unclear to what extent genes unique to an organism were the basis of their morphological, cellular and biological diversity (King and Wilson, 1975). Over the years, however, a large body of evo-devo work has led to the realization that much of the biological variation in extant animals has evolved based on an ancestral genetic toolkit (Peterson and Davidson, 2000).

Genes in such shared ancestral toolkits are often conserved both in sequence and developmental function across animals (e.g., *Hox* genes) (Hrycaj and Wellik, 2016). In other cases, conserved genes have been co-opted for additional, distinct biological roles, leading to pleiotropic gene functions (e.g., *distal-less*, *yellow*) (Panganiban et al., 1997; Gompel et al., 2005; Moczek and Rose, 2009; Khila et al., 2012). Both scenarios ultimately contribute to morphological diversity between species, within species, and between cell types within an organism, underpinned by a combination of differences in developmental gene regulation and modularity. Pleiotropy is widespread in genomes, can contribute to phenotypic variation, and may occur through a variety of molecular mechanisms (Guillaume and Otto, 2012), including alternative splicing, different substrate or binding partner affinities, localization to different cellular compartments or tissues, or the same gene product having more than one distinct biochemical property. Barring the extreme cases of "housekeeping" genes (usually ubiquitously expressed) and so-called "luxury" genes (expressed in only one tissue type) (King et al., 2013), most animal genes likely exhibit some degree of pleiotropy (Hodgkin, 1998).

Over the past two decades, multiple primary data observations and some synthetic overviews of the literature (see for example Broadus et al., 1998; Roegiers and Jan, 2000) have hinted at a potentially underappreciated example of pleiotropy that we wish to draw further attention to with this review: namely, that a number of genes sometimes dubbed "germ line genes" based on the initial primary characterization of their roles in the germ lines of animals, also have roles in the development and/or functioning of the nervous system. For example, on a genome-wide scale, tissue-specific transcriptome studies in both humans and mice have shown that the testes and nervous system are two tissues that share a larger overlap in their gene expression profiles and proteomes than they do with any other tissue types within the animal (Guo et al., 2005). Here we gather evidence for this dual tissue expression pattern across multiple metazoans. In cases where "germ line genes" are documented as playing a neural role in one species, we ask whether there is evidence that these genes play any neural role in additional species, and whether they share the same set of interactors. We provide possible molecular mechanistic explanations and suggest that these observations may be explained by co-option of pre-existing molecular interactions to new developmental contexts. Both germ cells and neurons use subcellular compartmentalization of gene products as a mechanism for proper cellular functioning. Neurons are highly compartmentalized cells, and localized translational control within and between synapses is an important mechanism regulating neuronal function (Holt et al., 2019). Likewise, germ cells often require subcellular localization of specific gene products for normal functioning of germ cells or patterning of early embryos, which can be achieved by localized translational control (Pushpa et al., 2017). In addition, both these tissues rely on small RNAs for proper functioning. Small RNAs are important for maintaining the genomic integrity of the germ line and also have key roles in memory and synaptic plasticity in the nervous system of animals (Saxe and Lin, 2011; Posner et al., 2019). Thus, we aim to summarize and synthesize data that may be relevant to understanding both the molecular and cellular basis of pleiotropy in this specific context. More generally, this approach may help shed light on the origins of cell type diversity and evolutionary novelty.

Genes With Shared Roles in the Germ Line and Nervous System

In the following sections, we present evidence from primary literature for genes best known for their role in the germ line, that are also expressed in the nervous system, either singly or in groups of gene products with conserved molecular interaction. Wherever possible, we present currently available data for the functions of these genes in both these tissues. For each example, we briefly summarize their roles in the germ line and in the nervous system (**Table 1**), providing a list of reported molecular interaction partners in both tissues (**Table 2**). In cases where, to our knowledge, no molecular interaction data are available, we point out evidence of their co-expression, acknowledging that co-expression may not reflect conserved molecular interactions. This gene list is not exhaustive, as it is necessarily limited to those that, to our knowledge, have been specifically examined in the context of both tissue types across animals. For each gene discussed, we note whether it predates animals or not, based on OrthoMCL-DB predictions (Chen et al., 2006). Because we aim to point out conserved molecular interactions reported in both cell types, we discuss those genes with more abundant co-IP and other interaction data in both germ line and nervous system first, and end with genes for which data are available primarily for only one tissue type. We discuss genes in groups, to indicate reported conserved molecular interactions between their gene products.

staufen (stau) *and* barentsz (btz)

staufen (stau) was first identified in a maternal effect genetic screen for *Drosophila melanogaster* mutants with anterior-posterior body polarity defects, while *barentsz* (*btz)* was identified in a female sterile chromosome screen for mutants with defects in localization of Stau protein (Schüpbach and Wieschaus, 1986; van Eeden et al., 2001). Stau belongs to a conserved family of animal proteins (Chen et al., 2006) that contain multiple double-stranded RNA binding domains, and *stau* orthologs are present in bilaterian outgroups, protostomes and deuterostomes (Heraud-Farlow and Kiebler, 2014). *btz* genes also appear to be animal-specific (Chen et al., 2006), and Btz protein is a component of the exon junction complex (Ariz et al., 2009), which regulates spliced mRNAs (Bono et al., 2006).

stau *and* btz *in the germ line*

During *D. melanogaster* oogenesis, Stau and Btz localize to the cytoplasm at the posterior of the oocyte, where they both have a role in primordial germ cell (PGC) specification and establishment of the anterior-posterior axis of the embryo (St Johnston et al., 1991; van Eeden et al., 2001). Stau is required for the posterior localization and translation of the mRNAs of oskar (*osk*), another gene whose products likely have evolved similar molecular interactions in both germ line and nervous systems [see "oskar (osk), nanos (nos), piwi and vasa (vas)"

TABLE 1 | Summary of germ line and nervous system roles of genes discussed in the text, listed here in alphabetical order.

Gene name(s)	Molecular feature(s) and function(s)	Germ line functions	Nervous system functions
barentsz and *staufen*	Stau: contains double RNA binding domains Btz: exon junction complex component	Germ cell specification, axial patterning	Plasticity and learning, mRNA trafficking, mRNA localization and translation, spine morphogenesis, asymmetric cell division and differentiation of neuroblasts
boule and *twine*	Bol: RNA-binding protein Twe: putative Cdc25-type tyrosine phosphatase	Gametogenesis in males	Axon and dendrite morphogenesis, neuronal development and neuronal communication
CPEB	RNA binding protein implicated in mRNA translation and localization via regulation of mRNA poly(A) tail length	Establishment of egg polarity and cytoskeletal network, germ cell development, meiosis entry, *oskar* and *gurken* translation and localization	Synaptic plasticity, neurogenesis, learning and memory, asymmetric cell division, RNA trafficking, translational control, regulation of mRNA poly(A) tail length
FMRP	RNA binding protein	Germ cell proliferation, maintenance and gamete development	Synaptic plasticity, neurogenesis, dendrite morphogenesis, RNA trafficking, translational control and regulation of mRNA poly(A) tail length
oskar	binds RNA (OSK domain), interacts with Vasa (LOTUS domain); predicted disordered region	Germ cell specification, nucleator involved in germ plasm assembly and posterior patterning	Neuroblast divisions in crickets; larval dendrite morphogenesis in *D. melanogaster*
nanos and *pumilio*	Nos: contains C2H2 Zn-finger domain; RNA-binding protein Pum: RNA-binding protein	Posterior embryonic patterning, translation inhibition	Long term memory, dendrite morphogenesis
piwi	PAZ-PIWI domain family member	Germ line development, gametogenesis, transposon silencing, small RNA biogenesis, in pluripotency, pan-germ line marker	Small RNA biogenesis, transposon silencing, mRNA translational control, long term memory
vasa	ATP-dependent DEAD box RNA helicase	Segregation and maintenance of germ line, pan-germ line marker, pluripotency, nuage component involved in modeling RNP complexes, RNA metabolism, small RNA biogenesis, chromosome condensation	In crickets, evidence for roles in neuroblast divisions

below] mRNA, and Stau and Btz form a complex and move together during this posterior localization event (van Eeden et al., 2001). Additionally, *btz* null mutants show defects in Stau protein and *osk* mRNA localization to the posterior of the oocyte (van Eeden et al., 2001).

