Molecular evolution of the brain transcription regulatory network affecting worker behaviour of honey bees (*Apis mellifera*)

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Abstract

The brain transcription regulatory network drives the behavioural states of honey bee workers. It is paradoxical that labile behaviour is guided by a network of evolutionary conserved pleiotropic transcription factors. So how does adaptive change in behaviour arise? I used a population genomics approach to estimate the strength of selection on coding and *cis*-regulatory mutations of transcription factors and their target genes in the honey bee brain transcription regulatory network. I found that replacement mutations in highly connected transcription factors and target genes experience significantly stronger negative selection relative to weakly connected transcription factors and targets. Interestingly, connectedness and network structure had minimal influence on the strength of selection on putative regulatory sequences for both transcription factors and their targets. This study suggests that adaptive evolution of complex behaviour can arise because of positive selection on protein-coding mutations in peripheral genes, and on regulatory sequence mutations in both transcription factors and their targets throughout the network.

Dedication

I dedicate my thesis to my mother who has supported me throughout my studies and inspired me to the study of biology and to my father who inspired me to discover nature.

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Chapter 1.

'The art of progress is to preserve order amid change and to preserve change amid order.' Alfred North Whitehead

Introduction

Understanding the genetics and evolution of complex traits is a central goal in biology. Behaviour is a complex phenotype that exhibits a high degree of variation within an individual's lifetime, within and between populations of the same species, and between species. Behavioural genetics research conducted over the past decade has emphasized the role of conserved genes in behavioural evolution. There is good evidence that behaviour, like most complex phenotypes, is controlled by gene regulatory networks that exhibit modularity and pleiotropy, and that genes and gene networks that influence behaviour in one organism also influence similar behaviours in evolutionary distant species (Anholt and Mackay, 2004; Reaume and Sokolowski, 2011; Zayed and Robinson, 2012). This conservation of gene action on behaviour has allowed researchers to study behavioural evolution within the framework of Evolutionary Developmental Biology (i.e.evo devo) (Carroll, 2008). The synthesis of behavioural genetics and evo devo has led to many insights (Linksvayer and Wade, 2005; Toth and Robinson, 2007; Toth and Robinson, 2009), including the existence of a genetic tool kit for behaviour (i.e. conserved gene modules that influence basic forms of behaviour across species), and that complex behaviours can evolve through the co-option of genetic modules that control simple forms of behaviour. In contrast to the evo devo paradigm, there is a burgeoning body of literature suggesting that novel taxonomically-restricted genes are important, and perhaps most prominent, in behavioural evolution (Johnson and Tsutsui, 2011; Chen et al., 2013; Ferreira et al., 2013; Simola et al., 2013; Harpur et al., 2014; Jasper et al., 2014; Sumner, 2014). Fortunately, genomics-enabled research on a variety of model and non-model organisms is providing a wealth of information on the contribution of novel and conserved genes to the genetic architecture of complex traits. Along with population genomic data on levels of selection acting on genes and regulatory sequences, evolutionary biologists are at the verge of ultimately testing the different theories of phenotypic evolution.

The different paradigms of phenotypic evolution make distinct predictions about the relative contribution of regulatory and protein-coding sequence changes. On one end of the spectrum, the evo devo paradigm emphasizes the role of adaptive regulatory sequence evolution (Wray, 2007; Carroll, 2008) because of the assumption that genes with multiple functions, or genes that interact with other genes, are expected to experience a great deal of constraint at their amino acid sequence (Fisher, 1930). Others have challenged this central assumption of the evo devo paradigm by arguing that seemingly ‘conserved’ proteins, including transcription factors, have several features that allow them to ‘escape’ the constraining influence of pleiotropy thereby allowing adaptive evolution via amino-acid changing mutations (Lynch and Wagner, 2008; Wagner and Lynch, 2008); such features include alternative splicing, modularity at the level of protein domain and structure, and the presence of mutable short or simple sequence motifs. At the other end of the spectrum, there is a growing interest in novel taxonomically restricted genes that are free to evolve new functions without suffering from the constraining effect of pleiotropy (Chen et al., 2013). Empirical evidence do not fully support any one of these three paradigms over the others – there is population genetic evidence for both adaptive protein sequence evolution and adaptive coding sequence evolution in many organisms (Andolfatto, 2005; Hoekstra and Coyne, 2007; Halligan et al., 2010; Halligan et al., 2013; Harpur et al., 2014; Wallberg et al., 2014). However, most previous tests of these paradigms involved correlating general rates of protein evolution with molecular features of genes and their position in regulatory networks (e.g. Hahn and Kern, 2005; Kim et al., 2007; Davila-Velderrain et al., 2014); data on the actual levels of positive or negative selection on coding sequences (Assis and Kondrashov, 2014) are seldom used. Moreover, we know very virtually nothing about how pleiotropy and the structure of gene regulatory networks affect patterns of regulatory sequence evolution.

