

Globularization and Domestication

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Abstract This paper aims to explore a potential connection between two hypotheses recently put forward in the context of language evolution. One hypothesis argues that some human-specific change(s) in the hominin brain developmental program habilitated the neuronal workspace that enabled “cognitive modernity” to unfold, also resulting in our globularized braincase. The other argues that the cultural niche resulting from our self-domestication favored the emergence of natural languages. In this article we document numerous links between the genetic changes we have claimed may have brought about globularization and neural crest cells, which have been claimed to explain the constellation of distinctive traits (physical, cognitive, and behavioral) found in all domesticated mammals. If these links turn out to be as robust as we think they are, globularization and self-domestication may well be closely related phenomena in the context of human evolution.

Keywords Globularization · Language-ready brain · Modern cognition · Full-fledged languages · Neural crest cells · Domestication syndrome

1 Introduction: Linking Two Hypotheses

This paper aims to explore a potential connection between two hypotheses recently put forward linking the language phenotype and genotype. Both are ultimately aimed to cast light on how our species’ ability to develop mental rule systems that are put to use in thought and communication appeared. One (Boeckx 2013; Boeckx and Benítez-Burraco 2014a; Theofanopoulou 2015) is the idea that the globularization of the braincase that characterizes our species (Lieberman et al. 2002; Bruner 2004) is the reflex of a genetically regulated specific brain growth pattern that provided the neural scaffolding for “cognitive modernity”, most distinctively our ‘language-readiness’. This species-specific brain growth trajectory has been well characterized by several authors (Neubauer et al. 2010; Gunz et al. 2010, 2012; Bastir et al. 2011; Scott et al. 2014; Hublin et al. 2015). They have highlighted the differential growth of the parietal lobe, the cerebellum, and the frontal pole, as well as the olfactory bulb and quite possibly the temporal lobe. The logic of correlated growth also leads us to expect differential growth at the level of the dorsal thalamus (Boeckx and Benítez-Burraco 2014a) and the corpus callosum (Theofanopoulou 2015). On the basis of this information, Boeckx and Benítez-Burraco (2014a, b, 2015) and Benítez-Burraco and Boeckx (2015a) have put forward a potential candidate gene set underlying this brain and skull growth trajectory, many of which show sign of positive selection in anatomically modern humans (AMHs).

The other idea at the heart of this paper concerns to (self-)domestication. As Thomas (2014) discussed extensively, self-domestication in our species can prove extremely valuable in understanding our cognitive behavior, and in particular what we will call below the grammaticalization of our mind. Interestingly, Wilkins et al. (2014) have

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Table 1 The genes related to globularization as discussed in Boeckx and Benítez-Burraco (2014a, b) and Benítez-Burraco and Boeckx (2015a)

<i>Candidate genes for globularization</i>				
<i>ABL1</i>	<i>AKT1</i>	<i>ANAPC10</i>	<i>APOE</i>	<i>ARHGAP32</i>
<i>ARHGEF6</i>	<i>ARX</i>	<i>ASCL1</i>	<i>ASPM</i>	<i>AUTS2</i>
<i>BAZ2A</i>	<i>BGLAP</i>	<i>BMP2</i>	<i>BMP7</i>	<i>CBL</i>
<i>CDC42</i>	<i>CDC42BPB</i>	<i>CDC42EP4</i>	<i>CDH1</i>	<i>CDKN1A</i>
<i>CEBPB</i>	<i>CEP192</i>	<i>CITED2</i>	<i>CKAP5</i>	<i>CLOCK</i>
	<i>CNTNAP2</i>	<i>CREBBP</i>	<i>CTIP2</i>	<i>CTNNB1</i>
<i>DCC</i>	<i>DIP2A</i>	<i>DISC1</i>	<i>DISP1</i>	<i>DLL1</i>
<i>DLX1</i>	<i>DLX2</i>	<i>DLX5</i>	<i>DLX6</i>	<i>DUSP1</i>
<i>DYRK1A</i>	<i>DYX1C1</i>	<i>EGFR</i>	<i>EGR1</i>	<i>ELAVL2</i>
<i>ELP4</i>	<i>EMX2</i>	<i>EP300</i>	<i>ERBB4</i>	<i>ETV4</i>
<i>EXOC6B</i>	<i>FEZF2</i>	<i>FGF7</i>	<i>FGF8</i>	<i>FGFR1</i>
<i>FLNA</i>	<i>FMR1</i>	<i>FOXA1</i>	<i>FOXA2</i>	<i>FOXG1</i>
<i>FOXO1</i>	<i>FOXP1</i>	<i>FOXP2</i>	<i>FRP</i>	<i>GAD1</i>
<i>GADD45G</i>	<i>GBX2</i>	<i>GLI3</i>	<i>GTF2I</i>	<i>GTF3C3</i>
<i>HES1</i>	<i>HOXA2</i>	<i>HRAS</i>	<i>ITGB4</i>	<i>KATNA1</i>
<i>KDM5B</i>	<i>LHX2</i>	<i>MAPK1</i>	<i>MAPK14</i>	<i>MECP2</i>
<i>MEF2A</i>	<i>MET</i>	<i>NCAM1</i>	<i>NCOA6</i>	<i>NFASC</i>
<i>NKX2-1</i>	<i>NODAL</i>	<i>NOTCH1</i>	<i>NOVA1</i>	<i>NR1H2</i>
<i>NRG1</i>	<i>NRG3</i>	<i>NTN1</i>	<i>OTX2</i>	<i>PAK5</i>
<i>PAK6</i>	<i>PARP1</i>	<i>PAX3</i>	<i>PAX6</i>	<i>PCDH11</i>
<i>PCMI</i>	<i>PCNT</i>	<i>PDX1</i>	<i>PIN1</i>	<i>PITPNA</i>
<i>PLAUR</i>	<i>POU3F2</i>	<i>PQBP1</i>	<i>PTEN</i>	<i>PTPRB</i>
<i>PVALB</i>	<i>RELN</i>	<i>ROBO1</i>	<i>ROBO2</i>	<i>RUNX1</i>
<i>RUNX2</i>	<i>RUNX3</i>	<i>SATB2</i>	<i>SFRP2</i>	<i>SHH</i>
<i>SIRT1</i>	<i>SIX3</i>	<i>SLIT1</i>	<i>SLIT2</i>	<i>SLITRK3</i>
<i>SMAD9</i>	<i>SMURF1</i>	<i>SOLH</i>	<i>SOX10</i>	<i>SOX2</i>
<i>SOX3</i>	<i>SOX9B</i>	<i>SPAG5</i>	<i>SPC7</i>	<i>SPP1</i>
<i>SRGAP2</i>	<i>SRGAP3</i>	<i>SRPX2</i>	<i>TBR1</i>	<i>TGF</i>
<i>TLE2</i>	<i>TLE3</i>	<i>TP53</i>	<i>TSC1</i>	<i>USF1</i>
<i>USH2A</i>	<i>VCAM1</i>	<i>VCAN</i>	<i>VDR</i>	<i>WNT5A</i>
<i>YAP1</i>	<i>ZBTB20</i>	<i>ZFH1B</i>		