stau *and* btz *in the nervous system*

Evidence from multiple animals suggests that Stau and Btz function together in neuronal cells via mechanisms similar to those observed in the germ line. Stau is concentrated in ribonucleoprotein (RNP) granules within *D. melanogaster* neurites in the larval nervous system, where it co-localizes with Btz and dFMR1 (Barbee et al., 2006). Such Stau-Btz-containing neuronal granules also contain molecules that are found in yeast and mammalian somatic P-bodies (e.g., Dcp1p, Xrn1p), suggesting that neuronal and germ line Stau-containing granules may be similar to somatic P-bodies in molecular composition (Barbee et al., 2006). Stau is also present in the *D. melanogaster* neuromuscular junction (NMJ). At the NMJ, it is localized to the post-synaptic compartment, where it regulates localization and translation of *coracle* (*cora*) mRNA (Gardiol and St Johnston, 2014). *cora* in turn promotes synaptic bouton formation, and accordingly loss of *stau* leads to a reduction in synaptic bouton number (Macchi et al., 2003). The same Stau domain that is required in oocytes for the translation and localization of the mRNA of *osk* [see *oskar (osk), nanos (nos), piwi and vasa (vas)* below] (Micklem et al., 2000), called "dsRNA binding domain 5," is also required for local *cora* translation at the NMJ, and Cora protein fails to localize to the NMJ in *stau* mutants lacking this domain (Gardiol and St Johnston, 2014). Furthermore, Tropomyosin II, which, like Stau, localizes *osk* to the oocyte posterior (Erdelyi et al., 1995), is also required for *cora*'s NMJ localization (Gardiol and St Johnston, 2014). Stau plays a critical role in asymmetric neuroblast divisions (Jia et al., 2015) and long-term memory formation in *D. melanogaster* (Dubnau et al., 2003), a role that appears conserved in the mollusk *Aplysia californica* (Liu et al., 2006).

In mouse and rat neurons, Stau is contained within RNP particles distributed along the somatodendrites of hippocampal neurons (Tang et al., 2001; Macchi et al., 2003). Btz also co-localizes with Stau in these granular RNPs in hippocampal neurons, and these two proteins co-immunoprecipitate from doubly transfected Baby Hamster Kidney fibroblasts (Macchi et al., 2003). Fritzsche et al. (2013) have recently reported a protein interactome for Stau- and Btz-RNPs in the rat brain, which includes some proteins also found in germ cells, such as Pum [see "nanos (nos) and pumilio (pum)" below] and FMRP [see "Fragile Mental Retardation Protein (FMRP), argonatue (AGO) piwi and staufen (stau)" below]. In mice and rats, Stau is implicated in spatial learning, novelty preference and explorative behavior (Berger et al., 2017; Popper et al., 2018), and in

TABLE 2 | Summary of selected gene products and their reported physical interactors in the germ line and in nervous system tissues, listed here in alphabetical order.

Gene	Interactor	Germ Line	Nervous System	References
Barentsz	eIF4AIII	Y2H, pull-down assay	Co-IP	Palacios et al., 2004; Fritzsche et al., 2013
	Mago Nashi	Co-IS	Co-IP	van Eeden et al., 2001; Fritzsche et al., 2013
	Staufen	Co-IS	Co-IP	van Eeden et al., 2001; Fritzsche et al., 2013
	Cup	Co-IS		Wilhelm et al., 2003
	Oskar	Co-IS		van Eeden et al., 2001; Fritzsche et al., 2013
	Piwi	Co-IS		Fritzsche et al., 2013
	FMRP		Co-IP	Fritzsche et al., 2013
	Pumilio	Co-IS	Co-IS	Vessey et al., 2006
Boule	**Orb2**	Co-IP		Xu et al., 2012
	Pumilio	Co-IS, Y2H, Co-IP		Moore et al., 2003
CPEB	**Oskar**	Co-IS, Co-IP, pull down		Chang et al., 1999; Rojas-Rios et al., 2015
	Gurken	Co-IS		Davidson et al., 2016
	Cup	Co-IS, Co-IP		Wong et al., 2011
	FMRP	Co-IS, Co-IP	Co-IS	Costa et al., 2005
	Pumilio	Co-IP		Eddy, 1975
	Boule	Co-IP		Knutson et al., 2017
	Neuroguidin	Co-IP	Co-IS	Jung et al., 2006
	CaMKII		Co-IS	Huang et al., 2002
	eIF4E	Co-IP, Y2H		Stebbins-Boaz et al., 1999
	Cyclin B1	Co-IP		Meijer et al., 2007
	Maskin	Co-IP, Y2H	Co-IS	Stebbins-Boaz et al., 1999; Huang et al., 2003
FMRP	GLD		Co-IP	Kwak et al., 2008
	Staufen		Co-IP, Co-IS	Barbee et al., 2006; Fritzsche et al., 2013
	Pumilio		Co-IS	Barbee et al., 2006; Vessey et al., 2006
	Nanos	Co-IP	Co-IS	Barbee et al., 2006; Megosh et al., 2006
	Piwi	Co-IP		Megosh et al., 2006
	Argonaute-1	Co-IP		Yang et al., 2007
Nanos	Cup	Y2H, Co-IP		Verrotti and Wharton, 2000
	Pumilio	Co-IP		Joly et al., 2013
	Twine	Co-IP		Joly et al., 2013
	Myosin Light chain	Y2H, Pull-down assay		Xu et al., 2010
	Staufen	Co-IS	Co-IS	Barbee et al., 2006
Oskar	Homer	Co-IP		Babu et al., 2004
	Staufen	Y2H		Breitwieser et al., 1996
	Cup	Y2H, Co-IP		Ottone et al., 2012
	Vasa	Y2H	Co-IS	Breitwieser et al., 1996; Ewen-Campen et al., 2012; Jeske et al., 2015, 2017
	Lasp	Y2H, Pull-down assay		Suyama et al., 2009
	Par-1	*in vitro* Kinase assay		Morais-de-Sa et al., 2013
	Piwi	Co-IS	Co-IS	Ewen-Campen et al., 2012
Piwi	**Vasa**	Co-IP	Co-IS	Megosh et al., 2006; Ewen-Campen et al., 2012
	FMRP	Co-IP		Megosh et al., 2006
	Kumo	Co-IP		Anand and Kai, 2012
	Vreteno	Co-IP		Handler et al., 2011
	Papi	Y2H, Co-IP		Liu et al., 2011
Pumilio	**Nanos**	Co-IP		Joly et al., 2013
	Twin	Co-IP		Joly et al., 2013
	CPEB	Co-IP		Ota et al., 2011
	DAZL	Co-IP		Ota et al., 2011
	Maskin	Co-IP		Ota et al., 2011
	Staufen		Co-IS	Barbee et al., 2006; Vessey et al., 2006
	FMRP		Co-IS	Barbee et al., 2006; Vessey et al., 2006
Staufen	Miranda		Y2H, Co-IS	Schuldt et al., 1998
	Barentsz	Co-IS	Co-IP, Co-IS	van Eeden et al., 2001; Macchi et al., 2003; Barbee et al., 2006; Fritzsche et al., 2013
	MAPK		Co-IP	Nam et al., 2008
	Oskar	Y2H, Co-IS		St Johnston et al., 1991; Breitwieser et al., 1996
	Inscuteable		Y2H	Li et al., 1997

(Continued)

TABLE 2 | Continued

Gene	Interactor	Germ Line	Nervous System	References
	FMRP		Co-IP, Co-IS	Villacé et al., 2004; Barbee et al., 2006; Price et al., 2006; Fritzsche et al., 2013
	Dynein		Co-IP	Villacé et al., 2004
	Beta-actin		Co-IP	Villacé et al., 2004
	Cdc42		Co-IP	Villacé et al., 2004
	Beta-tubulin		Co-IP	Villacé et al., 2004
	Kinesin		Co-fractionation	Mallardo et al., 2003
	Cup	Co-IP	Co-IS	Barbee et al., 2006
	Pumilio		Co-IS	Barbee et al., 2006; Vessey et al., 2006
	Piwi		Co-IP	Fritzsche et al., 2013
Vasa	dIF2	Y2H		Carrera et al., 2000
	Cup	Y2H, Co-IP		Ottone et al., 2012
	Oskar	Y2H	Co-IS	Breitwieser et al., 1996; Ewen-Campen et al., 2012; Jeske et al., 2015; Jeske et al., 2017
	Cyclin B	Co-IS		Yajima and Wessel, 2011a

Methods used to provide evidence for indicated gene interactions are abbreviated as follows: Y2H (yeast two hybrid), co-IP (co-immunoprecipitation), co-IS (colocalization in immunostaining). Genes discussed in the manuscript are indicated in bold.