The honey bee Apis mellifera has emerged as a model organism for studying the genetics and evolution of complex behaviours (Hunt et al., 2007; Page et al., 2012; Zayed and Robinson, 2012). Here I use several powerful genomic resources developed for the honey bee to examine if regulatory networks that influence behaviour follow the predictions of the evo devo paradigm for phenotypic evolution. Chandrasekaran et al. (2011) recently constructed a brain transcriptional regulatory network (TRN) influencing several aspects of worker behaviour, including behavioural maturation, foraging, and colony defence. The honey bee brain TRN is highly amenable to studies of how connectedness and network topology constrain behavioural and molecular evolution, especially given the recent availability of a large population genomic dataset for the honey bee (Harpur et al., 2014), which consists of genome wide polymorphism data for 11 A. mellifera scutellata diploid genomes and genome wide divergence data between A. mellifera and its sister species A. cerana.

I used the honey bee population genomic dataset to study the strength of selection on protein and putative cis-regulatory sequences of genes in the bee brain TRN. I tested the following hypotheses from the evo devo paradigm: 1) Highly connected TFs and target genes are predicted to experience stronger negative selection on nonsynoymous mutations relative to weakly connected TFs and target genes and 2) Genes with signs of adaptive amino acid sequence evolution are expected to be less central within the regulatory network. The evo devo paradigm does not explicitly make predictions about the relationship between pleiotropy and regulatory sequence evolution, but rather predicts that the evolution of regulatory sequences should be less constrained relative to protein sequence evolution, and that regulatory mutations are more likely to fuel adaptive evolution. I compared the average selection coefficient on mutations in putative cis-regulatory regions of strongly and weakly connected genes within the TRN to explore how network properties influence regulatory sequence evolution. Our study provides an important glimpse into the evolution of regulatory networks that influence complex behaviours.

Material and Methods

Sequencing, alignment, SNP calling and modified McDonald-Kreitman (MK) tests.

I recently sequenced 40 honey bee genomes, each at approximately 40X coverage, using Illumina Hi-Seq technology (Harpur et al. 2014). Alignment and polymorphism identification were described in detail by Harpur et al. (2014). I used a Bayesian implementation of the McDonald-Kreitman (MK) test, using SnIPRE (Eilertson et al. 2012), to determine the population size scale selection coefficient γ for 12,303 genes in the honey bee genome. Here, I used the population genomics dataset to study selection acting on putative cis-regulatory regions of the honey bee genome. I first estimated the number of polymorphic mutations in A. mellifera, and the number of fixed mutations between A. mellifera and its sister species A. cerana, in putative cis-regulatory regions of honey bee genes. Because the regulatory sequences of the honey bee genome have not been characterized, we considered the 1000 bp sequence upstream of each gene's start codon as a putative cis-regulatory region (Davidson, 2006; Li et al., 2006; Myers, 2014). I excluded upstream sequences that overlapped genes encoded by the 5 complementary DNA strand, resulting in putative cis-regulatory regions with an average size of 905 bp. These regions are expected to contain most of the sequences important for transcriptional and translational control, including the 5'UTR and important transcription factor binding sites (Davidson, 2006; Li et al., 2006; Myers, 2014). The cut-off would have certainly excluded some regulatory sequences that reside far upstream of genes (Negre et al., 2011) – sequences that are currently very difficult to annotate in the honey bee. Despite this important caveat, our population genomic analyses (see results) show an overall signature of negative purifying selection within 1 Kb upstream of genes, which is consistent with such regions having a functional role related to gene regulation (Dunham et al., 2012; Wittkopp and Kalay, 2012). Following, Torgerson et al. (2009), I studied the evolution of cis-regulatory regions using a modified MK test by comparing the ratio of fixed:polymorphic mutations in a cis-regulatory sequence of a gene to same ratio for silent sites in the same gene. The modified MK test was implemented using SnIPRE (Eilertson et al. 2012), which allowed to estimate the average population size scaled selection coefficients on regulatory sequence mutations. Similar to Harpur et al. (2014), I only used polymorphism data from African honey bee genomes, which represent a large population that is minimally impacted by human management (Harpur et al., 2012; Kent et al., 2012).

TRN construction and analysis

The honey bee brain TRN (Chandrasekaran et al., 2011) is freely available online (Web: http://price.systemsbiology.net/honeybee-transcriptional-regulatory-network). The dataset consisted of microarray probes for TFs and their targets in the bee brain TRN. I remapped the array probes to the honey bee's official gene set OGS v3.2 (Elsik et al., 2014) using Blastn v. 2.2.28+. I only retained probes that had perfect matches to OGS v3.2 gene predictions. I was able to blast match microarray probes to 191 transcription factors and 1597 target genes. I restricted the analyses to 184 TFs and 1521 target genes that had γ estimates for coding and putative regulatory sequences. I estimated the number of target genes for every transcription factor (k ranged from 1 to 161), and the number of transcription factors regulating every target (k ranges from 1 to 15). I plotted the regulatory network using Gephi (Bastian et al., 2009) and produced a directed graph with 1504 nodes and 5149 edges representing transcription factor - target interactions. Gephi was used to estimate betweenness centrality of the genes in the network. We used the R package poweRlaw (Gillespie, 2014) to fit a power law distribution to TRN connectedness using established methods (Clauset et al., 2009). Statistical tests were carried out using R. I used a one-tailed test to compare the γ of hub and non-hub TFs and targets, given a priori theoretical expectations and empirical findings regarding the relationship between pleiotropy/connectedness and molecular evolution. All other p-values are two-tailed. It is important to note that the honey bee brain TRN was developed by first selecting honey bee TFs that had robust orthologs to Drosophila TFs (Chandrasekaran et al., 2011); the bee brain TRN is thereby enriched for old taxonomically-conserved TFs and target genes. Current study of the bee brain TRN can therefore illuminate how ancestral gene networks influencing behaviours evolve, but tell us little about the role of taxonomically-restricted genes in behavioural evolution – a topic that was ecently discussed elsewhere (Harpur et al., 2014).