recently put forth domestication usually entails a constellation of distinctive traits (the “domestication syndrome”) many of them we believe related to the brain/cognitive changes that we think important for the evolution of language, and particularly, of globularity. According to Wilkins et al., the domestication syndrome, being triggered by different external stimuli, ultimately results from the hypofunction of the neural crest cells (NCCs) during embryonic development.

Our hypothesis is that the genetic changes we have claimed led to globularization are intimately related to those affected the NCCs, fueling (or being the main rationale for) the emergence of the (self-)domestication syndrome in our species, and ultimately, of full-fledged languages.

2 Domestication and the Grammaticalization of Mind

It is now clear that a rich “Universal Grammar” is not necessary (nor adequate) to capture properly and (biologically speaking) realistically all the complexity that the grammars of the world’s languages exhibit (Boeckx 2014). Rather, the very nature and context of cultural learning appear to be key in capturing all this grammatical paraphernalia (Hurford 2011; Kirby 2012; Smith and Kirby 2008; Thompson et al. 2016). But as Thomas (2014) points out, a major problem facing any attempt to account for language structure through a cultural mechanism is that the processes required by such a mechanism are only possible if we assume the existence of a range of preconditions, which we may call the “cultural niche”. The special social, behavioral, and neural conditions of human culture have been highlighted by Tomasello over a decade (see Tomasello 2009, 2014): we are indeed a super-social primate.

Thomas (2014) thinks that the behavioural, cognitive and temperamental outcomes of self-domestication might have formed the preconditions or the niche for the emergence of structured language through a cultural process. Thomas is not alone in this. Recently, Deacon (2009) and Hare and Tomasello (2005) have appealed to the idea of self-domestication and relaxed selective pressures to capture key aspects of our behavioral modernity, pointing out that sensitivity to communicative intent, at the heart of our communicative/pragmatic competence, characterize domesticated species in general. To add to this, Okanoya and colleagues have for several years now documented phenotypic differences between two vocal learning birds: the white-rumped munia and its domesticated variant, the Bengalese finch, and argued that domestication masked various selection pressures, particularly species recognition, thereby permitting increased variation and complexity (specifically in the syntax of their songs), and that this process was then reinforced by female preferences (Okanoya 2012; Kagawa et al. 2012, 2014; Takahasi and Okanoya 2010).

The intuition that our species, steeped as it is in culture, shares some aspects of domestication is indeed a venerable one. As Thomas (2014) observes, already the ancient Greeks had a single term “hemeros” to refer to domesticated animals and civilized people (Greeks); and another term “agrios” to refer to both wild animals and ‘savages’. Darwin himself in 1871 referred to “civilized men” as “in one sense highly domesticated”. But it was the observation that humans also share many of these typical characteristics of domesticated species that motivated people like Boas in 1938 to suggest that humans might also be thought of as domesticated. Even a cursory look at the fossil record

highlight changes in anatomically modern humans that closely resemble the ones attested in domesticated animals: reduced skeletal and cranial robusticity, changes in dentition, retention of juvenile characteristics, changes in temperament (compared to other living primates), reduction of sexual dimorphism, etc. All these features suggest that domestication may have taken place as part of the emergence of AMHs, although, of course, once in place, it may have intensified in our recent history. This is how we suggest to reinterpret evidence like the decrease in brain size in the last 50,000 years (Bednarik 2012, 2014), or the reduction of brow ridge projection and the shortening of the upper facial skeleton in humans from the Middle Pleistocene to recent times, plausibly resulting from a reduction in androgen reactivity (Cieri et al. 2014).

As is characteristic of the literature on domestication, Thomas focuses on selectionist considerations when it comes to examining a number of the possible accounts of how humans might have become self-domesticated. Specifically, Thomas considers three, not necessarily mutually exclusive accounts: (a) an account that links self-domestication to a process of adaptation to the human-made environment (an environment in which humans have lived longer than any other species), (b) a second account that links self-domestication to humans having undergone selection against aggression (linked to the idea of domestication as selection on temperament), and (c) a process with effects analogous to artificial selection may have also been in operation in humans; in particular, the idea that culturally mediated constructs of mate-choice may have resulted in humans applying something akin to artificial selection to themselves (an idea that others, such as Vendramini 2014, if somewhat fancifully, have linked to the context of AMHs/Neanderthals interactions).