humans Stau is required for normal dendritic arborization during neuroblastoma cell differentiation *in vitro* (Peredo et al., 2014). Interestingly, when expressed *in vivo* in *D. melanogaster*, GFP-tagged mouse Btz localizes to the oocyte posterior, suggesting that it can interact with *D. melanogaster* Stau (Macchi et al., 2003). However, despite this colocalization with *D. melanogaster* Stau, mouse Btz is unable to perform the function of *D. melanogaster* Btz in localizing *osk* mRNA to the posterior of the oocyte cytoplasm (Macchi et al., 2003), suggesting that not all Btz/Stau functional molecular interactions are conserved across species.

stau *and* btz: *additional relevant expression data*

stau is expressed or required in the germ line outside of fruit flies as well. In zebrafish, morpholino-mediated knockdowns of the *stau* paralogs *stau1/2* abrogate the formation of Vasa-positive PGCs (Ramasamy et al., 2006). In mice, *stau* mRNA is expressed in oocytes and during meiosis in males (Saunders et al., 2000). In human oocytes, immunofluorescence studies show that STAU protein is present throughout all stages of oocyte maturation, and that its subcellular localization changes throughout oogenesis, initially dispersed throughout the cytoplasm and later localized into large discrete granules at the cortex (De Santis et al., 2015). As in *D. melanogaster* oocytes (St Johnston et al., 1991; van Eeden et al., 2001), Stau localization to a specific region of the *Xenopus laevis* oocyte cytoplasm is required to specify PGCs (Yoon and Mowry, 2004). Human Staufen (STAU1/2) and Barentsz (CASC3) are both expressed in multiple tissues outside of the germ line and nervous system (Uhlen et al., 2015).

Fragile Mental Retardation Proteins (FMRP), argonaute (AGO), piwi *and* staufen (stau)

Fragile Mental Retardation Proteins (FMRP) are conserved RNA binding proteins that may have origins predating animals, based on the prediction of a putative ortholog in the green alga *Micromonas* (Chen et al., 2006). FMRPs underlie human Fragile X syndrome, which is an X-linked dominant disorder causing mental retardation and cognitive impairment (Ashley et al., 1993; Inoue et al., 2000). This defect is caused by an expansion of a CGG trinucleotide repeat in the *FMR1* gene, correlated with transcriptional silencing and loss of the gene product FMRP (Verkerk et al., 1991; Verheij et al., 1993). Mammalian FMRP is a member of a small protein family consisting of members FMRP, FXR1 and FXR2, all of which are RNA binding proteins containing two K homology (KH) domains and one RGG box (Siomi et al., 1995; Zhang et al., 1995). FMRP/FXR proteins also contain protein-protein interaction and 60S ribosomal subunit interaction domains (Ashley et al., 1993; Siomi et al., 1996; Wan et al., 2000). FMRP is predominantly detected in the cytoplasm of cells in multiple human tissues (Uhlen et al., 2015), including neurons, glial cells, and spermatogonia, but can also be detected in the nucleus (Devys et al., 1993; Verheij et al., 1993). The presence of nuclear localization (NLS) and export (NES) signals (Eberhart D. E. et al., 1996), suggest that it may function as a nucleo-cytoplasmic shuttle protein for RNA. *In vitro* experiments suggest that FMRP binds a selective but abundant fraction of brain RNA, but little is currently known about the identity of these targets (Ashley et al., 1993; Brown et al., 1998). FMRP associates with polyribosomes (Khandjian et al., 1996; Tamanini et al., 1996; Feng et al., 1997) and negatively regulates translation (Laggerbauer et al., 2001; Li et al., 2001; Zhang et al., 2001). While all three orthologs of the FMRP/FXR family are found in multiple vertebrates, only one homolog, called *dfmr1*, has been reported in *D. melanogaster* (Wan et al., 2000).

FMRP, AGO and piwi *in the germ line*

FMRP plays roles in germ line development in *D. melanogaster* and mammals, in both cases via interactions with Piwi or Piwi-related proteins of the *Argonaute* family (AGO). In *D. melanogaster* Dfmr1 protein co-immunoprecipitates with Ago1 in ovaries and in adult testes (Yang et al., 2007; Bozzetti et al., 2015). Similarly, in embryos Dfmr1 forms a complex with Piwi during the formation of the specialized cytoplasm, called germ plasm, that ensures PGC specification in *D. melanogaster*

(Megosh et al., 2006). In *dfmr1* homozygous null mutants, the ovaries contain fewer germ line stem cells (GSC) than controls, suggesting that *dfmr1* is required for GSC maintenance (Yang et al., 2007). *dfmr1* and *piwi* mutants show similar phenotypes of defective pole plasm and reduced PGC number (Megosh et al., 2006). In mice, *FMR1* knockout mice display macroorchidism, a disorder in which males have abnormally large testes, in this case caused by an increased postnatal proliferation of Sertoli cells (Slegtenhorst-Eegdeman et al., 1998), which are associated with and required for correct development of male gametes. In mouse testes and in human embryonal carcinoma cell lines derived from testes, *FMR1* and *AGO1* regulate *miRNA-383*, implicating *FMRP* in small RNA-mediated gene regulation in the mammalian germ line (Tian et al., 2013).

FMRP, AGO, piwi *and* stau *in the nervous system*

FMRP is implicated in multiple neuronal functions in fruit flies and mice, including synaptic plasticity (Padmashri et al., 2013; Feuge et al., 2019), dendritic morphogenesis (Feuge et al., 2019), and olfactory learning and memory (Nimchinsky et al., 2001; Bolduc et al., 2008; Sears et al., 2019). Some studies report that homozygous *FMR1* knockout mice display defects in dendritic spine morphology (e.g., Nimchinsky et al., 2001; Bolduc et al., 2008) [but see Feuge et al. (2019) for a report of no abnormal dendritic spine morphology in FMRP knockout mice]. FMRP also appears important for adult mouse neurogenesis: *FMR1* knockout mice show misregulation of multiple genes expressed in adult neural progenitor cells (Liu et al., 2018), increased neural progenitor cell proliferation and incorrect neuronal fate specification (Luo et al., 2010), significant reduction in hippocampal neurogenesis (Guo et al., 2011), and reduced hippocampal-dependent learning (Guo et al., 2011). Furthermore, in *D. melanogaster,* Dfmr1 and Ago1 are required for the regulation of synaptic plasticity (McBride et al., 2005; Bolduc et al., 2008; Sudhakaran et al., 2014). *Dfrm1* loss of function mutants show ectopic axon growth (Tessier and Broadie, 2008), and trans-heterozygotes for *dfmr1* and *Ago1* have overgrown synapses and abnormally elaborate synaptic terminals compared to wild type flies and single heterozygotes (Jin et al., 2004). This phenotype is reminiscent of that of homozygous *FMR1* knockout mice, which some researchers report have dendritic spines that are longer than controls (Comery et al., 1997; Nimchinsky et al., 2001) [but see Feuge et al. (2019)]. The molecular functions of FMRP in neurons include trafficking RNA in both fruit fly (Estes et al., 2008) and mouse (Antar et al., 2005; Dictenberg et al., 2008) neurons, regulating length of the mRNA poly(A) tail (Bienkowski et al., 2017), and local translational regulation in both dendrites and cell bodies of neurons (Darnell et al., 2011; Darnell and Klann, 2013). FMRP also co-immunoprecipitates with Stau in rat neurons (Price et al., 2006), and complexes with Stau in transfected human cells and differentiated human neuroblasts (Villacé et al., 2004). An ortholog of *FMRP* has been identified in the cnidarian *Hydractinia echinata* (HyFMR1), where it is expressed in neural precursors and nerve cells in the mature polyp (Guduric-Fuchs et al., 2004).

nanos (nos) *and* pumilio (pum)

nanos (nos) and *pumilio* (*pum)* were first identified in genetic screens for *D. melanogaster* embryos with posterior and abdominal specification defects (Lehmann and Nüsslein-Volhard, 1987; Nüsslein-Volhard et al., 1987; Lehmann and Nusslein-Volhard, 1991). Pum belongs to a conserved RNA-binding protein family that is found across eukaryotes (Zamore et al., 1997; Zhang et al., 1997; Gamberi et al., 2002; Chen et al., 2006). Its signature PUF domain is named after *D. melanogaster* Pumilio and the *Caenorhabditis elegans* translational regulator FBF (fem-3-binding factor) (Zhang et al., 1997). PUF proteins are implicated in post-transcriptional gene regulation (Wang et al., 2018), stem cell maintenance (Lin and Spradling, 1997; Forbes and Lehmann, 1998; Crittenden et al., 2002; Ariz et al., 2009), axial patterning (Lehmann and Nüsslein-Volhard, 1987; Nüsslein-Volhard et al., 1987; Lehmann and Nusslein-Volhard, 1991), and learning and memory (Dubnau et al., 2003). *nos* is an animal-specific gene (Chen et al., 2006) maternally required for the development and maintenance of the *D. melanogaster* germ line, and zygotically for embryonic patterning and PGC migration in the developing embryo (Wang and Lehmann, 1991; Wang et al., 1994; Kobayashi et al., 1996). Pum proteins often function together with Nos proteins during development (Sonoda and Wharton, 1999; Parisi and Lin, 2000; Jaruzelska et al., 2003), including in the germ line and nervous system, as detailed below.

