Phylogenetic Analysis Supports a Link between DUF1220 Domain Number and Primate Brain Expansion

Fabian Zimmer and Stephen H. Montgomery*

Department of Genetics, Evolution & Environment, University College London, United Kingdom

*Corresponding author: E-mail: stephen.montgomery@cantab.net.

Accepted: June 19, 2015

Abstract

The expansion of DUF1220 domain copy number during human evolution is a dramatic example of rapid and repeated domain duplication. Although patterns of expression, homology, and disease associations suggest a role in cortical development, this hypothesis has not been robustly tested using phylogenetic methods. Here, we estimate DUF1220 domain counts across 12 primate genomes using a nucleotide Hidden Markov Model. We then test a series of hypotheses designed to examine the potential evolutionary significance of DUF1220 copy number expansion. Our results suggest a robust association with brain size, and more specifically neocortex volume. In contradiction to previous hypotheses, we find a strong association with postnatal brain development but not with prenatal brain development. Our results provide further evidence of a conserved association between specific loci and brain size across primates, suggesting that human brain evolution may have occurred through a continuation of existing processes.

Key words: autistic spectrum disorder, brain evolution, DUF1220 domains, NBPF, primates.

Introduction

The molecular targets of selection favoring brain expansion during human evolution have been sought by identifying dramatic, lineage-specific shifts in evolutionary rate. The increase in DUF1220 domains during human evolution provides one of the most dramatic increases in copy number (Popesco et al. 2006; Dumas et al. 2012). A single copy of this protein domain is found in *PDE4DIP* in most mammalian genomes. In primates, this ancestral domain has been duplicated many times over, reaching its peak abundance in humans where several hundred DUF1220 domains exist across 20–30 genes in the Nuclear Blastoma Breakpoint Family (NBPF) (Vandepoele et al. 2005; Dumas et al. 2012). The majority of these map to 1q21.1, a chromosomal region with complex, and unstable genomic architecture (O'Bleness et al. 2012, 2014).

Interspecific DUF1220 counts show a pattern of phylogenetic decay with increasing distance from humans (Popesco et al. 2006; Dumas and Sikela 2009; Dumas et al. 2012). In humans, DUF1220 dosage has also been linked to head circumference (Dumas et al. 2012), and severe neurodevelopmental disorders, including autism spectrum disorder (ASD) and microcephaly (Dumas et al. 2012; Davis et al. 2014). The severity of ASD impairments is also correlated with 1q21.1 DUF1220 copy number suggesting a dosage effect (Davis et al. 2014). Taken together, these observations led to the suggestion that the expansion of DUF1220 copy number played a primary role in human brain evolution (Dumas and Sikela 2009; Keeney, Dumas, et al. 2014).

Although functional data are limited, they provide some indication of how DUF1220 domain copy number count influences brain development. DUF1220 domains are highly expressed during periods of cortical neurogenesis, suggesting a potential role in prolonging the proliferation of neural progenitors by regulating centriole and microtubule dynamics to control key cell fate switches critical for neurogenesis (Keeney, Davis, et al. 2014). *PDE4DIP*, which contains the ancestral DUF1220 domain, does indeed associate with the spindle poles (Popesco et al. 2006) and is homologous to *CDK5RAP2*, a centrosomal protein essential for neural proliferation (Bond et al. 2005; Buchman et al. 2010), which coevolved with brain mass across primates (Montgomery et al. 2011).

Two previous analyses report a significant association between DUF1220 copy number and brain mass, cortical neuron number (Dumas et al. 2012), cortical gray and white matter, surface area, and gyrification (Keeney, Davis, et al. 2014). However, several limitations in these analyses restrict confidence in the results. First, DUF1220 copy number was assessed across species using a BLAT/BLAST (BLAST-like alignment tool/Basic Local Alignment Search Tool) analysis with a query sequence from humans, which introduces a bias that could partly explain the observed phylogenetic decay. Second, counts were not restricted to those domains occurring in functional exonic sequence and therefore many DUF1220 domains found in human pseudogenes were included in the analyses. Third, the analyses were limited to a small number of species (4–8 primates), using parametric statistics that may not be suitable for count data, and which do not correct for phylogenetic nonindependence (Felsenstein 1985). This is not a negligible issue, as it can result in the overestimation of statistical significance (Carvalho et al. 2006). Finally, previous phenotypic associations have been reported for multiple cortical phenotypes all of which are strongly correlated with one another or are nonindependent. Therefore, to date, these studies have not provided evidence for a specific association with neocortex size, neither have they tested the strength of the association with different periods of brain development, which may provide new clues as to the functional relevance of DUF1220 domain copy number.