Results

Selection on regulatory and coding sequences in the honey bee genome.

We had previously estimated the average population size scaled selection coefficient γ on nonsynonymous mutations in 12,303 genes in the honey bee genome since divergence between A. mellifera and A. cerana (ca. 5 MYA) (Harpur et al., 2014). Here I used a variant of the MK test (Torgerson et al., 2009; implemented using Eilertson et al., 2012) to estimate the average γ on mutations in putative cis-regulatory sequences by comparing the ratio of polymorphic:fixed mutations within 1 kb upstream of a gene's start codon to the ratio of polymorphic:fixed synonymous mutations at the same gene. I was able to estimate γ on the putative cis-regulatory sequences of 10,807 genes in the honey bee genome (Fig. 1). I found most (93%) cis-regulatory sequences to have estimates of γ consistent with neutral or nearly neutral evolution ($-1< \gamma < 1$). About 6% of cis-regulatory sequences have $\gamma<-1$, indicative of negative purifying selection, while 1% of sequences have signs of positive selection ($\gamma >1$). In contrast to evolution of protein coding sequences (average $\gamma \sim 0$), the average mutation in cis-regulatory regions appear to be weakly deleterious (average $\gamma = -0.4$). This pattern was previously observed in humans (Torgerson et al., 2009) and most likely results from an observational bias: sequences from rapidly evolving regulatory regions will have many mismatches between A. mellifera and A. cerana, which results in lower alignment scores and coverage, and would have been removed from the dataset based on our quality control filters. As such, direct comparisons of the selection coefficient on coding and regulatory mutations are not appropriate. Instead, I examined the influence of a gene's connectedness and position within the TRN on regulatory and protein sequence evolution in separate analyses.

Network topology and evolution of TFs and their target genes

I studied patterns of selection on coding and regulatory mutations in 170 transcription factors (TFs) and 1334 of their target genes in the honey bee brain TRN. Similar to other regulatory networks (Babu et al., 2004; Nicolau and Schoenauer, 2009), the honey bee brain TRN is approximately scale-free, whereby the distribution of connectedness (k) between the network nodes (i.e. genes) has a very long tail (SI Figure 1). Scale-free networks contain a large number of genes with a small number of connections, and a small number of genes with a large number of connections – often called 'hub' genes. The number of connections, k, between nodes in a scale-free network follows a power law, at least above a certain value of k (Nicolau and Schoenauer, 2009). Connectedness varied between 1 and 161 in the honey bee brain TRN, and we found the tail of the connectedness distribution to follow a power law ($x_{min}=42$, $\propto=3.00$; H0 = power law: Goodness of fit: 0.088, $p = 0.32$). I elected to analyse the dataset by categorizing genes as hub or non-hub, following Wang et al. (2010a), because analyses based on linear models or correlations do not adequately deal with the scale-free properties of regulatory networks (i.e. the distribution of connections within the TRN is not normal). Following Wang et al. (2010a), I considered the top 20% of most connected TFs as hubs ($k > 44$ connections). Hub TFs were more central in the network as evidenced by a significantly higher estimate of eigenvector centrality relative to non-hub TFs (Wilcoxon test, $p<2.2e-16$). I found that hub TFs had a significantly lower mean coding γ than non-hub transcription factors (Figure 2A, Wilcoxon 1-tailed $p=0.0025$), and that hub TFs were significantly enriched for genes with negative coding γ (Chi square enrichment $p=0.015$) relative to non-hub TFs. In contrast to coding γ, hub TFs and non-hub TFs did not significantly differ with respect to cis-regulatory γ (Figure 2C, Wilcoxon 1-tailed $p=0.27$). Hub and non-hub TFs did not significantly differ in terms of sequence coverage and length at regulatory and coding sites (SI Table 1).

Similar to TFs, I used connectedness to classify target genes in the TRN into hubs (top 20%) and non-hubs based on k. Hub target genes within the TRN were regulated by four or more TFs, and were significantly more central within the network relative to non-hub target genes (Wilcoxon $p=2.2e-16$). Similar to the differences between hub TFs and non-hub TFs, hub target genes had significantly lower coding γ (Figure 2B, Wilcoxon 1-tailed $p=0.0425$), but not cis-regulatory γ (Figure 2D, Wilcoxon 1-tailed $p=0.12$) relative to non-hub target genes. Hub and non-hub target genes did not significantly differ in terms of sequence coverage and length at regulatory and coding sites (SI Table 1).

Where is positive selection acting within the TRN?