nos *and* pum *in the germ line*

In *D. melanogaster, nos* and *pum* act together as inhibitors to repress *hunchback* and *bicoid* translation in the posterior of the embryo (Wharton and Struhl, 1991; Zamore et al., 1999). Pum is thought to directly bind *hunchback* and *bicoid* mRNAs, and to bring Nos to the repression complex (Murata and Wharton, 1995; Sonoda and Wharton, 1999). *nos* and *pum* are required in the germ line for continued egg chamber production during oogenesis, by regulating the germ line stem cell to cystoblast fate transition via translational repression of oocyte differentiation genes (Wang et al., 1994; Lin and Spradling, 1997; Forbes and Lehmann, 1998; Szakmary et al., 2005; Joly et al., 2013). *nos* is required in embryonic development for PGC survival and migration (Kobayashi et al., 1996; Sano et al., 2001; Hayashi et al., 2004; Sato et al., 2007), as well as for patterning the abdomen and embryo posterior (Wang and Lehmann, 1991; Wang et al., 1994).

Requirements for, and genetic and physical interactions between, Nos and Pum in the germ line are conserved in many animals. In *C. elegans*, *nos-1*, *nos-2* and a subset of *pumilio*-related genes (*fbf-1*/*fbf-2, puf-6*/*puf-7* and *puf-8*) are required for various aspects of PGC development, including PGC migration, cell death and proliferation (Subramaniam and Seydoux, 1999). In *X. laevis* oocytes, Pum protein co-immunoprecipitates with a *X. laevis* ortholog of *nos* (Nanos1; also called Xcat2) (Lai et al., 2011), and binds *cyclin B* transcripts (Nakahata et al., 2001). In addition to their conserved physical interaction, at least some targets of Nos/Pum may also be conserved: in *D. melanogaster*,

these proteins also bind to and repress translation of *cyclin B1* (Kadyrova et al., 2007). In zebrafish, Pum2 is expressed in male and female gonads, and is important for germ cell and nervous tissue development (Wang et al., 2012). Furthermore, a zebrafish homolog of *nos* is involved in PGC maintenance and migration into the future gonad (Koprunner et al., 2001).

nos and pum *in the nervous system*

nos and *pum* also play roles in the development and function of the nervous system of multiple taxa. For example, in *D. melanogaster*, Nos colocalizes with RNA granules in dendrites, and both *nos* and *pum* are needed for appropriate dendrite morphogenesis, suggesting that they may repress mRNA translation in the nervous system as they do in the germ line (Ye et al., 2004). In larval class IV neurons, *nos* mRNA requires *osk* for appropriate localization, as described below (Xu et al., 2013). In addition, long-term memory in *D. melanogaster* requires *pum* (Dubnau et al., 2003; Chen et al., 2008).

In mice, Pum2 is localized with RNP particles in the somatodendritic region of hippocampal neurons (Vessey et al., 2006), and Pum1 and Pum2 are required for hippocampal neurogenesis and proper functioning (Zhang et al., 2017). Furthermore, mouse Pum2 is implicated in forming stress granules under metabolic stress in neurons, in dendritic morphogenesis, and in regulating the synaptic function along dendritic shafts (Vessey et al., 2006, 2010). Interestingly, *nos1* knockdown mice show no detectable neural defects in terms of behavior or fertility (Haraguchi et al., 2003). In the *C. elegans* genome, there are three *nos*-related genes and at least ten PUF-domain proteins (Lynch et al., 2011), and PUF-domain proteins have been shown to play memory-related important roles in axonal and presynaptic regions (Lee and Schedl, 2006; Arey et al., 2019). One of these Pum-like proteins, FBF-1, is needed for the change in *C. elegans* odor sensitivity that comes with prolonged exposure, known as odor adaptation (Kaye et al., 2009). Pum also binds to the 3′UTR of the cGMP-dependent kinase EGL-4 and promotes its translation (Kaye et al., 2009). Of the three *nos*-related genes, NOS-1 is required for odor adaptation (Kaye et al., 2009).

nos *and* pum: *additional relevant expression data*

Outside of bilaterians, there is also evidence for expression and function of *nos* and *pum* orthologs in the germ line. In the sexual polyp of the hydroid *H. echinata*, a *pum* ortholog and the *nanos* ortholog *nos2* are both expressed in oocytes (Kanska and Frank, 2013), as are *nos* orthologs in the jellyfish *Podocoryne carnea* (Torras et al., 2004) and *Clytia hemisphaerica* (Leclère et al., 2012). In *H. magnipapillata, nos* orthologs *Cnnos1* and *Cnnos2,* are both expressed in the germ line (Mochizuki et al., 2000). In the anthozoan *Nematostella vectensis,* the *nos* ortholog *Nvnos2* is expressed in putative germ cells during embryogenesis and in developing oocytes (Extavour et al., 2005; Torras and Gonzalez-Crespo, 2005). *nos* orthologs are also expressed in developing gametes in the sponges *Sycon ciliatum* (Leininger et al., 2014) and *Oscarella lobularis* (Fierro-Constain et al., 2017). In zebrafish, Pum2 is expressed in the brain (Wang et al., 2012). In *H. echinata,* reduction of Nos2 causes a reduction in nematogenesis (production of stinging cells called nematocytes, considered a type of neural cell) and an increase in neurogenesis (Kanska and Frank, 2013). In sponges, while putative neural tissues remain difficult to identify based on bilaterian-centric cell type criteria (Dunn et al., 2015), expression of *nos* has been reported in globular cells and cross cells, two candidate sensory cell types unique to sponges (Mah and Leys, 2017).

oskar (osk), nanos (nos), piwi *and* vasa

The insect-specific gene *oskar* (*osk*) was first identified in the fruit fly *D. melanogaster* as a maternal-effect gene that is necessary and sufficient for specifying both the germ line and the posterior abdomen of the embryo (Lehmann and Nüsslein-Volhard, 1986; Ephrussi et al., 1991; Chen et al., 2006). Osk proteins have two conserved, well-folded domains on either side of a region of predicted high disorder (Jeske et al., 2015; Yang et al., 2015). The N terminal domain is a LOTUS domain (also called an OST-HTH domain) (Anantharaman et al., 2010) similar to that of TUDOR5 and TUDOR7 proteins (Ewen-Campen et al., 2012), and is predicted to dimerize (Jeske et al., 2015; Yang et al., 2015) and bind Vasa protein (Markussen et al., 1995; Breitwieser et al., 1996; Vanzo and Ephrussi, 2002; Jeske et al., 2017). The C terminal domain is known as the OSK domain and is implicated in binding *nanos* (see below), *oskar, germ cell less* and *polar granule component* mRNAs (Jeske et al., 2015; Yang et al., 2015).

osk, nos, piwi *and* vasa *in the germ line*

In *D. melanogaster*, *osk* is expressed from the maternal genome during oogenesis, and *osk* mRNA is deposited into the developing oocyte in a process dependent on Splicing *oskar* Location Elements (SOLE) in its 3′UTR (Ghosh et al., 2012). SOLE recruitment of Exon Junction Complex components, including *barentsz, mago nashi,* and *tsunagi*, is required for proper *osk* ribonucleoprotein (RNP) granule motility into the oocyte, and for posterior localization of *osk* within the oocyte (Ghosh et al., 2012). Posterior localization of *osk* also requires interactions with Staufen (St Johnston et al., 1991; see below) and Kinesin proteins (Brendza et al., 2002). Posteriorly localized *osk* mRNA is translated into two protein isoforms, Short Osk and Long Osk (Markussen et al., 1995). Short and Long Osk differ by an N terminal 138 amino acid (aa) addition (Markussen et al., 1995). The current model of the distinct functions of these isoforms is as follows: Long Osk localizes to endocytic membranes at the oocyte posterior (Vanzo et al., 2007; Tanaka and Nakamura, 2008), anchors both *osk* mRNA and Short Osk (Vanzo and Ephrussi, 2002; Tanaka et al., 2011), and stabilizes mitochondrial accumulation (Hurd et al., 2016). Short Osk localizes to electron-dense organelles called polar granules and recruits products of genes required for germ cell and posterior identity specification including *vasa*, *nanos*, and *piwi* (see below) (Markussen et al., 1995; Breitwieser et al., 1996; Vanzo et al., 2007). Although *osk* likely evolved in a last common insect ancestor (Lynch et al., 2011; Ewen-Campen et al., 2012; Blondel et al., 2020), the Long