Here, we use nucleotide Hidden Markov Models (HMMs) (HMMER3; Eddy 2011) to more accurately query the DUF1220 domain number of distantly related genomes. After filtering these counts to limit the analysis to exonic sequence, we use phylogenetic comparative methods that correct for nonindependence to test whether DUF1220 copy number is robustly associated with brain size, whether this is due to an association with pre- or postnatal brain development, and whether the association is specific to the neocortex.

Table 1
DUF1220 Count Data

Species	O'Bleness et al. (2012)	nHMM	
		Whole Genome	Functional Exonic with CM Promoter
Homo sapiens	272	302	262
Pan troglodytes	125	138	32
Gorilla gorilla	99	97	32
Pongo abelii	92	101	27
Nomascus leucogenys	53	59	6
Papio anubis	—	75	15
Chlorocebus sabaeus	—	48	16
Macaca mulatta	35	74	10
Callithrix jacchus	31	75	9
Tarsius syrichta	—	47	2
Microcebus murinus	2	4	1
Otolemur garnettii	3	4	2

Results

We confirm significant interspecific variation in DUF1220 counts across primates (table 1, fig. 1). Phylogenetic Generalized Least Square (PGLS) regressions (Pagel 1999) using square-root, or $\log_{10}$-transformed DUF1220 counts support previous reports of an association with brain volume (SQRT: $t_{10} = 3.165$, $P = 0.005$, $R^2 = 0.455$; $\log_{10}$: $t_{10} = 4.770$, $P < 0.001$, $R^2 = 0.655$). The same associations are also found after excluding *Homo sapiens* from the analysis (SQRT: $t_9 = 3.810$, $P = 0.002$, $R^2 = 0.569$; $\log_{10}$: $t_9 = 3.952$, $P = 0.002$, $R^2 = 0.586$). However, these data transformations may not be appropriate for count data where models based on Poisson distributions provide more accurate results (O'Hara and Kotze 2010).

Using a Bayesian approach that corrects for phylogenetic nonindependence and fits a Poisson distribution to the DUF1220 count data (MCMCglmm; Hadfield 2010), we again find evidence that CM-associated exonic DUF1220

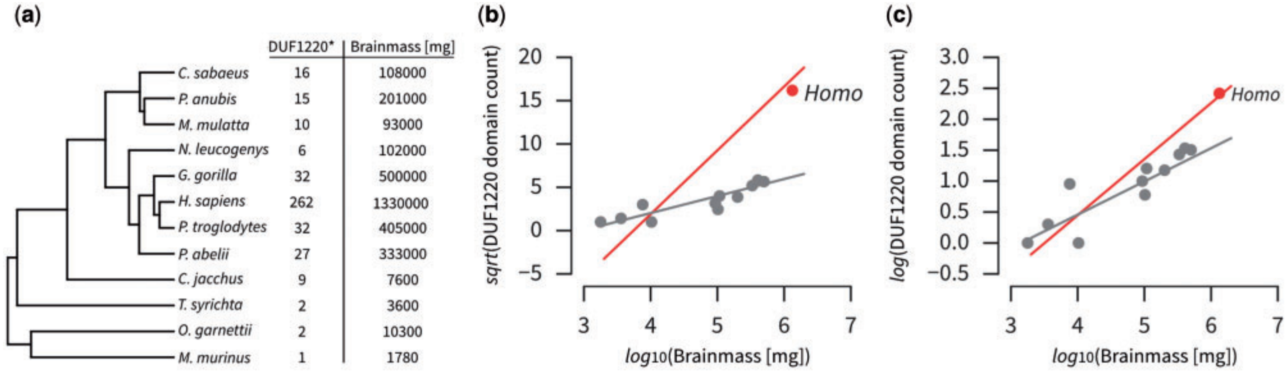

Fig. 1.— (*a*) Phylogeny of Ensembl primate genomes showing the number of DUF1220 domains in functional, annotated genes with a CM promoter, and brain mass. (*b*) The relationship between square-root transformed DUF1220 counts and $\log_{10}$(brain mass), and (c) the relationship between $\log_{10}$ transformed DUF1220 counts and $\log_{10}$(brain mass). The regression lines are shown with (red) and without (gray) the inclusion of the *H. sapiens* data. In all cases, they are significant.