I mapped all genes with signatures of positive selection on coding and cis-regulatory sequences in the TRN (Figure 3). I also estimated betweenness for each gene in the TRN; betweenness is a global measure of centrality (Borgatti and Everett, 2006) which ranges from 1, indicating most central or at the core of the network, to 0, indicating the outside perimeter or the periphery of the network. I compared the average betweenness of genes with substantial signs of positive (γ>1) and negative (γ<-1) selection. I found that proteins with signatures of positive selection on their coding sequences had significantly lower betweenness relative to proteins with signatures of negative selection, indicating that adaptively evolving proteins are often more distant from the network core relative to proteins with signs of negative selection (Figure 4A, Wilcoxon, two tailed p=0.04). In contrast, I did not find a significant difference in the betweenness of genes with positive selection on their cis-regulatory sequences relative to those with negative selection on their cis-regulatory sequences (Figure 4B, Wilcoxon two-tailed p=0.4). This indicates that genes with regulatory sequences experiencing positive selection reside in the approximately the same locations within the TRN as genes with regulatory sequences experiencing negative selection.

Discussion

I examined how gene position within a network influenced the average selection coefficient γ on putative cis-regulatory and replacement mutations in 1,504 genes in the honey bee brain TRN. Present results support a ‘mosaic’ view of phenotypic evolution by illuminating how the scale-free properties of regulatory networks (Wang et al., 2010b; Le Nagard et al., 2011; Wagner and Zhang, 2011) facilitate adaptive evolution involving both coding and regulatory mutations.

Several lines of evidence suggest that the most connected, and likely most pleiotropic, proteins within the bee brain TRN experience the greatest levels of purifying selection, as predicted by Fisher (1930) and the Evo Devo paradigm (Carroll, 2008). Despite the large number of factors that influence the rate of molecular evolution of genes (Xia et al., 2009) I consistently found that the most connected genes in the TRN had the strongest signatures of negative selection on their coding sequence. In brief, transcription factors that regulate hundreds of target genes experience, on average, stronger negative selection on their coding sequence relative to transcription factors the regulate a few target genes (Fig 2A). Hub transcription factors likely have to interact with many other co-factors, in addition to binding target promoter sites, which may be responsible for the stronger levels of purifying selection on their amino acid sequence. Similar to hub transcription factors, hub target genes that are regulated by many transcription factors experience stronger negative selection on their coding sequence relative to target genes that are regulated by a few transcription factors. Target genes that are regulated by multiple TFs may be expressed in multiple tissues or during multiple contexts relative to target genes regulated by a few TFs resulting in greater pleiotropy and stronger purifying selection, as evident from our analysis (Fig 2B). It is important to note that several genes within the TRN had signs of adaptive protein evolution; most of these genes were transcription factor targets, and most resided near the periphery of the TRN. Lynch and Wagner (2008) and Wagner and Lynch (2008) previously argued that proteins, including conserved TFs, have features that allow them to escape from the negative effects of pleiotropy. Present population genomic data are not fully consistent with the Lynch and Wagner hypotheses because the most central and most connected TFs or targets do experience stronger levels of negative selection versus peripheral and weakly connected TFs or targets; a relationship that is more inline with the classic evo devo paradigm. It is very likely that the scale-free properties of TRNs hold the key for reconciling the predictions of the evo devo paradigm with the empirical data showing that amino-acid changes do contribute to adaptive evolution. The classic evo devo paradigm assumes that most genes are constrained by pleiotropy, while studies of TRN structure clearly show that only a few genes are highly connected and central, while most genes are weakly connected and peripheral. Although pleiotropy does appear to curtail adaptive protein sequence evolution of the few most connected and most central genes within a TRN, adaptive protein evolution is still a powerful evolutionary force for most TRN genes that reside at the network periphery.

In stark contrast to the influence of TRN topology on protein coding evolution, I found that connectedness matters little with respect to levels of selection on putative cis-regulatory regions. The average selection coefficient on regulatory sequence mutations of hub transcription factors was similar to that of non-hub transcription factors (Fig 2C). Similarly, the selection coefficient on regulatory sequences of hub target genes was similar to those of non-hub target genes. Genes with signs of adaptive regulatory sequence evolution were found in similar locations within the TRN as genes with negative selection on their regulatory sequences. Present analysis indicates that network properties do not significantly shape the selection pressures acting on regulatory sequences within the TRN. It is not clear how this evidence support the evo devo paradigm because the evo devo paradigm does not make explicit predictions about the relationship between pleiotropy, connectedness and regulatory sequence evolution. On one hand, the finding that putative cis-regulatory sequences evolve independently of TRN connectedness and topology appears to support an important assumption of the evo devo paradigm: pleiotropy or connectedness of a protein only influences the protein's amino acid sequence, not its cis-regulatory sequence. On the other hand, another interpretation of the evo devo paradigm suggests that the most connected and pleiotropic genes should have the greatest levels of adaptive regulatory evolution, while the least connected genes should have the least levels of adaptive regulatory evolution (i.e. regulatory sequence evolution compensates for constrained amino acid sequences); present findings do not support this idea. It would appear that adaptive regulatory sequence evolution can occur throughout any compartment of the regulatory network.