Osk domain and isoform appear to have evolved only within the Diptera (Blondel et al., 2020).

osk, nos, piwi *and* vasa *in the nervous system*

Evidence for a role for *osk* in the nervous system comes from studies of two insects, *D. melanogaster* and the cricket *Gryllus bimaculatus*. In the cricket, *Gb-osk* mRNA and protein are enriched in neuroblasts in the embryonic nervous system (Ewen-Campen et al., 2012) and in the adult brain (Ewen-Campen and Extavour, unpublished). First identified in a grasshopper (Wheeler, 1891), neuroblasts are neural stem cells found in all pancrustaceans (insects and crustaceans) (Lear, 2001; Richter et al., 2010). Neuroblasts arise from the ventral ectoderm during embryogenesis and divide asymmetrically to produce all of the neurons of the nervous system. *Gb-osk* RNAi in cricket embryos results in broken or reduced lateral axon tracts, a phenotype that is consistent with neuronal division defects (Ewen-Campen et al., 2012). Neuroblasts of *G. bimaculatus* also express Vasa and Piwi proteins (Ewen-Campen et al., 2012), raising the possibility that Osk may interact with these proteins in neuroblasts, as it does in the germ line in other contexts (see section on Vasa below). In *D. melanogaster, osk* co-localizes with *nanos* (*nos*) mRNA in larval class IV neurons, and is required for correct localization of *nos* mRNA within these neurons (Xu et al., 2013).

osk, nos, piwi, *and* vasa: *additional relevant expression data*

Gene expression data suggest that *osk* also specifies germ cells in the ant *Messor pergandei*, and *osk* knockdown experiments in the wasp *Nasonia vitripennis* show that the germ cell and posterior identity specification roles of *osk* are conserved in this insect as well (Lynch et al., 2011). However, *osk* is not required for germ line establishment, maintenance or function in the cricket *G. bimaculatus* (Orthoptera) (Ewen-Campen et al., 2012).

piwi, argonaute (Ago), aubergine (aub) *and small RNAs*

PIWI proteins are evolutionarily conserved RNA binding proteins (e.g., Bohmert et al., 1998; Moussian et al., 1998; reviewed in Thomson and Lin, 2009; Ku and Lin, 2014) found across metazoan and plant genomes (Chen et al., 2006). The founder ortholog of this group was first identified in a *D. melanogaster* screen for genes that abolish asymmetrical divisions in germ line stem cells (GSCs) (Lin and Spradling, 1997), and named after the male sterility phenotype caused by loss of function mutations (PIWI: P-element induced wimpy testis). The PIWI clade of proteins belongs to the Argonaut/PIWI protein family (AGO/PIWI, also known as the PAZ-PIWI domain or PPD family of proteins) (Thomson and Lin, 2009; Ku and Lin, 2014).

piwi, AGO, aub *and small RNAs in the germ line*

PIWI proteins are expressed in germ cells or their progenitors in many animals, and their functions in the germ line have been extensively studied in a wide range of animals (Juliano et al., 2011). PIWI germ line functions include germ line determination, germ line stem cell (GSC maintenance), spermiogenesis, and silencing transposon expression in the germ line genome both at the epigenetic and post-transcriptional levels (Thomson and Lin, 2009; Ku and Lin, 2014). The latter role is performed via interaction with small RNAs, including but not limited to PIWI-associated small RNAs (piRNAs) (Iwasaki et al., 2015; Furrer et al., 2017; Rojas-Rios and Simonelig, 2018). Like *vasa*, *piwi* is also expressed in multiple somatic stem cell types outside of bilaterians.

piwi, AGO, aub *and small RNAs in the nervous system*

PIWI-related proteins play critical functions in the soma as well as the germ line (Ross et al., 2014). This includes roles in the central nervous system of all major groups of animals, including deuterostomes, protostomes, and bilaterian outgroups (Juliano et al., 2011), as illustrated by the following examples: In the sea slug *A. californica,* Piwi protein interacts with a DNA methyltransferase to control the expression of CREB2, a long-term memory repressor, during long-term memory formation (Rajasethupathy et al., 2012). The zebrafish *piwi* ortholog *ziwi* is expressed in the eye, the forebrain, and the midbrain during organogenesis (Tan et al., 2002). In the nematode *C. elegans*, the PIWI protein PRG-1 represses axonal regeneration in adult mechanosensory neurons (Kim et al., 2018). Mouse *piwi* orthologs (*miwi* genes) are expressed in the adult brain (Leighton et al., 2019), and *miwi* colocalizes with piRNAs to form RNP puncta in the dendrites of cultured hippocampal neurons (Lee et al., 2011). LNA-based antisense inhibition of one of these piRNAs results in a significant decrease in dendrite spine area (Lee et al., 2011). Further, knockdown of *piwi*-like genes in the mouse hippocampus affects adult behavior, as assayed in an experimental fear-conditioning paradigm (Leighton et al., 2019). In *D. melanogaster,* PIWI-related proteins Argonaute (Ago3) and Aubergine (Aub) are expressed at different levels in distinct subsets of neurons in the mushroom body (Perrat et al., 2013), the substrate for learning and memory within the insect brain (Heisenberg, 2003). Lower expression levels of Ago3 and Aub correlate with increased expression of transposable elements in the adult fly brain (Perrat et al., 2013), consistent with the proposed role of Piwi-related proteins in suppressing transposable element mobility (Thomson and Lin, 2009; Ku and Lin, 2014). This heterogeneity of Aub and Ago expression levels is speculated to contribute to behavioral variability (Perrat et al., 2013).

piwi, AGO, aub *and small RNAs*: *additional relevant expression data*

Expression of *piwi* orthologs during gametogenesis has been documented in multiple cnidarians (Seipel et al., 2004; Leclère et al., 2012; Plickert et al., 2012). The homoscleromorph sponge *O. lobularis* expresses a *piwi* ortholog in germ cells during spermatogenesis and oogenesis (Fierro-Constain

et al., 2017). In another sponge, the demosponge *Ephydatia fluviatilis*, a *piwi* homolog is expressed in choanocytes and archeocytes (Funayama, 2010; Funayama et al., 2010; Alié et al., 2015), which is relevant to the sponge germ line because gametogenic cells are thought to be derived from one or both of these cell types in these animals (Funayama, 2010). In the ctenophore *Pleurobrachia pileus*, *piwi* is expressed in the adult male and female germ line (Alié et al., 2010). Neural cell type expression of *piwi* orthologs is also present in non-bilaterians. In the cnidarian *Clytia hemisphaerica*, *piwi* is expressed in nematogenic and neural stem cells (Denker et al., 2008), and in the ctenophore *P. pileus*, *piwi* is expressed in the apical organ, which is an aboral sensory organ (Alié et al., 2010).

vasa *and* piwi

vasa encodes a highly conserved DEAD box-containing ATP-dependent RNA helicase (Hay et al., 1988; Lasko and Ashburner, 1988) that is expressed in the germ line of every animal studied to date (Ewen-Campen et al., 2010; Gustafson and Wessel, 2010; Yajima and Wessel, 2011b). DEAD box helicases predate animals (Chen et al., 2006) and are implicated in a broad range of biological functions including transcription, translation, splicing, ribosome biogenesis, nuclear export, and mRNA degradation (Linder, 2006; Lasko, 2013). *vasa* expression is also a hallmark of many types of stem cells, where it is proposed to interact with the products of the *piwi*, *bruno*, and *PL10* genes in a conserved gene network to help maintain pluripotency (Alié et al., 2010; Juliano et al., 2010; Fierro-Constain et al., 2017).

vasa *and* piwi *in the germ line*

First discovered for its role in abdomen formation during embryonic development in *D. melanogaster* (Schüpbach and Wieschaus, 1986), *vasa* encodes a protein found in the cytoplasm of animal germ cells and required for one or both of germ cell specification and germ line development in multiple animals (reviewed in Yajima and Wessel, 2011b). Vasa protein is a component of germ line RNP granules, and has predicted roles in regulating mRNA translation, including that of *nanos* (Gavis et al., 1996; see below) and *gurken* (Tomancak et al., 1998), potentially by interacting with initiation factor dIF2 (Carrera et al., 2000). During the cell cycle, *vasa* may be regulated by the meiotic checkpoint pathway (Ghabrial and Schupbach, 1999), can associate with the spindle (Carré et al., 2002; Oyama and Shimizu, 2007), and is implicated in regulation of mitotic chromosome condensation (Pek and Kai, 2011; Yajima and Wessel, 2011a,b; Schwager et al., 2015). Vasa protein interacts physically with Piwi protein in the germ line of mice (Kirino et al., 2010) and *D. melanogaster* (Megosh et al., 2006), and in cultured ovarian cells of the silkworm *Bombyx mori* (Xiol et al., 2014). Vasa, like Piwi, is involved in the small RNA biogenesis pathway in many animals (Vagin et al., 2004; Shirayama et al., 2014; Xiol et al., 2014; Dehghani and Lasko, 2016; Spracklin et al., 2017). Vasa and Osk proteins also physically interact in the germ line, where the LOTUS domain of Osk binds Vasa and facilitates its helicase activity (Jeske et al., 2015; Yang et al., 2015; Jeske et al., 2017).