counts are associated with brain mass across primates ($n = 12$, posterior mean = 1.927, 95% confidence interval [CI] = 0.800–3.040, $P_{MCMC} = 0.001$). This association is robust to the exclusion of *H. sapiens* (posterior mean = 1.271, 95% CI = 0.490–2.019, $P_{MCMC} = 0.003$), and found when hominoids ($n = 5$, posterior mean = 3.679, 95% CI = 0.966–6.258, $P_{MCMC} = 0.018$) or anthropoids ($n = 9$, posterior mean = 2.019, 95% CI = 0.352–3.684, $P_{MCMC} = 0.010$) are analyzed alone, suggesting a consistent phylogenetic association. When body mass is included as a cofactor in the model, the positive association is restricted to brain mass (table 2*a*, fig. 1*a*).

Separation of pre- and postnatal development specifically links DUF12220 number to postnatal brain growth. Analyzed separately, the association with prenatal brain growth is weaker ($n = 11$, posterior mean = 1.758, 95% CI = –0.039 to 3.543, $P_{MCMC} = 0.023$) than with postnatal brain growth (posterior mean = 1.839, 95% CI = 0.895–2.808, $P_{MCMC} = 0.001$). If both traits are included in the same model, only the positive association with postnatal brain growth remains (table 2*b*, fig. 2*b* model 1). Multiple regression analysis also confirms that the association is specific to postnatal brain growth, rather than postnatal body growth (table 2*b* model 2).

Finally, we not only examined the hypothesized relationship with neocortex volume (e.g., Keeny, Davis, et al. 2014; Keeny, Dumas, et al. 2014), but also considered cerebellum volume, as this region coevolves with the neocortex (Barton and Harvey 2000), has expanded in apes (Barton and Venditti 2014), and shows high levels of NBPF expression (Popesco et al. 2006). When the rest-of-the-brain (RoB) is included as a cofactor, to account for variation in overall brain size, a positive association is found for neocortex volume but not cerebellum volume (table 2*c* models 1-3, fig. 2*c*).

Table 2

MCMCglmm Results of Multivariate Models

Model	Posterior Mean	95% CI	P_{MCMC}
(*a*) Brain Mass and Body Mass			
1. log(brain mass)	4.105	2.163 to 6.000	0.001
+ log(body mass)	−1.986	−3.544 to −3.900	0.988
(*b*) Prenatal and Postnatal Growth			
1. log(prenatal brain growth)	−2.158	−4.471 to 0.106	0.967
+ log(postnatal brain growth)	3.319	1.470 to 4.982	0.002
2. log(postnatal brain growth)	2.910	1.641 to 4.151	<0.001
+ log(postnatal body growth)	−1.241	−2.442 to −0.052	0.977
(*c*) Brain Regions			
1. log(neocortex volume)	5.961	0.720 to 11.173	0.014
+ log(RoB volume)	−5.817	−13.322 to 1.120	0.953
2. log(cerebellum volume)	3.699	−5.857 to 12.611	0.186
+ log(RoB volume)	−2.435	−13.869 to 10.132	0.681
3. log(neocortex volume)	6.076	−0.139 to 12.5712	0.025
+ log(cerebellum volume)	−0.369	−9.5128 to 8.961	0.526
+ log(RoB volume)	−5.494	−15.814 to 5.288	0.872

Discussion

Our phylogenetic analyses substantiate the hypothesis that the increase in DUF1220 number coevolves with brain mass (Dumas et al. 2012; Keeney, Davis, et al. 2014), and may contribute to the proximate basis of primate brain evolution. We extend the results of previous studies by demonstrating specific associations with neocortex volume, and postnatal brain growth rather than prenatal brain growth. Together these results imply a role for DUF1220 in evolutionary changes in the maturation and postnatal development of the neocortex. Previous hypotheses concerning the phenotypic relevance of DUF1220 domain number have focused on their possible contribution to neurogenesis (Dumas and Sikela 2009; Keeny, Davis, et al. 2014; Keeny, Dumas, et al. 2014). This is supported by homology to genes with known functions in cell cycle dynamics (Popesco et al. 2006; Thornton and Woods