Present analyses shed light on the evolution of regulatory networks influencing complex behaviour. Highly connected genes within the honey bee brain TRN exhibit stronger patterns of purifying selection on amino acid replacement similar to highly connected genes in other types of networks studied so far. Also, genes with signs of adaptive protein evolution tend to be concentrated at the network periphery, as previously documented for proteins in the Human Interactome (Kim et al., 2007). I found that connectedness does not influence the strength of selection on regulatory sequences of highly connected genes. This study suggests that the scale-free properties of regulatory networks, with a few large modules and many small modules, allows for both coding and regulatory sequence mutations to contribute to adaptive evolution. Based on our findings, we expect adaptive evolution of regulatory networks influencing complex traits to proceed through positive selection on coding mutations in peripheral genes and on regulatory mutations in TFs and their targets across the regulatory networks. Previously, strong evidence was presented that novel taxonomically-restricted genes have the highest rates of adaptive protein evolution in the honey bee genome (Harpur et al., 2014). A recent analysis also pointed to an increased expansion of regulatory sequences in social genomes (Simola et al., 2013). Going forward, it will be important to study how novel taxonomically restricted genes interact with conserved TRN modules with expanded regulatory features to influence the evolution of complex behaviours in social insects.

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Tables

Table S1. Coverage and sequence length for *cis*-regulatory and coding regions of the genes in the TRN. Wilcoxon rank sum test 2-tailed p-values are reported for all tests.

Groups compared	Mean±SEM	p value
Average cis-regulatory read depths of hub and non-hub TFs	hub=33.5±0.9 non-hub=34.6±0.5	0.5
Average cis-regulatory read depths of hub and non-hub targets	hub=33.8±0.2 non-hub=33.9±0.2	0.4
Average number of bps covered in cis-regulatory region of hub and non-hub TFs	hub=895±34.4 non-hub=855±19.5	0.2
Average number of bps covered in cis-regulatory region of hub and non-hub targets	hub=798.5±12.8 non-hub=830.7±8.7	0.1
Average coding read depths of hub and non-hub TFs	hub=37.4±1 non-hub=36.6±0.5	0.7
Average coding read depths of hub and non-hub targets	hub=37±0.2 non-hub=37.1±0.2	0.8

Table S2: Coding and *cis*-regulatory γ of transcription factors in the TRN.

TF_ID	k	g	cis_g	TF_ID	k	g	cis_g
GB53401	13	0.073601454	-0.971773495	GB49604	34	-0.241132071	-0.637329786
GB42382	12	-0.470471795	-0.865072009	GB47828	42	-0.433802231	-0.214318433
GB52323	7	-0.694562487	-0.012910613	GB42706	48	-0.599155325	-0.513096548
GB47329	54	-0.324462615	-0.808695785	GB53826	16	-0.364130508	-0.476827986
GB41753	18	0.083415652	-0.476346426	GB42321	15	-0.439174075	-0.593873819
GB40454	75	-0.668382795	-0.322482942	GB51231	13	0.343478536	-0.620927342
GB45540	37	-0.363934832	0.089269002	GB49105	11	0.375817593	-0.50684708
GB45062	29	0.053927945	-0.664658788	GB41516	2	-0.290499254	-0.821433067
GB50795	18	-0.025549443	0.033029327	GB50048	3	-0.26984821	0.238233896
GB41639	7	0.010616997	0.477137982	GB42178	12	0.109232507	0.095980982
GB40871	6	0.323142158	-0.651248219	GB48121	16	0.289593514	0.018663213
GB55103	44	-0.117351025	-0.127812249	GB41865	66	-0.480615657	-0.470776851
GB41450	2	-0.182209508	-0.89895452	GB51904	7	1.558469774	0.253174538
GB48271	55	-0.263775022	-1.158795511	GB50342	4	0.114765898	-0.545146161
GB48273	82	-0.247537645	-0.790967356	GB42758	19	0.857015696	-0.378704081
GB47234	7	0.416913946	-0.556000091	GB40407	16	-0.154312967	0.247089834
GB51518	10	0.188875623	-0.568830833	GB43632	7	-0.276669499	-0.480445231
GB44883	113	-0.316601627	-0.500080531	GB44836	53	-0.453725018	-0.606382572
GB48002	6	-0.244161648	-0.63898414	GB42142	114	-0.29479687	-0.479423881
GB45040	2	-0.119804465	-0.480941986	GB52687	2	-0.817287365	0.186390988
GB44656	85	0.033970851	-0.063765738	GB48239	23	-0.423984973	-0.280536361
GB51909	2	1.068925315	-0.712693409	GB54092	1	-0.270291441	0.385143744
GB49611	44	-0.495227282	-0.730247721	GB47799	1	0.572548171	-0.083080971
GB47260	11	0.673895155	-0.976105317	GB54953	69	-0.05134601	-0.697512975
GB48360	3	-0.096144425	-0.250003743	GB43778	22	-0.039012471	-0.681723913
GB47788	15	-0.108795652	-0.065871277	GB45414	1	0.904339429	0.767720431
GB45841	22	0.462823111	0.076005121	GB52904	1	0.732760284	0.313522078
GB50435	14	0.434025591	-0.407141056	GB52628	1	-0.863124021	-0.490062644
GB46509	16	-0.548959605	-0.506337415	GB55576	11	-0.079299429	-0.258692226
GB52047	2	0.725092764	-0.00026553	GB53318	7	0.813284197	-0.071324136
GB51085	9	0.258803818	-1.457876612	GB42049	12	0.381277881	-0.276830593
GB47820	54	-0.291330873	-0.87528455	GB53328	5	0.78682598	-0.216077948
GB43159	39	0.421127537	-0.377306377	GB46387	42	0.229675851	0.562008679
GB47052	9	1.536035764	-0.838387705	GB55387	36	1.016725974	-1.74026812
GB44870	57	-0.37743103	-0.314686618	GB51059	1	-0.584220211	-0.431779569
GB47443	1	-0.811323984	-0.472865926	GB54168	38	0.169450393	-0.370380333
GB52304	10	0.272322956	-0.855281777	GB41968	20	0.155801675	-0.421397786
GB40150	69	-0.209903213	0.970920277	GB41522	9	-0.465021299	-0.941434288
GB51757	134	-0.35002865	-0.45250824	GB51133	5	-0.127988813	-0.749672698
GB46211	1	-0.521999774	-0.787495074	GB50071	10	-0.34099787	0.150511494
GB40453	1	-0.485561654	-0.81438514	GB41803	7	-0.274535116	-1.310967307
GB55635	1	-0.457191809	-0.369425801	GB55837	15	0.182667907	-0.594741398
GB52988	56	-0.374501293	-0.568826303	GB49315	2	0.785516514	-0.305395368