vasa *and* piwi *in the nervous system*

To our knowledge, the only reported examples of a role for *vasa* in the nervous system come from (1) the cricket *G. bimaculatus*, where it is found co-expressed along with *piwi* and *osk* in neuroblasts (Ewen-Campen et al., 2012), and (2) cells of the apical sensory organ in the ctenophore *Pleurobrachia pileus* (Alié et al., 2010). Its function in these invertebrate nervous systems remains to be elucidated.

vasa *and* piwi: *additional relevant expression data*

We note that in multiple animals, *vasa* expression is also a hallmark of pluripotent and somatic stem cell lineages, which can give rise to both germ line and neural cells. These include the archaeocytes of the sponge *E. fluviatilis* (Alié et al., 2015), the interstitial cells of the cnidarians *H. magnipapillata* and *H. echinata* (Mochizuki et al., 2001; Rebscher et al., 2008), the presumptive founder cells of the larval posterior growth zone of the annelid *Platynereis dumerilii* (Rebscher et al., 2007), the stem cells of the colonial tunicate *Botryllus schlosseri* (Sunanaga et al., 2006; Rosner et al., 2009; Kawamura and Sunanaga, 2011), and the neoblasts of the platyhelminths *Macrostomum lignano* (Pfister et al., 2008), *Dugesia japonica* (Shibata et al., 1999), *Schmidtea mediterranea* (Wagner et al., 2012), and *Schistosoma mansoni* (Wang et al., 2013).

boule (bol) *and* twine (twe)

boule (bol) is a member of the Deleted in Azoospermia (DAZ) RNA-binding protein family, which contains the autosomal *dazl* and *bol* genes, and the human Y-linked *DAZ* gene (Shah et al., 2010). Although not reported in plant or fungal genomes to date, *bol* may predate animals based on identification of a putative ortholog in the slime mold *Dictyostelium discoideum* (Chen et al., 2006). In the bony fish lineage, a *bol* duplication likely gave rise to the *Daz-like* gene (*Dazl*), which then underwent a transposition to the Y chromosome in primates to give rise to *DAZ* (Shah et al., 2010). *DAZ* family members display predominant male germ line expression patterns, and *DAZ* family genes are crucial for germ cell development and meiotic progression across animals (summarized in Kim and Rhee, 2016).

bol *and* twe *in the germ line*

bol was first identified in a mutagenesis screen for *D. melanogaster* male-sterile mutants (Castrillon et al., 1993). *twe* was identified by multiple independent studies (Jimenez et al., 1990; Alphey et al., 1992; Courtot et al., 1992) that searched for orthologous or functionally analogous genes to the cdc25 phosphatase that regulates mitotic entry in *Schizosaccharomyces pombe* (Russell and Nurse, 1986). *bol* mutants fail to undergo male meiosis, but homozygous female *bol* mutants are fertile (Eberhart C. G. et al., 1996). Bol controls the translation of *twe,*

allowing meiotic entry in males (Courtot et al., 1992; Maines and Wasserman, 1999). The *D. melanogaster* meiotic entry defect can be rescued by the *X. laevis bol* ortholog *Xdazl* (Houston et al., 1998), and human and mouse DAZ can also partially rescue *D. melanogaster bol* loss of function (Houston et al., 1998; Xu et al., 2003). Orthologs of *bol* and *twe* also play a role in sperm maturation in haploid males in the sawfly *Athalia rosae* (Hymenoptera), which normally abort meiosis I but maintain meiosis II to produce haploid sperm (Sekine et al., 2015). As in *D. melanogaster, bol* knockdowns in *A. rosae* show no apparent defects in females (Sekine et al., 2015). Bol is also expressed in the testis in male mammals. In mice and humans, Bol protein is present in the cytoplasm of developing spermatocytes and can be detected through meiosis (Xu et al., 2001). Loss of *dazl* function in mice leads to defects in gametogenesis in both sexes (Ruggiu et al., 1997). As in *D. melanogaster*, *bol* homozygous mutant male mice are infertile, but females are viable and fertile (Shah et al., 2010). Bol also co-localizes to RNPs that form under stress (called stress granules) in mouse male germ cells (Kim and Rhee, 2016). In *X. laevis*, knockdown of the maternally expressed ortholog *Xdazl* reduces the number of PGCs and perturbs PGC migration during embryogenesis (Houston and King, 2000). In contrast to the fly, mouse, human and frog *bol* genes, the *C. elegans bol* ortholog *daz-1* plays a role in oocyte determination rather than in spermatogenesis (Karashima et al., 2000). In wild type hermaphroditic worms, germ cells undergo two developmental decisions, the first from mitotic proliferation to meiosis in the L4 larval stage, and the second from sperm to oocyte production in young adults (Karashima et al., 2000). RNAi against *daz-1* in *C. briggsae* leads to continuous sperm production, indicating a disruption in the spermatogenesis/oogenesis switch (Karashima et al., 2000).

bol *and* twe *in the nervous system*

While *bol* expression is not detected in the human brain (Uhlen et al., 2015), *bol* and *twe* also function in the nervous system in adult *D. melanogaster* (Joiner and Wu, 2004), where an isoform of *bol* that is not found in the testis is expressed in the cytoplasm and extending neurites of most cells throughout the adult brain (Joiner and Wu, 2004). Bol negatively regulates developmental axon pruning in *D. melanogaster* (Hoopfer et al., 2008). Over-expression of *bol* throughout the nervous system leads to defects in neuronal communication between the retina and the lamina, abnormal locomotory behavior in wandering larvae, and lethality before the third larval stage (Joiner and Wu, 2004). The neuronal *bol* isoform interacts genetically with *twe* in the nervous system, just as *bol* does in the germ line (Joiner and Wu, 2004).

CPEB, Maskin, *and* eIF4E

Cytoplasmic polyadenylation element binding protein (CPEB) is a member of an animal protein family implicated in binding the 3'UTRs of mRNAs at cytoplasmic polyadenylation element (CPE) sites, and in controlling their translation and cytoplasmic localization via regulation of their poly(A) tail lengths (Hake and Richter, 1994; Wells et al., 2000). Some animals have multiple paralogs of *CPEB* genes in their genomes: *D. melanogaster* has two *CPEB* genes, whereas *X. laevis*, mice, humans and *C. elegans* have four (Chen et al., 2006). The C-terminal half of the CPEB protein contains RNA binding domains (RBDs), including two RNA-recognition motifs (RRM domains) and a zinc finger domain (ZZ domain), which are used to establish *CPEB* gene relationships (Hake et al., 1998; Mendez and Richter, 2001; Fernandez-Miranda and Mendez, 2012). Pairwise sequence alignments of the RBDs of different *CPEB* genes show that *CPEB* genes form two subgroups (Hake et al., 1998; Mendez and Richter, 2001; Fernandez-Miranda and Mendez, 2012). One subgroup, which includes the *D. melanogaster oo18 RNA binding protein* (*orb)* (Christerson and McKearin, 1994; Lantz et al., 1994), mouse CPEB1 (Tay and Richter, 2001) and *X. laevis* CPEB1 (Hake and Richter, 1994), are expressed and required in the germ line for initiation of translation of CPE-containing mRNAs. *CPEB* genes in the second group are more broadly expressed in several somatic tissues, including the nervous system, in addition to the germ line. Their examples include *D. melanogaster orb2* (Hafer et al., 2011), mouse CPEB2-4 (Kurihara et al., 2003; Theis et al., 2003), and human CPEB3 and CPEB4 (Kikuno et al., 2004). Given that *CPEB* genes control mRNA expression across tissues, developmental stages and species, some have speculated that they do so via a mechanism of local translational control that is evolutionarily conserved, involving the cytoskeleton, eukaryotic initiation factor (eIF4E) and the eIF4E binding protein Maskin (Stepien et al., 2016).