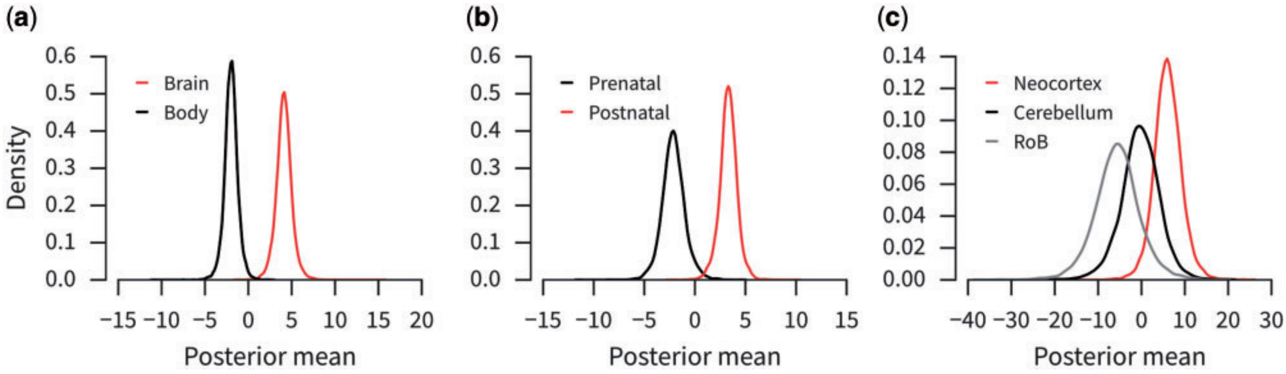

Fig. 2.— (*a*) Posterior means of the association between DUF1220 count and brain mass (red) and body mass (black). (*b*) Posterior means of the association between DUF1220 count and postnatal brain growth (red) and prenatal brain growth (black). (*c*) Posterior means of the association between DUF1220 count and neocortex volume (red), cerebellum volume (solid black), and rest-of-brain volume (dashed black).

2009), relevant spatial and temporal expression patterns (Keeney, Davis, et al. 2014), and an effect on the proliferation of neuroblastoma cell cultures (Vandepoele et al. 2008). However, a direct effect of variation in DUF1220 domain number on neural proliferation has not been demonstrated (Keeney et al. 2015).

If DUF1220 domains do regulate neurogenesis, we would expect them to coevolve with prenatal brain growth, as cortical neurogenesis is restricted to prenatal development (Bhardwaj et al. 2006). Our results instead suggest a robust and specific relationship with postnatal brain development. Existing data on DUF1220 domain function suggest two potential roles that may explain this association: 1) a contribution to axonogenesis through initiating and stabilizing microtubule growth in dendrites; and 2) a potential role in apoptosis during brain maturation. Both hypotheses are consistent with the reported association between variation in DUF1220 dosage and ASD (Davis et al. 2014). Indeed, an emphasis on postnatal brain growth is potentially more relevant for ASD, which develops postnatally, accompanied by a period of accelerated brain growth in early postnatal development (Courchesne et al. 2011).

Microtubule assembly is essential for dendritic growth and axonogenesis (Conde and Cáceres 2009). *PDE4DIP*, which contains the ancestral DUF1220 domain, has known functions in microtubule nucleation, growth, and cell migration (Roubin et al. 2013). There is also evidence that NBPF1 interacts with a key regulator of Wnt signaling (Vandepoele et al. 2010) that has important roles in neuronal differentiation, dendritic growth, and plasticity (Inestrosa and Varela-Nallar 2014). Consistent with this function, DUF1220 domains are highly expressed in the cell bodies and dendrites of adult neurons (Popesco et al. 2006). A role for DUF1220 domains in synaptogenesis could potentially explain the association with ASD severity (Davis et al. 2014). ASD is associated with abnormalities in cortical minicolumns (Casanova et al. 2002) and cortical white matter (Hazlett et al. 2005; Courchesne et al. 2011), both of which suggest a disruption of normal neuronal maturation (Courchesne and Pierce 2005; Minshew and Williams 2007).

Alternatively, NBPF genes are also known to interact with NF-κB (Zhou et al. 2013), a transcription factor implicated in tumor progression, with a range of roles including apoptosis and inflammation (Karin and Lin 2002; Perkins 2012). Postnatal apoptosis has a significant influence on brain growth (Kuan et al. 2000; Polster et al. 2003; Madden et al. 2007), including regulating neuronal density (Sanno et al. 2010), and apoptotic genes may have been targeted by selection in relation to primate brain expansion (Vallender and Lahn 2006). Disruption of apoptosis causes microcephaly (Poulton et al. 2011), potentially explaining the association between DUF1220 dosage and head circumference (Dumas et al. 2012). The association of NF-κB with inflammatory diseases (Tak et al. 2001) is also intriguing, given the growing evidence that the inflammatory response is linked to the risk and severity of ASD (Meyer et al. 2011; Depino 2012).