GB47991	19	-0.027730584	0.240289607	GB44679	122	-0.643467267	-0.771975163
GB52746	1	0.213655117	-0.313481111	GB44791	130	1.463840547	0.166224267
GB55002	1	-0.580569844	-1.553650406	GB55306	1	0.789411302	-0.192672611
GB40147	2	0.448555707	-0.490572878	GB40387	28	-0.049605927	-0.447203323
GB51521	3	0.066177922	-0.919088006	GB45501	31	-0.015645663	0.191824271
GB54984	20	-0.464356076	-0.489890017	GB45051	14	-0.030830662	-1.096437279
GB52852	4	0.196303127	-0.475299428	GB44974	4	-0.703377383	-0.616413307
GB53250	5	-0.395892692	-0.470169174	GB49751	10	0.100180552	-0.209276507
GB50732	12	-0.352619505	-0.780808238	GB50534	9	0.043149073	-0.195828824
GB53398	95	0.697529179	-0.423034727	GB53167	4	-0.516818529	-0.813937573
GB44361	10	0.034896443	-0.768593166	GB53164	37	0.141052803	-0.210985304
GB51421	6	-0.511810985	-0.692627053	GB41239	2	0.760423624	-0.382630287
GB47596	3	-0.610842757	-1.036508134	GB52625	44	-0.413708437	-1.229585447
GB42021	20	-0.394315549	-0.933971395	GB55033	3	0.184166872	-0.52042773
GB44351	11	-0.165070971	-0.470790158	GB53296	18	1.0253354	-0.645367797
GB46219	51	-0.230909602	-0.485535536	GB54432	2	0.224567137	-0.61817144
GB49953	96	0.27014007	-0.128353592	GB41167	26	-0.232199542	-0.271887563
GB51395	6	-0.21058025	-0.470218056	GB54118	117	-0.172216621	-0.683754236
GB51725	63	-0.231848784	-0.56065271	GB54841	44	-0.074815432	-0.674795595
GB49869	33	0.009373516	-0.620062845	GB51615	3	0.195914244	-0.165497169
GB41600	4	-0.51047471	-0.65174688	GB44532	8	0.075694275	-0.720179539
GB43179	61	-0.317679616	-0.895679857	GB44229	37	0.581028599	-0.73314335
GB56017	28	0.441694808	0.129283055	GB42213	2	0.356179831	-0.245135152
GB48579	33	-0.33259412	-0.508702567	GB41647	3	-0.761268848	-0.587261057
GB45259	161	-0.283621701	-0.296269582	GB53031	42	-0.209637335	-0.640288153
GB46757	9	0.352546435	-0.823594831	GB50020	14	-0.24915727	-0.766067728
GB43462	1	-0.732054365	-0.282139023	GB54378	9	0.039358354	-0.546167032
GB48028	2	0.659149503	0.377782554	GB45655	6	0.381268488	-0.655718241
GB42329	8	-0.472731162	-0.090667658	GB44418	71	-0.566983163	-0.374883712
GB48366	29	-0.146498815	-0.589515248	GB52058	6	-0.265983528	-0.269196947
GB46492	142	-0.304314807	-1.009344046	GB40911	86	-0.106404775	-0.332975906
GB48999	11	0.716001929	-0.55118581	GB44259	63	-0.18893582	-0.720714709
GB46523	44	-0.176249941	-0.328434707	GB48690	31	-0.09137546	-0.773525348
GB43953	1	-0.122877147	-0.629494874	GB52114	6	-0.14119774	-0.260163127
GB45074	13	0.867512094	-0.204762942	GB53921	101	0.815528836	0.332209539
GB40564	1	-0.572406093	-0.587407138	GB47057	2	0.340528458	-0.432809722
GB44042	6	0.258787872	-0.356435794	GB49969	3	-0.112233873	-0.280892445
GB41654	35	-0.069833686	-0.842852909	GB47515	14	0.219897389	-0.190379436
GB44032	15	0.034144498	0.195762513	GB53417	6	-0.160473656	-0.608513934
GB44031	43	0.275534805	-0.378261736	GB44976	33	0.002612203	0.370560271
GB43847	4	-0.56741327	-0.180550639	GB55540	51	0.057162173	0.161501258
GB55012	56	-0.637990988	-0.613998738	GB44585	15	-0.126976986	-0.436858171

Table S3: Coding and *cis*-regulatory γ of target genes in the TRN.