3 Domestication and Neural Crest Cells

It is a well-established fact that domesticated animals possess a distinctive and unusual suite of heritable traits not seen in their wild progenitors (what Wilkins et al. 2014 refer to as the “domestication syndrome”). Remarkably, the suite of characteristics that typifies domestication is consistent across most species, and include depigmentation, floppy ears, reduced ears, shorter muzzles, smaller teeth, docility, smaller brain or cranial capacity, neotenus (juvenile) behavior, curly tails, and affect reproductive cycles (more frequent estrous cycles). Of course, not all of these characteristics are found in all domesticates, but nearly all domesticated species exhibit a significant subset of these characteristics (Price 2002). Indeed, some of the hard tissue characteristics are actually used by

archaeologists as diagnostic of domestication having occurred (Zeder et al. 2006).

As Wilkins et al. (2014) point out, most explanations focus on particular traits, while neglecting others, or on the possible selective factors involved in domestication rather than the underlying developmental and genetic causes of these traits. To correct this, Wilkins et al. (2014) put forth the idea that the domestication syndrome results predominantly from mild NCCs deficits during embryonic development. NCCs are the vertebrate-specific class of stem cells that first appear during early embryogenesis at the dorsal edge (hence the term “crest”) of the neural tube and then migrate ventrally throughout the body in both the cranium and the trunk, giving rise to the cellular precursors of many cell and tissue types and indirectly promoting the development of others. As noted above, the motivation behind Wilkins et al.’s (2014) hypothesis is that the development of the diverse traits characteristic of the domestication syndrome is closely linked to NCCs. This is especially true in the case of size and function of the adrenal glands, which play a central role in the physiology of both fear and stress responses. Adrenal hypofunction and reduced stress hormone levels are well documented in domesticated species and have been induced experimentally by selection for tameness during experimental domestication of foxes and rats. Accordingly, Wilkins et al. (2014) conjecture that initial selection for tameness leads to reduction of neural-crest-derived tissues of behavioral relevance, via multiple preexisting genetic variants that affect NCC numbers at the final sites, and that this neural crest hypofunction produces, as an unselected byproduct, the morphological changes in pigmentation, jaws, teeth, ears, etc. exhibited in the domestication syndrome.

Wilkins et al. (2014) go on to examine the underlying genetic basis for the NCC hypofunction, and include a list of genes that will be the center of our attention below. Specifically, our aim in the remainder of this paper is to show that many connections exist between the set of genes we have highlighted in the context of globularization in our past and ongoing research, and NCCs. We think that these connections are well worth taking into account given the idea that AMH is a self-domesticated species. We close with a few promising avenues of research this paper opens up.

4 Globularization and Neural Crest Cells

The idea we would like to explore in this section is that genetic changes we claimed led to globularization may be closely linked to those that affect NCCs in domestic animals, given the well-attested roles of some of the core genes we have examined in the context of globularization

at the level of the neural crest (as discussed in Boeckx and Benítez-Burraco 2014a, b; Benítez-Burraco and Boeckx 2015a, b core candidates for globularization fulfil the following criteria: they have experienced some evolutionary change after our split from Neanderthals/Denisovans; they play some role in brain growth, regionalization, and/or neural interconnection; they have been associated to conditions in which language, or cognitive properties often associated with language, are impaired, and they are candidates for craniosynostosis or some other similar condition affecting skull development and sutures). To test this possibility, we checked the literature to determine whether (and to what extent) (some of) the “domestication syndrome” genes highlighted by Wilkins et al. (2014) are also important for globularization and/or have changed in our lineage compared to Neanderthals and Denisovans. We also searched the literature via PubMed and OMIM (<http://www.ncbi.nlm.nih.gov/omim/>) to know more about the aberrant phenotypes linked to the mutation of these neural crest genes potentially implicated in globularization. We focused on clinical conditions and symptoms of interest for globularization (as described in Boeckx and Benítez-Burraco 2014a, b; Benítez-Burraco and Boeckx 2015a), including “language disorder”, “cognitive disorder”, “intellectual disability”, “syntactic deficit”, “semantic deficit”, “phonological deficit”, “speech deficit”, “dyslexia”, “schizophrenia”, “autism”, “autism spectrum disorder”, etc. We have also proceeded the other way around: we made extensive search of the literature to learn how many of (and to what extent) our candidates are involved in the development and function of the neural crest and could be also regarded as “neural crest genes”. We relied as well on computer tools to learn about the robustness of the links we posited, but also to uncover new links between the two sets of genes. For this, we mostly relied on String 10 (<http://string-db.org/>). String 10 predicts direct/physical and indirect/functional associations between proteins that derive from four sources: genomic context, high-throughput experiments, conserved coexpression, and the knowledge previously gained from text mining (Szklarczyk et al. 2011). As for phylogenetic changes, we determined the ancestral or derived nature of the genes of interest (compared to Neanderthals and Denisovans) and explored potential connections with other genes selected in AMHs. We also relied on available data on other molecular changes that occurred after our split from Neanderthals, including changes in promoter or enhancer activity, human-specific conserved deletions (hCONDELs), etc.

As far as Wilkins et al.’s (2014) candidates (their Table 2) are concerned, we found that all but one of them are related to (a) our putative globularization network, and/or (b) have changed recently in our species and/or (c) give rise to cognitive deficits that affect language and our mode

of cognition when they are mutated. We will review these links briefly (see also Fig. 1).

To begin with, three SOX genes are highlighted by Wilkins et al. (2014): *SOX10*, *SOX9*, and *SOX2*. *SOX10* is an interactor of *PAX3* (another of Wilkins et al.’s 2014 candidates) and *POU3F2* (Smit et al. 2000). Interestingly, *POU3F2* interacts with *FOXP2*, a gene that has been consistently related to language and speech deficits (Maricic et al. 2013). AMHs show a derived allele of the binding site which is less efficient in activating transcription than the Neanderthal/Denisovan allele (Maricic et al. 2013). *POU3F2* regulates neuronal migration and identity during the development of the neocortex (McEvelly et al. 2002; Sugitani et al. 2002) and has been linked to bipolar disorder (Mühleisen et al. 2014), and to developmental and language delays, intellectual disability, schizophrenia and autism spectrum disorders (ASD) (Huang et al. 2005; Lin et al. 2011; Potkin et al. 2009). Moreover, both *PAX3* and *SOX10* are robust candidates for Waardenburg syndrome, a complex condition in which sensorineural hearing loss is a prominent symptom (developmental delay is observed as well, but it may be subsidiary of hearing loss). Interestingly, *SOX10* is hypermethylated in the brain of schizophrenics (Iwamoto et al. 2005).