If DUF1220 domain number does contribute to the evolution of postnatal brain growth, this contrasts with results of previously studied candidate genes with known roles in neurogenesis that coevolve with prenatal brain growth (Montgomery et al. 2011). This suggests a two-component model of brain evolution where selection targets one set of genes to bring about an increase in neuron number (e.g., Montgomery et al. 2011; Montgomery and Mundy 2012a, 2012b), and an independent set of genes to optimize neurite growth and connectivity (e.g., Charrier et al. 2012). NBPF genes may fall into the latter category. This two-component model is consistent with comparative analyses that indicate pre- and postnatal brain developments evolve independently, and must therefore be relatively free of reciprocal pleiotropic effects (Barton and Capellini 2011).

Finally, these results add further evidence that many of the genetic changes that contribute to human evolution will be based on the continuation or exaggeration of conserved gene-phenotype associations that contribute to primate brain evolution more broadly (Montgomery et al. 2011; Scally et al. 2012). Understanding the commonalities between human and nonhuman primate brain evolution is therefore essential to understand the genetic differences that contribute the derived aspects of human evolution.

Materials and Methods

Counting DUF1220 Domains

HMMER3.1b (Eddy 2011) was used to build an HMM from the DUF1220 (PF06758) seed alignment stored in the PFAM database (Finn et al. 2014). The longest isoforms for all proteomes of 12 primate genomes from Ensembl v.78 (Cunningham et al. 2015) (fig. 1*a*) were searched using the protein DUF1220 HMM (hmmsearch, E value < 1e-10) (supplementary table S1, Supplementary Material online). We extracted the corresponding cDNA regions to build a DUF1220 nucleotide profile HMM (nHMM) using a MAFFT sequence alignment, allowing for more sensitive analysis across a broad phylogenetic range. The DUF1220 nHMM was used to search the complete genomic DNA for all 12 species. These counts were filtered to remove any DUF1220 domains not located in annotated exonic sequence, or located in known pseudogenes.

We next filtered our counts to limit them to exonic sequence in close proximity to the NBPF-specific Conserved-Mammal (CM) promoter (O'Bleness et al. 2012). To do so, we built a nucleotide HMM for the CM promoter based on a MAFFT (Katoh et al. 2002) alignment of the 900-bp CM region upstream of human genes *NBPF4*, *NBPF6*, and *NBPF7*. Using this CM promoter nHMM, we searched 1,000-bp up- and downstream of genes containing DUF1220 domains for significant CM promoter hits (nhmmer, *E* value < 1e-10). This provided final counts for DUF1220 domains within exonic regions and associated with the CM promoter (table 1). These counts were used in subsequent phylogenetic analyses. In the supplementary information, Supplementary Material online, we compare our counts with previous estimates and discuss possible sources of error. All scripts and data used in the analysis are freely available from: https://github.com/qfma/duf1220

Phylogenetic Gene-Phenotype Analysis

PGLS regressions were performed using log-transformed phenotypic data and log- or square root-transformed DUF1220 count data in BayesTraits (Pagel 1999). Phylogenetic multivariate generalized mixed models were implemented using a Bayesian approach in MCMCglmm (Hadfield 2010), to test for phylogenetically corrected associations between DUF1220 counts and log-transformed phenotypic data (supplementary table S2, Supplementary Material online). All analyses were performed using a Poisson distribution, as recommended for count data (O'Hara and Kotze 2010), with uninformative, parameter expanded priors for the random effect (G: $V = 1$,n $\nu = 1$, alpha.$\nu = 0$, alpha.$V = 1{,}000$; R: $V = 1$, $\nu = 0.002$) and default priors for the fixed effects. Phylogenetic relationships were taken from the 10k Trees project (Arnold et al. 2010). We report the posterior mean of the cofactor included in each model and its 95% CIs, and the probability that the parameter value is greater than 0 (P_{MCMC}) as we specifically hypothesize a positive association (Dumas et al. 2012). Alternative data treatments lead to similar conclusions (supplementary information, Supplementary Material online).

Acknowledgments

The authors thank James Sikela, Majesta O'Bleness, Chris Venditti, Charlotte Montgomery, Andrew Moore, and Jarrod Hadfield for advice and comments, and Judith Mank's lab at UCL for support. S.H.M. thanks the Leverhulme Trust for funding.

Supplementary Material

Supplementary information, figures S1–S3, and tables S1–S3 are available at *Genome Biology and Evolution* online (http://www.gbe.oxfordjournals.org/).

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Associate editor: George Zhang