target_id	k	g	cis_g	target_id	k	g	cis_g
GB56032	4	0.031004048	-0.443817482	GB47823	3	0.715335759	0.279567906
GB56003	5	0.176785876	-0.583273041	GB47822	2	-0.076879124	-0.725936773
GB55945	4	-0.438543402	-0.18671137	GB47821	3	-0.130936041	-0.364251991
GB55943	2	0.35160906	-0.422947159	GB47816	4	-0.262006053	-0.423644152
GB55926	1	-0.228416744	-0.393677981	GB47779	2	1.062615809	-0.299872149
GB55920	6	-0.277467447	-0.381510993	GB47746	3	-0.900376593	-1.041871462
GB55919	3	-0.457309879	-0.674597589	GB47744	4	-0.040765193	-1.070227279
GB55916	4	-0.155556039	-1.379440929	GB47736	2	-0.24983277	-0.478471657
GB55902	4	-0.46608636	-0.648049182	GB47735	3	0.027708338	0.100382712
GB55900	2	0.143133735	-0.434898907	GB47724	4	0.277512965	-0.121403288
GB55888	1	0.298821138	0.146385133	GB47684	2	-0.25304297	-0.536645206
GB55877	3	0.821633216	0.517057058	GB47678	3	0.070482307	-0.504601567
GB55847	4	-0.294122234	-0.669297819	GB47657	3	-0.13924708	-0.194092629
GB55843	4	0.808857778	0.297991353	GB47651	3	-0.944409595	-0.508615159
GB55824	3	-0.211647166	-0.187067714	GB47632	3	0.356147573	-0.51378383
GB55800	5	0.095849932	-0.382508499	GB47629	4	-0.100673485	-0.62716444
GB55797	3	0.348729741	-0.614819015	GB47617	2	-0.56101142	-0.532553007
GB55786	2	0.115395008	-1.214517774	GB47605	2	0.06378609	-0.337260272
GB55784	1	-0.086023599	0.058718305	GB47602	4	-0.384408389	-0.650673722
GB55777	3	-0.124905128	-0.479611626	GB47599	4	-0.599545876	-0.226977144
GB55773	1	-0.351239611	-0.685690851	GB47590	4	-0.218293839	-0.18493222
GB55760	6	0.378498095	-0.359135121	GB47588	3	0.152301349	-0.354735359
GB55730	3	-0.531692709	-0.783609661	GB47576	3	0.467819953	-0.891606889
GB55715	2	-0.11595748	-1.371306112	GB47573	3	-0.840870138	-0.975312422
GB55704	3	-0.181524246	-0.716018385	GB47516	3	1.890452285	-0.223257616
GB55693	1	-0.225933861	-0.577837117	GB47508	1	0.123085922	0.002146276
GB55650	2	1.382404724	0.408357528	GB47502	4	-0.240317959	-0.350930251
GB55629	3	0.157552704	0.129351252	GB47496	3	0.529755075	-0.978424555
GB55619	3	1.174917727	-0.999350702	GB47495	4	0.174796969	0.015869309
GB55600	2	0.113707972	-0.976248052	GB47472	4	-0.32343218	-0.593653332
GB55591	2	1.507454732	5.581077598	GB47465	3	0.151123124	-0.533331246
GB55589	2	0.172070742	-0.420866516	GB47455	3	-0.772621	-0.781864968
GB55584	4	0.048251969	0.400161723	GB47450	3	-0.026956901	-0.932932315
GB55575	3	0.818907461	-0.298164995	GB47434	3	-0.439628044	-0.246182591
GB55567	4	0.084058025	-0.648243567	GB47432	3	-0.238323735	-0.169775332
GB55566	4	-0.537026139	-0.479311961	GB47431	3	-0.363148136	-0.438565443
GB55564	3	-0.873644874	-0.982543292	GB47425	4	-0.112005381	0.225589697
GB55539	4	-0.821872474	-0.548260643	GB47409	4	-0.45622757	-0.842687691
GB55530	3	0.062992905	-0.622331157	GB47393	2	0.112095633	0.291082569
GB55528	4	0.30340473	-0.14321446	GB47392	4	0.511142138	-0.323821748
GB55526	4	0.145763279	-0.664360583	GB47390	3	0.14271633	0.274797837
GB55522	3	-0.464589318	-0.589027405	GB47385	6	0.708300542	-0.415483113
GB55503	3	0.07012584	-0.512850901	GB47372	3	0.580424467	0.097843431
GB55499	3	2.73153061	0.022424746	GB47345	4	-0.241841915	-0.365838387
GB55495	1	-0.041487716	-1.066621257	GB47321	5	0.229696045	-0.517055222
GB55489	3	0.131437699	-0.706437683	GB47311	4	-0.044648234	-0.309275397