We regard *SOX9* of interest too because it mediates the retinoic acid-induced *HES1* expression. Retinoic acid has proven to be important for brain plasticity (Luo et al. 2009), learning and memory (Etchamendy et al. 2003; Jiang et al. 2012). Importantly, it closely interacts with *FOXP2* (Devanna et al. 2014) and with the genes related to globularization (Benítez-Burraco and Boeckx 2014). In turn, *HES1* is a direct interactor of *RUNX2*, our core candidate underlying the changes that prompted globularization, because of its central role in suture ossification (Yoshida et al. 2003; Lattanzi et al. 2012), its involvement in the development of hippocampal GABAergic neurons (Pleasure et al. 2000; Benes et al. 2007) and of the thalamus (Reale et al. 2013); its involvement in the regulation of osteocalcin (Paredes et al. 2004) and osteopontin (Shen and Christakos 2005), which are important for both bone formation and brain organization (see Schroeter et al. 2006); and the fact that a selective sweep in this gene occurred after our split from Neanderthals (Green et al. 2010). The *Hes1* pathway is related to language development and craniofacial development (reviewed in Boeckx and Benítez-Burraco 2014b). Additionally, *Hes1* is involved in the development of both GABAergic neurons (Long et al. 2013) and dopaminergic neurons (Kameda et al. 2011). Finally, the transcriptional activation of *Hes1* is a key step in the *Slit/Robo* signaling pathway that we believe important for the externalization of language (reviewed in Boeckx and Benítez-Burraco 2014b). We wish note as well that the phosphorylation of *Sox9* is regulated downstream