CPEB, Maskin *and* eIF4E *in the germ line*

D. melanogaster orb was the first identified member of the CPEB family of translational regulators and is required to establish polarity in developing eggs and early embryos (Lantz et al., 1992, 1994; Christerson and McKearin, 1994). *orb* controls translation and polyadenylation of mRNAs including *oskar* and *gurken* (Chang et al., 1999, 2001; Tan et al., 2001; Castagnetti and Ephrussi, 2003; Norvell et al., 2015; Davidson et al., 2016), and organizes and repolarizes the microtubule cytoskeleton during *D. melanogaster* oogenesis by interacting with Actin, Dynein and Kinesin (Barr et al., 2019a,b). In *C. elegans*, CPEB homologs (called CPB-1,2,3 and FOG-1) are required for the switch from sperm to egg production during germ cell development, and control germ cell fate by regulating the translation of specific mRNAs (Luitjens et al., 2000; Jin et al., 2001). CPEB interactions are also well studied in *X. laevis* oocytes, where CPEB homologs are required for normal oocyte maturation, and also regulate the cell cycle in early embryos (Stebbins-Boaz et al., 1996; Groisman et al., 2000; Groisman et al., 2002; Igea and Mendez, 2010). Co-immunoprecipitation, protein pull downs and yeast two-hybrid assays have shown that in *X. laevis,* CPEB1 directly binds both the eukaryotic translation initiation factor eIF4E, and the 4E-binding protein Maskin (Stebbins-Boaz et al., 1999; Cao and Richter, 2002; Meijer et al., 2007). It has been suggested that such a CPEB-Maskin-eIF4E interaction may serve as a typical example for 3′UTR-mediated translational repression across metazoans (Stebbins-Boaz et al., 1999). Indeed, *D. melanogaster* Orb from ovary

extracts has also been shown to immuno precipitate with eIF4E (Wong et al., 2011).

CPEB, Maskin *and* eIF4E *in the nervous system*

D. melanogaster orb2 is expressed in several somatic tissues, including the nervous system at all stages of development (Hafer et al., 2011). *orb2* mRNA and protein expression are detectable in the central and peripheral embryonic nervous systems (Hafer et al., 2011). In the central nervous system of embryos and larvae, Orb2 protein expression is largely limited to cell bodies, and functions in asymmetrical cell division (Hafer et al., 2011). In adult neurons, *orb2* is localized at the synaptic terminals, and is required for learning and memory (Keleman et al., 2007; Kruttner et al., 2012; Majumdar et al., 2012). In the sea slug *A. californica*, CPEB forms prion-like multimers in neurons. *D. melanogaster* Orb2 injected into *A. californica* neurons also forms such aggregates (Si et al., 2003, 2010), suggesting that these aggregates may be relevant to learning and memory in these animals, as they may contribute to synapse-specific differences (Fiumara et al., 2015). In sensory neurons, ApCPEB co-localizes in RNA granules that also contain eIF4E, FMRP, and Stau (Barbee et al., 2006; Chae et al., 2010). A second *A. californica* CPEB homolog, ApCPEB4, has a role in long-term facilitation, although it lacks a prion-like domain (Lee et al., 2016). In both mammalian and *A. californica* neurons, CPEB is required for mRNA shuttling, and it co-localizes with and polyadenylates multiple mRNAs (Huang et al., 2002, 2003; Chae et al., 2010). In *X. laevis* and mouse neurons, CPEB colocalizes with Maskin in a complex containing Kinesin and Dynein, suggesting that it may regulate mRNA transport and translation in dendrites (Huang et al., 2003) similar to its role in the germ line. In mice, CPEB3 interacts with the Actin cytoskeleton and has been shown to act as a functional prion as well (Stephan et al., 2015), with CPEB expression at synapses in rodent brains being required for synaptic plasticity (Wu et al., 1998), the cellular basis for memory and learning.

DISCUSSION

Here we have highlighted many genes that, following their initial characterization in the germ line, were discovered to also have neural roles. For many such genes with a neural role in one species, there is evidence for a neural role in other species as well, often with the same set of core molecular interaction partners (**Table 2**). We consider that the data currently available are too limited for us to propose whether the germ line roles or the neural roles of these genes represent their putative ancestral functions in a last common ancestor of animals [but see Ewen-Campen et al. (2012) for a proposal that *oskar*'s role in the insect germ line is derived, resulting from co-option from a putative neural role]. It is clear that relying on single gene expression patterns alone to identify homologies can be misleading (Wagner et al., 2012; Wang et al., 2013), and we are not proposing to use such data as the sole criteria for this purpose (Tautz, 1998; Nielsen and Martinez, 2003). Instead, our aim here is to suggest possible explanations for the molecular and cellular basis for this pleiotropy by looking at the properties of the molecular mechanisms of these shared genes, which may be linked to the evolution of cell-type specific functions.

Regulatory Commonalities of Germ Line and Nervous System

We begin by highlighting some independent yet interesting similarities between the germ line and the nervous system. First, germ cells, pluripotent stem cells, and undifferentiated or abnormally organized embryonic cells have been reported to differentiate towards neural cell fate under a number of circumstances. For example, in *C. elegans*, germ cells that lose *P*-granules can ectopically express somatic markers, including neuronal markers (Knutson et al., 2017). In induced human PGC-like cells generated from pluripotent stem cells, BLIMP1 is actively required to promote PGC fate and to repress neuronal differentiation (Sasaki et al., 2015). Dissociated *X. laevis* embryonic animal cap cells are able to upregulate the neural marker N-CAM despite the absence of normal spatial organization (Sato and Sargent, 1989) Embryonic stem (ES) cells spontaneously and readily exhibit aspects of neural identity under specific culture conditions (Tropepe et al., 2001). When plated at low densities in phosphate buffered saline, mouse ESCs can express *nestin* and *Sox1*, which is suggestive of neural stem cell differentiation (Smukler et al., 2006). It has therefore been suggested that neuronal fate is a preferred differentiation program for cells that lose their germ line identity or pluripotency (Knutson et al., 2017).

Second, the gene expression profiles of human and mouse testes and brain are highly similar to each other (Guo et al., 2003, 2005). Whether or how the two tissues communicate to regulate this similar gene expression is unclear, although Guo and colleagues (Guo et al., 2005) speculate that the hypothalamus-pituitary-gonadal axis (Plant, 2015; Kaprara and Huhtaniemi, 2018) may play a role. Finally, such observations may also help explain the link between disruption of genes with known roles in the germ line, and neural disease phenotypes. For example, the *D. melanogaster* tumor suppressor gene *brain tumor* (*brat*), together with *nos* and *pum*, represses translation in female germ line stem cells (Sonoda and Wharton, 2001), and *brat* loss of function mutations also cause tumors in the brain (Arama et al., 2000). Additionally, ectopic expression of at least 26 genes normally expressed in the germ line, may be linked to malignant brain tumor growth in *D. melanogaster* (Janic et al., 2010). Thus, it is possible that some shared or similar biological processes link these genes to both germ line and neural tissue types outside of mammals as well.

A Shared Molecular Basis for Pleiotropy

In this review we have summarized some of the evidence for the expression and functional requirements for a number of genes in the above mentioned two cell types. However, in most cases the molecular mechanisms linking the function of these genes to the cellular execution of neural or germ line fate remain unclear.

It is therefore difficult to determine whether this pleiotropy is a result of the same molecular function in apparently unrelated biological processes, or because some or all of these genes have multiple molecular functions per gene. In principle, it could be the case that these genes have the same immediate downstream partners in both tissue contexts, but their subsequent interactors or secondary targets are different, leading to differences in cellular responses to the activities of these genes within each tissue. Nevertheless, in the following section, we propose some possible explanations, based on shared molecular functions of these genes, for the potentially close or labile relationship between germ line and neural cell fates.

Cytoplasmic Aggregates: The Roles of RNP Granules in Germ Line and Nervous System

One way to understand the repeated conservation of expression, molecular function and interactions of these genes in neural tissues and germ lines, is by considering whether the products of these genes have functional or biochemical properties that could make them particularly suited for use by these cell types. We note that products of most of the genes discussed here share three notable properties. First, they are RNA binding proteins (e.g., Osk, Piwi, Vasa, Stau, Nos, FMRP), and play multiple roles in RNA biology including localization (e.g., Stau, Osk), translational activation (e.g., Vas, and Stau), and translational repression (e.g., Nos, Pum, Stau). Second, many of them break cellular symmetry by becoming asymmetrically localized within the cytoplasm or facilitating the asymmetrical localization of other molecules (e.g., Osk, Stau/Btz, Nos). Third, the majority catalyze the formation of and/or localize to RNP granule complexes, which are in turn sometimes asymmetrically distributed within the cell (e.g., germ granules in *D. melanogaster*). RNP granules are electron dense, non-membrane bound cytoplasmic aggregates of RNAs and proteins (Eddy, 1975; Ikenishi, 1998). The assembly of proteins within RNPs is often transient or reversible, and RNPs are important for the localization, stability and translational control of their RNA (and protein) cargo (Arkov and Ramos, 2010; Voronina et al., 2011; Schisa, 2012; Gao and Arkov, 2013). Moreover, in addition to giving RNP granules their functionality in translational control, RNA Binding Proteins (RBPs) have been noted to commonly have regions of low sequence complexity and prion-like domains, both of which can mediate RNP granule assembly and disassembly (Brangwynne et al., 2009; Han et al., 2012; Kato et al., 2012; Molliex et al., 2015; Sudhakaran and Ramaswami, 2017).