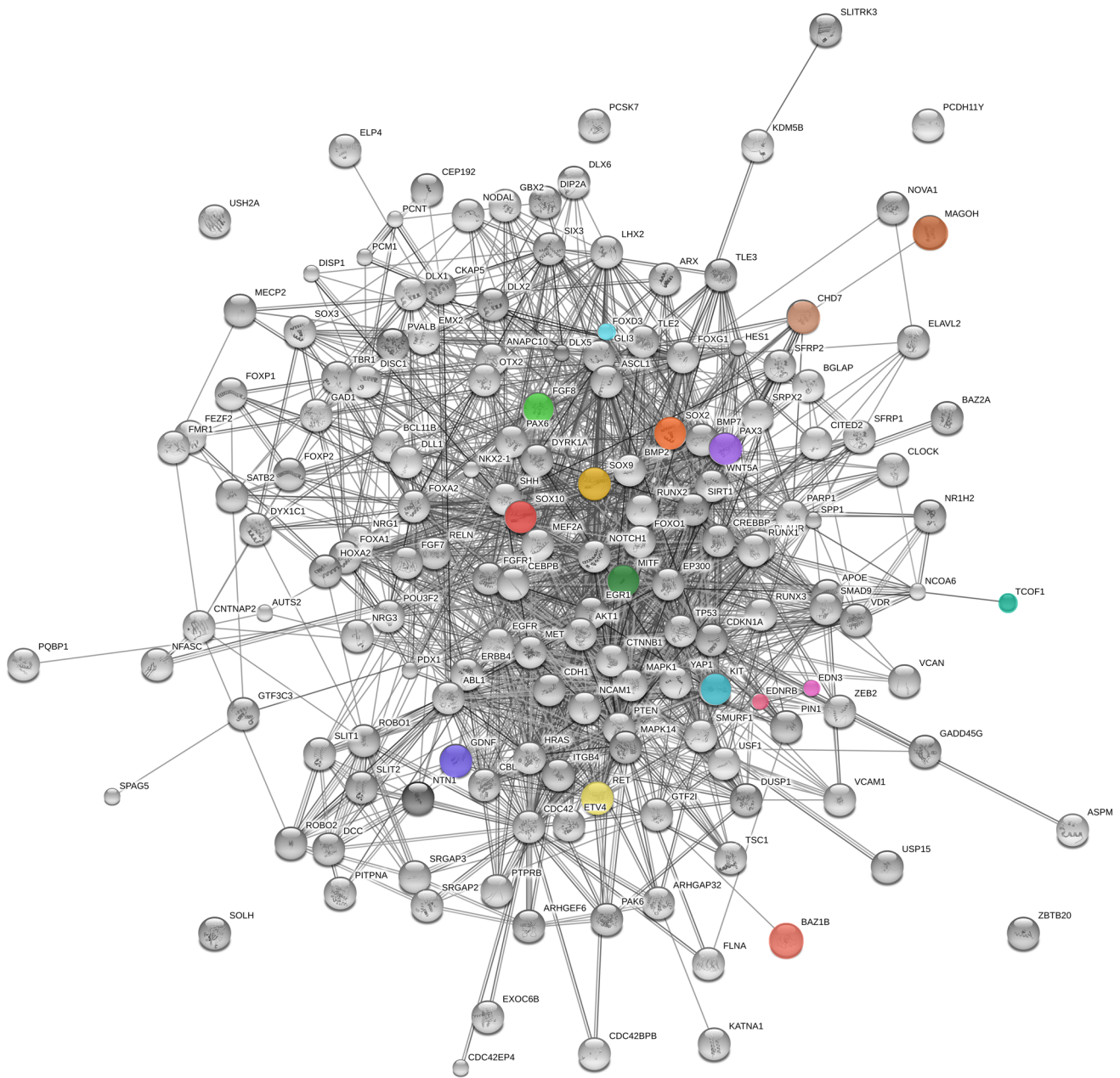


Fig. 1 The genes related to globularization and the genes related to the “domestication syndrome”. The network was generated by String 10 with the proteins discussed in Boeckx and Benítez-Burraco (2014a, b) and Benítez-Burraco and Boeckx (2015a) (see Table 1) and the candidate genes for domestication advanced by Wilkins et al. (2014). The medium confidence value was .0400 (this lower value enables to find a greater number of potential interactions among proteins; this lower value is then compensated for by checking whether the predicted interactions can be confirmed in the literature or in databases provided by functional assays). In this confidence view, stronger associations between proteins are represented by thicker lines. The figure does not represent a fully connected graph, but readers are asked to bear in mind that String 10 predicts associations between proteins that derive from a limited set of databases. The

material discussed in the main text lead us to suspect connections between the globularization genes and the domestication genes that String does not generate (although we wish to note that just letting String add a few interactors, not discussed in this paper, yield a fully connected graph). It should be *emphasized* that the nature of String 10 is essentially predictive, and not explanatory. Although we have confirmed all the links we discuss here in the literature, they need to be confirmed at the brain level and in relation to language. Additionally, the diagram only represents the potential connectivity between the involved proteins, but this has to be mapped onto particular biochemical networks, signaling pathways, cellular properties, aspects of neuronal function, or cell-types of interest that can be confidently related to aspects of language development and function

of Bmp signaling (Li et al. 2013). Importantly for us, two of the BMPs, namely BMP2 and BMP7, are core components of our gene network important for globularization (reviewed in Boeckx and Benítez-Burraco 2014a). Finally, we wish also note that *sox9a* expression is reduced in the pharyngeal arches of zebrafish in which *dlx2a* is knocked down (Sperber et al. 2008). DLX2, another of our core candidates, is important for tooth and craniofacial development (Jeong et al. 2008; Gordon et al. 2010), but also contributes to regulate thalamic development (Jones and Rubenstein 2004). According to McKinsey et al. (2013) *Dlx2* (and *Dlx1*) controls some important steps of neuronal proliferation within the cortex via *Zfmx1b*, which is mutated in Mowat–Wilson syndrome (McKinsey et al. 2013), a condition characterized by speech delay, mental retardation, microcephaly, delayed motor development, hypertelorism, and cupped ears with fleshy, upturned lobules (Adam et al. 2006). Importantly, neural crest-specific removal of *Zfmx1b* in mouse gives rise to a wide range of neurocristopathies resembling Mowat–Wilson syndrome (Van de Putte et al. 2007). Moreover, the lack of *Zfmx1b* gives rise as well to multiple NCC defects causing Hirschsprung disease–mental retardation syndrome (Van de Putte et al. 2003). Interestingly, an hCODEL (not shared with Neanderthals) exists upstream *SOX9* (McLean et al. 2011).

Lastly, *SOX2* is one of the transcription factors that are differentially expressed in several postmitotic thalamic nuclei (Vue et al. 2007). *SOX2* is one of the components of the SHH–GLI signaling pathway that we feel has played a significant role in the anatomical and physiological events leading to globularization (Boeckx and Benítez-Burraco 2015, Boeckx et al., manuscript), but also in NCC fate (more on SHH below). Specifically, *Sox2* input and differential Gli-binding affinity have been shown to provide context and positional information in *Shh*-directed neural patterning. In the neural tube, GLI-bound *cis*-regulatory modules (CRMs) are enriched for *SOX* binding motifs, and *SOX2* (among other *SOX* factors) acts as neural-specific GLI co-factors (Oosterveen et al. 2012, 2013; Peterson et al. 2012). Moreover, *SOX2* regulates *PQBPI*, a gene linked to developmental delay, intellectual disability and microcephaly (Li et al. 2013), which also interacts with *POU3F2* (Li et al. 2013). According to the Human Brain Transcriptome Atlas *PQBPI* is expressed highly in several key regions of the brain in the context of globularization (cerebellum, hippocampus, and olfactory bulb). Interestingly, *SOX2* is involved as well in the enhancer effect of human endogenous retroviruses (HERVs) on brain genes related to schizophrenia, specifically *PRODH* (Suntsova et al. 2013). And similarly to the other two *SOX* genes reviewed above, *SOX2* is also regulated by *RUNX2*, some of the *DLXs* genes, and some of the BMPs. Hence, the transcriptional activity of *Sox2* is downregulated by *Runx2*

and *Dlx5* in response to interleukin-6 in bone marrow-derived mesenchymal multipotent cells (Yoon et al. 2014). In addition, *SOX2* interacts with BMP signalling. For example, Li et al. (2015) have recently found that a BMP–Smad4–SHH–Gli1 signalling network provides a niche supporting transient *Sox2*+ dental epithelial stem cells in mouse molars. Importantly for our hypothesis, *SOX2* is predicted (according to String 10) to interact specifically with *BMP7* via *NOG*, an inhibitor of BMP signalling and a protein important for dopamine neuron production (Chiba et al. 2008). As we noted above, *BMP7* is closely related to some of our core candidates (*BMP2*, *RUNX2*, *DLX1*, and *DLX2* among others) and plays a pivotal main role in osteogenesis (Cheng et al. 2003) and skull and brain development (Yuge et al. 2011; Segklia et al. 2012). Mutations of *BMP7* cause eye anomalies, deafness, developmental delay, and learning disabilities (Wyatt et al. 2010). Finally, together with *OTX2* and *PAX6*, *SOX2* plays a key role in controlling eye development, potentially affecting orbit size, a feature known to have changed in our species, compared to other extinct hominin species.

Among Wilkins et al.'s (2014) candidates we have found other genes that interact (according to Kuhlwillm et al. 2013) with *RUNX2*, our key candidate for globularization. One of them is *MTIF*. Interestingly, an hCODEL (although shared with Neanderthals) exists upstream *MTIF* in AMHs (McLean et al. 2011). Also *GDNF* is differentially expressed after *RUNX2* transfection. This gene is predominantly expressed in the pulvinar neostriatal interneuronal ensemble (Hidalgo-Figueroa et al. 2012), but also in the visual cortex (Pochon et al. 1997). *GDNF* is involved in dopaminergic differentiation (Christophersen et al. 2007) and also promotes formation of neuronal synapses by ligand-induced cell adhesion (Ledda et al. 2007). Interestingly for our hypothesis, *GDNF* is predicted (according to String 10) to interact with *NCAM1*, the carrier of polysialic acid (one of the neural crest stem markers) and a protein related to schizophrenia, bipolar disorder and Alzheimer's disease (Atz et al. 2007), and to working memory performance (Bisaz et al. 2013). In turn, *NCAM1* interacts with *VCAM1*, known to bear a fixed change (D414G) in AMHs compared to Neanderthals/Denisovans (Pääbo 2014, his table S1). *NCAM1* is a potential target of *RUNX2* too (Kuhlwillm et al. 2013), but also of *FOXP2* (Konopka et al. 2009).

Additionally, we have found that four of Wilkins et al.'s (2014) candidates (*Magoh*, *Fgf8*, *piebald (l)*, and *Ret*) are targets of *FOXP2* (according to Spiteri et al. 2007; Vernes et al. 2011). We regard this an interesting link, provided that *FOXP2* (together with *ROBO1*) is a core component of the machinery responsible for the two neural components often presented as critical for vocal learning: the direct cortico-laryngeal connection and the cortico-thalamo-basal

ganglia pathway. As we review in Boeckx and Benítez-Burraco (2014b) *FOXP2* and its interactome show strong links with our set of genes related to globularization and language-readiness. *Magoh* is involved in RNA splicing and its loss leads to a disorganized, microcephalic brain with fewer neurons (Silver et al. 2010). Interestingly, the splicing of *MAGOH* has a AMH-specific pattern (Lin et al. 2010). *FGF8* encodes a protein involved in the regionalization of brain tissues in mammals (Fukuchi-Shimogori and Grove 2001). *FGF8* interacts with *RUNX2* via *FGFR1*, a candidate for craniosynostosis and Pfeiffer syndrome (Rossi et al. 2003), but also with *DLX2* (according to String 10). The expression of *FGF8* is also under the control of the *SHH-GLI* signaling pathway that we highlighted above as important for globularization (see Boeckx et al. manuscript for details). Specifically, both *SHH* and *GLI3* modulates the *FGF8/WNT* signaling source in the forebrain (Kobayashi et al. 2010; Rash and Grove 2011). Interestingly, $\approx 98\%$ of Altaic Neanderthals and Denisovans gained a non-synonymous change in *GLI3* that appears to be mildly disruptive (Castellano et al. 2014). *FGF8* is a candidate for holoprosencephaly, a condition characterized by forebrain malformations, severe neurocognitive impairment, and midline facial anomalies (Sarnat and Flores-Sarnat 2001; Solomon et al. 2012). Concerning *piebald (l)* (also known as *EDNRB*), it is a candidate for Waardenburg syndrome (Read and Newton 1997), a condition involving sensorineural hearing loss and (subsidiary) developmental delay. Finally, *RET* is also found to be differentially expressed after *RUNX2* transfection in neuroblastomic cells (Kuhlwilm et al. 2013). The *RET* regulatory function is conserved from human to zebrafish without sequence similarity (Fisher et al. 2006).

With regard to *Tcof1*, another of Wilkins et al.'s (2014) candidate, it contains a *LIS1* motif (Emes and Ponting 2001). *LIS1* (also known as *PAFAH1B1*) regulates neuronal migration and axonal growth (Smith et al. 2000; Toyo-oka et al. 2003; Shu et al. 2004). Mutations in *LIS1* reduces brain size and give rise to different types of lissencephalies (Reiner et al. 1993; Lo Nigro et al. 1997) with different degrees of impact on linguistic abilities (Leventer et al. 2001). Individuals with *LIS1* duplications had subtle brain defects, including microcephaly and dysgenesis of the corpus callosum. Importantly for our hypothesis, *TCOF1* is also bound by *RUNX2* based on ChIP analyses (Young et al. 2007). *Tcof1* also acts as a modifier of *Pax3* during enteric nervous system development (derived from vagal NCC) (Barlow et al. 2013). *TCOF1* is a candidate for Treacher Collins syndrome, an autosomal-dominant condition involving mandibulofacial dysostosis. Heterozygous knockout of *Tcof1* in mice causes severe craniofacial malformation (Dixon and Dixon 2004; Shows and Shiang 2008).

Additionally, we have found signs of positive selection in other genes highlighted by Wilkins et al. (2014) Hence, *FoxD3*, a transcriptional regulator essential for neural crest development, depends on *Nodal* (one of our candidates) for regulating zebrafish dorsal mesoderm development (Chang and Kessler 2010). *FOXD3* is one of the enriched transcription factors in present-day human-specific differentially methylated regions (DMRs) (Gokhman et al. 2014). Similarly, a human-specific conserved deletion (hCONDEL) (although shared with Neanderthals) exists upstream *CDH7* (McLean et al. 2011). Finally, the last two genes in Wilkins et al.'s (2014) list are also of interest for us. *WSTF* (also known as *BAZ1B*) plays a key role in chromatin remodeling and nucleosome repositioning (Kitagawa et al. 2003). *BAZ1B* belongs to the core 1.5 Mb region commonly deleted in Williams syndrome (Somerville et al. 2005). Finally, *piebald (s)* (also known as *EDN3*) is significantly dysregulated in autistic children (Glatt et al. 2011). Like *SOX10*, *EDN3* is also a candidate for Waardenburg syndrome type 4, a rare neural crest disorder combining sensorineural hearing loss and pigmentation defects (as in Waardenburg syndrome) and aganglionosis (as in Hirschsprung disease).