RNP granules are found in both germ line and somatic cells. Depending on the tissue they are found in, RNP granules are referred to in the literature by various names, including polar or germinal granules in germ cells, stress granules and processing bodies in somatic cells, and neuronal granules in neurons (reviewed in Voronina et al., 2011). All described classes of RNP granules share multiple components with each other (reviewed in Kulkarni and Extavour, 2017). Functional amyloid-like assemblies like RNP granules can govern cellular processes both in the germ line, including PGC specification and spermatogenesis (reviewed in Voronina et al., 2011), and in the soma, including in the consolidation of memory in the nervous system (Si et al., 2003, 2010; Si and Kandel, 2016). In the latter context, proteins with prion-like domains, which may facilitate amyloid-like assemblies, localize at neuronal synapses and form active, stable complexes with self-perpetuating properties central to memory storage (Si et al., 2003, 2010; Sudhakaran and Ramaswami, 2017). We note that Oskar and FMRP have predicted prion-like domains (McBride et al., 2012; Boke et al., 2016). Germ line and neural cells also share the commonality of regulating translation at specific sites within the cell, e.g., the oocyte posterior in the case of germ plasm formation (Lehmann, 2016), or at select neuronal synapses in the case of neurons, leading to synaptic plasticity (Kang and Schuman, 1996; Si et al., 2003).

Small RNA Biogenesis as a Regulator of Gene Expression in Germ Cells and Neurons

Piwi, its related protein Aubergine, and Vasa are among the many RNA binding proteins that are associated with and indispensable for small RNA biogenesis in the germ line (Ku and Lin, 2014). piRNAs are endogenous small non-coding RNAs that are proposed to maintain the genomic integrity of germ cells by limiting transposon mobility (Aravin et al., 2001, 2006; Girard et al., 2006; Grimson et al., 2008). piRNAs associate with the Argonaute family member Piwi (e.g., Mochizuki et al., 2002), and other members of this family (e.g., Ago3) interact with other small RNAs, including miRNAs and siRNAs (Girard et al., 2006; Vagin et al., 2006; Brennecke et al., 2007; Houwing et al., 2007; Kim et al., 2009). Small RNA-mediated gene silencing occurs at both transcriptional and post-transcriptional levels, and is an important mechanism controlling gene expression (Holoch and Moazed, 2015). piRNAs were first characterized in the germ line, but recent reports support their existence in somatic tissues as well, including neural tissues (Lee et al., 2011; Rajasethupathy et al., 2012; Ross et al., 2014). Indeed, in *A. californica*, after the germ line, the nervous system is amongst the tissue types that show relatively high selective enrichment for piRNAs (Rajasethupathy et al., 2012). There is evidence for primary piRNA biogenesis in the germ line and neurons (Rajasethupathy et al., 2012; Mani and Juliano, 2013; Kim et al., 2018) consistent, with a functional role for piRNAs in both cell types. For example, Piwi and piRNAs regulate Myosin-Va in the central nervous system of mammals (Naisbitt et al., 2000; Lee et al., 2011), control local translation in mouse neuronal dendrites (Lee et al., 2011), mouse dendritic spine development (Lee et al., 2011), neuronal migration (Viljetic et al., 2017), and may be linked to growth of malignant brain tumors (Janic et al., 2010). Finally, piRNAs regulate transposon activity both in the brain and in the germ line (reviewed in Mani and Juliano, 2013). Retrotransposons are highly active in neural tissues and contribute to proper neuronal differentiation and generation of somatic mosaicism in the brain (Muotri et al., 2005; Coufal et al., 2009). Thus, piRNAs are crucial both for

the germ line, and for normal development and function of the nervous system, which may help explain why we observe that genes important for their biogenesis are expressed in both tissue types.

Challenges in Determining the Evolutionary Sequence of Co-option Events

Co-option of partial or complete gene networks in different biological contexts is common (Jacob, 1977). Novel traits may evolve either by the co-option of pre-existing gene networks that operate in functional modules, or by building a new gene network for each new developmental context (Sanetra et al., 2005; Monteiro and Podlaha, 2009). Based on the observations summarized herein, we propose that the germ line and nervous tissues of animals contain examples of gene network co-option, given that the genes involved are pleiotropic, and that we do not think it likely that the germ line and nervous system are homologous organ systems. In principle, one way of co-opting a gene network could be by recruiting an upstream regulator of an existing network into a new developmental context. This is what we previously proposed may have happened in the case of *oskar* in germ plasm (Ewen-Campen et al., 2012). In both cricket (Ewen-Campen et al., 2012) and fly (Xu et al., 2013) nervous systems, *oskar* is co-expressed with *vasa*, *piwi* and/or *nanos*, genes whose products function together in multiple other cellular contexts as discussed above. Given that germ plasm in insects is likely a derived mechanism of PGC specification (Extavour and Akam, 2003; Lynch et al., 2011; Ewen-Campen et al., 2013), we propose that the functional links among these genes are likely to predate the evolution of insect germ plasm, suggesting that they were co-opted to the germ line context from a preexisting somatic role (Ewen-Campen et al., 2012).

When moving beyond insects to consider all animals, because there have been fewer reported instances to date of the expression or function of these genes in the nervous system outside of bilaterians, one might wish to hypothesize that the germ line functions of these gene evolved first, and then were co-opted to the nervous system in Bilateria. However, the functions of these genes have been explored primarily in a small number of study systems, heavily biased toward the Bilateria. Moreover, the diversity of cell types, including neural cell types, outside of Bilateria are not as well studied at the molecular level as are those of bilaterians. The evidence that the earliest metazoans were highly complex animals is mounting (Halanych, 2015; Whelan et al., 2017; Paps, 2018; Laumer et al., 2019), and may well displace the traditional view that early animals were "simple" with few differentiated cell types, lacking complex reproductive or sensory systems. We therefore consider it premature to speculate on whether the ancestral function of these genes in animals, was in the germ line or in the nervous system. Rather than thinking about the patterns in their putative ancestral functions in establishing a particular cell type, we could consider the hypothesis that the cellular function of translational control in RNP granules is the relevant conserved ancestral role of this machinery in eukaryotes. This could explain why striking phenotypes are particularly or easily observed in neurons and germ cells, because these cell types rely heavily on translational regulation for their biological functions. The advent of animal-specific genes like *nos* and *osk* may have permitted the emergence of tissue-specific versions of this machinery, deployed specifically in germ lines and nervous systems to refine or augment their regulation of translation.

CONCLUSION

We note that an association between many of the genes discussed herein and "stemness" or cellular multipotency, has already been pointed out by several researchers: the general proposal is that these genes may have been components of an ancestral animal toolkit in stem cells, regardless of the fate of their differentiated progeny (e.g., Alié et al., 2010, 2015; Juliano et al., 2010; Fierro-Constain et al., 2017). Here we speculate that if, as in many extant animals, ancient metazoans generated gametes from germ line stem cells, and/or neurons from neuroblasts, the observed association of these genes with pluripotency may also help explain the gene expression overlap in germ line and nervous tissues. Going forward, technical advances including single-cell RNA sequencing, chromatin architecture analysis and proteomics, and improved microscopy and computational methodologies including machine learning, might make it possible to test such hypotheses experimentally (e.g., Siebert et al., 2019). The case we have discussed here, of the germ line and the nervous system, is an example of the broader, fundamental question of how the same molecular mechanisms can underlie different cell identities. Once putative ancient cell type inventories are reconstructed for important evolutionary nodes, we can perhaps begin to unravel how ancient cell types, in some cases expressing highly similar machinery, diversified into extant cell types that make up the tissues and organ systems of living animals (Kin, 2015; Arendt et al., 2016), helping answer some of the questions that we have raised here.

AUTHOR CONTRIBUTIONS

CE conceived of the project. DL, AK, and CE compiled the evidence from primary literature. AK and CE wrote the manuscript. All authors contributed to the article and approved the submitted version.

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