As we pointed out above, we made as well an extensive survey of the PubMed literature to know whether our candidates can be regarded as “neural crest genes”. The whole list of them, as resulting from our research on the molecular underpinnings of globularization and language-readiness (reviewed in Boeckx and Benítez-Burraco 2014a, b; Boeckx and Benítez-Burraco 2015a), currently encompasses 152 genes (see Table 1) Interestingly, we discovered that nearly 60 % of them play a role related to the neural crest. In the first part of this section we have focused on the genes that also belong to Wilkins et al.'s (2014) list. Below we provide an overview of the most promising connection between the neural crest and our set of genes (our selection was based on the volume of references currently available and degree of confidence in databases and computer tools like String 10.) (see Fig. 1).

To begin with, *BMP7* differentiates cortical neural stem cells into a variety of neural crest lineages (Gajavelli et al. 2004). Similarly, *BMP2* (also mentioned above) is required for regulating the migration of NCCs (Correia et al. 2007) and also recruits multipotent neural crest progenitors (Glejzer et al. 2011). Also *CDC42* controls neural crest stem cell proliferation (Fuchs et al. 2009). Inactivation of *Cdc42* in NCCs causes craniofacial and cardiovascular morphogenesis defects (Liu et al. 2013). Concerning *CITED2*, this is an important neural crest gene (Yin et al. 2002). According to Bamforth et al. 2001 mice lacking *Cited2* exhibit adrenal agenesis, neural crest defects and exencephaly. Moreover, *CITED2* has been implicated in a new disease pathway involved in Hirschsprung's disease

(Tang et al. 2015). Regarding its phylogenetic relevance, we wish note that Prüfer et al. (2014) highlight a highly disruptive intergenic change near *CITED2* that is 99 % derived in AMHs and ancestral in both Altai Neanderthals and Denisovans. Moreover, *CITED* show strong links with genes important for language and globularization. To begin with, it is a regulatory target of FOXP2 (Nelson et al. 2013). Additionally, it interacts, via LHX2 (another of our candidates for globularization), with ROBO1 (Marcos-Mondéjar et al. 2012), one of the best-known candidate genes for dyslexia (Hannula-Jouppi et al. 2005), and crucially involved in the neural establishment of vocal learning abilities (Wang et al. 2015). Regarding CTNBN1, this gene temporally controls, as part of the Wnt/ β -catenin signalling pathway, multiple steps of neural crest development, from neural crest induction, lineage decisions, to differentiation (Hari et al. 2012). Dlx1 and Dlx2 are robust neural crest markers too (Ishii et al. 2012) and are involved in patterning and morphogenetic processes in the neural crest-derived mesenchyme (Mallo 2001). Both Dlx5 and Dlx6 are crucial for aspects of neural crest development (Ruest et al. 2003). Specifically, DLX5 positions the neural crest at the border of the neural plate (McLarren et al. 2003). FGF genes (*FGF7* and *FGF8*) are known to act in combination with BMP genes to generate the cranial neural crest (Endo et al. 2012). In turn, NCCs regulate the amount of Fgf8 produced by the anterior neural ridge (ANR) and the isthmus (the two brain organizers) via the secretion of anti-BMP signalling molecules (Le Douarin and Dupin 2012). Also *FGFR1* (together with MAPK signalling) is responsible for neural crest induction (Stuhlmiller and García-Castro 2012). Moreover, Fgfr1 patterns the pharyngeal region to create a permissive environment for neural crest cell migration (Trokovic et al. 2003). Concerning *Pax3*, it is among the earliest genes activated in neural crest progenitors and cooperates in neural crest patterning (Maczkowiak et al. 2010; Bae et al. 2014; Plouhinec et al. 2014). In turn, *Pax6* is involved in regulating the migration of NCCs from the anterior midbrain (Matsuo et al. 1993). SLITs and ROBOs (as part of the Slit/Robo signalling) are necessary to confine early NCCs to the ventral migratory pathway in the trunk (Jia et al. 2005). Moreover, Slits affect the timely migration of NCCs via the Robo receptor (Giovannone et al. 2012). Concerning *SHH*, we have already pointed out the important role played by the SHH signalling pathway in NCC fate. Specifically, Shh promotes the survival of NCCs (Delloye-Bourgeois et al. 2015) and the development of multipotent neural crest progenitors (endowed with both mesenchymal and neural potentials) (Calloni et al. 2007). Importantly, Shh signalling is required for cranial neural crest morphogenesis and chondrogenesis (Wada et al. 2005). Moreover, NCCs receive both Bmp and Shh signalling to induce *Satb2*

expression, which is another of our candidates (Sheehan-Rooney et al. 2013). Interestingly as well, a neural crest deficit in Down syndrome mice is associated with deficient mitotic response to Shh (Roper et al. 2009). Finally, we wish highlight *VCAN*, which encodes versican-1, a protein that guide migratory NCCs (Dutt et al. 2006) and which shows a fixed N3042D change in AMHs (Pääbo 2014; table S1).

Finally, we wish note that the recent epigenomic profiling of human and chimpanzee NCCs (Prescott et al. 2015) has revealed significant divergence across species in craniofacial cis-regulatory landscapes, resulting in expression differences of crucial NCC regulators and ultimately, in human facial variation. Some of these enhancers with a species-bias overlap with human accelerated regions (HARs). Among the genes that are flanked by species-biased enhancers and that show species-biased expression profile one finds some of our candidates (e.g. *PAX3*). Moreover, these human-biased enhancers have been found to be clustered in super-enhancers. Interestingly, among the genes potentially regulated by these super-enhancers we have found some of our candidates too (e.g. *SRGAP2*, and *MECP2*). Importantly, although Prescott and colleagues found that Denisovans and Neanderthals primarily share the human-like variants of some key regulatory motifs, they found as well a small set of changes that are unique to modern humans compared to these extinct hominins. Interestingly, this divergence largely results from cis-sequence changes rather than changes in the trans regulatory environment, and to some extent from the activity of retroelements (many of them belonging to ERV1, ERVL-MaLR, and ERVK subclasses), which have been hypothesised to have played a key role in the genomic changes that brought about modern language (Benitez-Burraco and Uriagera 2016).

5 Discussion

In all fairness we are still not in a position to prove the functional connections we have sought to highlight in this paper. Because most genes involved in development are pleiotropic, playing a role in different tissues and at different times, the connections found in silico or inferred from the literature need to be validated in vitro and in vivo in tissues of interest to achieve a more satisfactory level of certainty. In particular, we still do not understand our globularization network well enough to be able to demonstrate that changes in the expression of (some of) the genes we have examined reduce the input to the neural crest, giving rise to the sort of hyporegulation that Wilkins et al. (2014) highlight in their work. But we would like to list two promising lines of research that we think could reinforce the connection we have tried to establish here.

Firstly, we find it particularly interesting that Wilkins et al. (2014) characterize the reduced neural crest input at the heart of the “domestication syndrome” as an instance of “mild neurocristopathy”. Interestingly, mutations in some of our candidates for language-readiness result in neurocristopathy (plausibly via the interaction with the neural crest genes). In this context, Hirschsprung disease strikes us again as a good starting point for future exploration, considering that the list of genes related to the disease includes many of our candidates, like *ASCL1*, *DLX1*, *MAPT*, *NRG1*, *ROBO1*, *SLIT2*, *SOX2*, *SOX10*, and *ZFHX1B* (Jiang et al. 2011; Tang et al. 2015). Additionally, there appears to exist comorbidity of neurocristopathy and skull/brain/face anomalies (Sjamsudin et al. 2001; Jian et al. 1995; Parry et al. 2013). Interestingly, in the case of Parry et al. (2013), the gene they focus on, *GSC*, interacts with some of our core candidates, including *DLX* genes and *MEF2* genes (Miller et al. 2007; Fossat et al. 2012). Exploring this comorbidity should help validate some of the links we posited above.

The constellation of symptoms observed in ASD could lend support to the view that the link between globularization and neural crest function (and between language-readiness and language change via domestication) is a robust one, and particularly, that the changes in the globularization network and the NCC-derived network of the sort we have highlighted in this paper resulted in a distinctive modification of the cognitive phenotype of ancient hominins. Accordingly, ASD entails anomalies in the skull and the brain, cognitive and language deficits, and an abnormal presentation of the “domestication syndrome” (see Benítez-Burraco et al. 2016; Theofanopoulou and Boeckx 2016 for reviews from different angles). Although the involvement of the neural crest in the aetiopathogenesis of ASD has not been documented in detail, we wish note

that neurocristopathies commonly involve autistic features (Fernell et al. 1999). Interestingly too, ASD candidates are overrepresented among the genes known to be involved in the “domestication syndrome” and the set of genes important for language-readiness and many of these genes show altered expression profiles in the brain of autists (Benítez-Burraco and Murphy 2016; Benítez-Burraco et al. 2016).

6 Conclusion

The globularization of the brain and braincase seems to be related to emergence of other traits that we believe important for modern language, including the refinement of the neural substrates for ‘externalization’ (via the *ROBO/SLIT/FOXP2* interactomes) (see Boeckx and Benítez-Burraco 2014b for details) or new inter- and intrahemispheric connections underlying modern cognition (via the *SHH-GLI* pathway, the *AUTS2* interactome, etc.) (see Benítez-Burraco and Boeckx 2015a, b; Boeckx et al. manuscript for details). The evidence we have reviewed in this paper suggests to us that a globularized brain and brain case may also be linked to the developmental/genetic context for a domestic phenotype, which could then have been selected for the reasons Thomas (2014) discussed (see Fig. 2). Put another way, globularization may be part of Deacon’s (2009) discussion of ‘relaxation of selection’, leading to a niche favoring cultural selection.

This is not to say that globularization and self-domestication are one and the same. It is well established that globularization led to a critical change at the level of the parietal lobe and associated parietal bone (Bruner 2004, 2010; Bruner et al. 2015). Crucially, though, calvarial bones arise from two embryonic tissues, namely, the neural crest and the mesoderm. Unlike the frontal bone, which is neural crest-derived, the parietal bone is paraxial mesodermal-derived (Quarto et al. 2010). If posterior braincase changes were driving globularization, as Bruner contends, these changes cannot be entirely reduced to NCC-related (i.e. domestication-related) changes.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

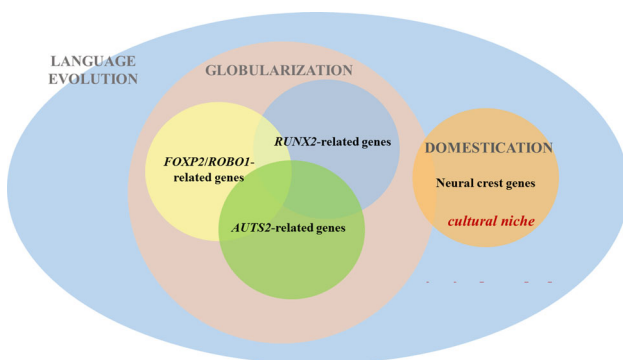


Fig. 2 The constellation of potential gene networks accounting for the emergence of modern languages. As noted in the main text, these networks remain to be tested experimentally, although the links are supported by ample evidence in the literature

Human and Animal Rights Their research did not involve human participants or animals.

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