GB55482	4	-0.596955973	-0.817775909	GB47304	3	-0.1462871	-0.252189682
GB55456	1	-0.278964573	-1.170195515	GB47300	4	1.445676503	-0.69656926
GB55455	3	-0.237000082	-0.933804429	GB47280	4	-0.441537927	-0.752865375
GB55454	4	-0.134698434	-0.391190463	GB47274	4	0.056046871	-0.874456099
GB55441	3	-0.313688122	-0.569850095	GB47266	5	0.889554063	-0.296760284
GB55434	2	0.554198488	0.025395001	GB47258	1	-0.694886081	-1.022391068
GB55429	3	1.381732305	-0.421327491	GB47224	4	0.302251669	-0.056700942
GB55413	4	0.795249784	-0.292152958	GB47217	4	1.737768205	-0.582745352
GB55400	3	-0.153148124	-0.636547419	GB47209	3	-0.097482097	-0.287545893
GB55395	1	0.599858308	-0.263819982	GB47200	1	0.886967239	-0.647763406
GB55393	3	2.227867106	0.03173439	GB47199	4	-0.621389992	-0.486869683
GB55364	4	0.722044005	0.719041629	GB47139	2	-0.126728827	-0.200090141
GB55359	2	-0.318156828	-0.655519052	GB47138	5	-0.200414033	-0.433228111
GB55357	2	2.158885472	-0.9272608	GB47089	4	-0.477020317	-1.347270357
GB55348	2	-0.104130576	-0.48500479	GB47045	5	-0.615890352	-0.807602806
GB55324	3	-0.280569536	-0.120981274	GB47039	1	-0.266725597	-0.527621395
GB55317	2	-0.146672226	-0.400641475	GB47014	3	0.208722706	-0.450423396
GB55296	3	-0.088624277	-0.475861428	GB47011	2	-0.205423576	-0.645976866
GB55288	3	0.000960017	-0.747403049	GB47009	2	0.466868082	-0.018911978
GB55282	4	-0.954517695	-0.611573242	GB47007	4	0.214567111	-0.508419393
GB55274	3	0.220744044	-0.069687076	GB46963	3	-0.783728366	-0.478063187
GB55247	3	0.682098904	-0.652191485	GB46928	5	-0.56053744	-0.513432649
GB55237	3	1.399002449	-0.266478878	GB46915	3	-0.095203469	-0.45528005
GB55165	5	-0.336345425	-0.93851924	GB46914	2	1.256533592	-0.192695788
GB55160	1	-0.472668368	-0.153821506	GB46909	3	-0.33420545	-0.038693601
GB55151	4	-0.341631492	-0.793271401	GB46907	3	-0.446847154	-0.537587275
GB55102	3	-0.583164541	-0.743580875	GB46900	2	-0.038073596	-0.290284835
GB55096	2	-0.141646969	-1.032873985	GB46898	4	-0.204660769	-0.524699437
GB55082	4	-0.027248324	-0.028781089	GB46888	3	-0.159823565	-0.891948612
GB55074	4	-0.338859041	-1.135148015	GB46881	3	0.762760299	0.115641922
GB55020	3	0.181855804	-0.06391823	GB46878	4	0.306932481	-1.05482955
GB55017	3	0.537070963	-0.156633799	GB46767	2	-0.488797429	-0.225003647
GB55016	3	0.278021277	-1.142901463	GB46766	5	-0.490502334	-0.977171327
GB55015	2	-0.314056934	-0.640555359	GB46760	3	-0.179127594	-0.546629091
GB55009	4	0.090612266	0.101842032	GB46743	6	-0.47353297	-0.417708275
GB55008	1	-0.573027421	-1.039319321	GB46740	3	0.483431414	0.461892304
GB55003	4	-0.059107366	-0.007363694	GB46735	3	-0.283502664	0.209837516
GB55001	5	-0.06953133	-0.141861061	GB46732	1	-0.789438912	-0.245996858
GB54994	3	0.002729158	-0.261618508	GB46729	2	1.943208697	-0.399447511
GB54987	3	-0.096200754	0.758917231	GB46727	3	0.217835392	-0.861768039
GB54977	4	0.205952548	-0.369841021	GB46707	3	-0.541973244	-1.01156367
GB54974	3	0.009377998	-0.737904308	GB46696	3	0.385921599	-0.042209466
GB54971	4	-0.496331671	-0.974791349	GB46684	2	-0.341694851	0.263944596
GB54967	3	0.155193363	-0.380813018	GB46681	3	-0.064995242	-0.418360008
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GB48034	3	-0.017405819	-0.749851838	GB40145	3	0.616957597	1.495541272
GB48018	4	-0.314805667	-1.089246771	GB40118	1	1.332828051	-0.238248697
GB48009	3	0.146836612	0.387896225	GB40113	5	0.447666217	-0.01343942
GB48005	2	-0.2876716	-0.135013562	GB40108	3	-0.037294933	-0.524390135
GB47996	3	-0.838482116	-0.652941843	GB40102	4	-0.218134394	0.064420759
GB47992	3	1.140959732	0.907620666	GB40092	3	-0.642327184	-0.949728745
GB47971	4	0.101697714	0.862444705	GB40089	3	0.19576995	-0.28622725
GB47940	3	-0.335127708	-0.887097246	GB40084	1	0.149463616	0.150819735
GB47928	2	0.221447287	-0.068306114	GB40076	2	-0.370951261	-0.49179335
GB47876	8	-0.123665261	-1.368084102	GB40074	4	-0.861029285	-0.205348381
GB47847	2	0.486075633	-0.208956989	GB40071	5	-0.091378265	-0.813893839
GB47831	3	-0.039605823	-0.004215898	GB40057	4	-0.262375195	-0.294172101
GB47829	2	0.193385713	-0.331302376	GB40012	3	0.237303398	-0.316557571

Figures.

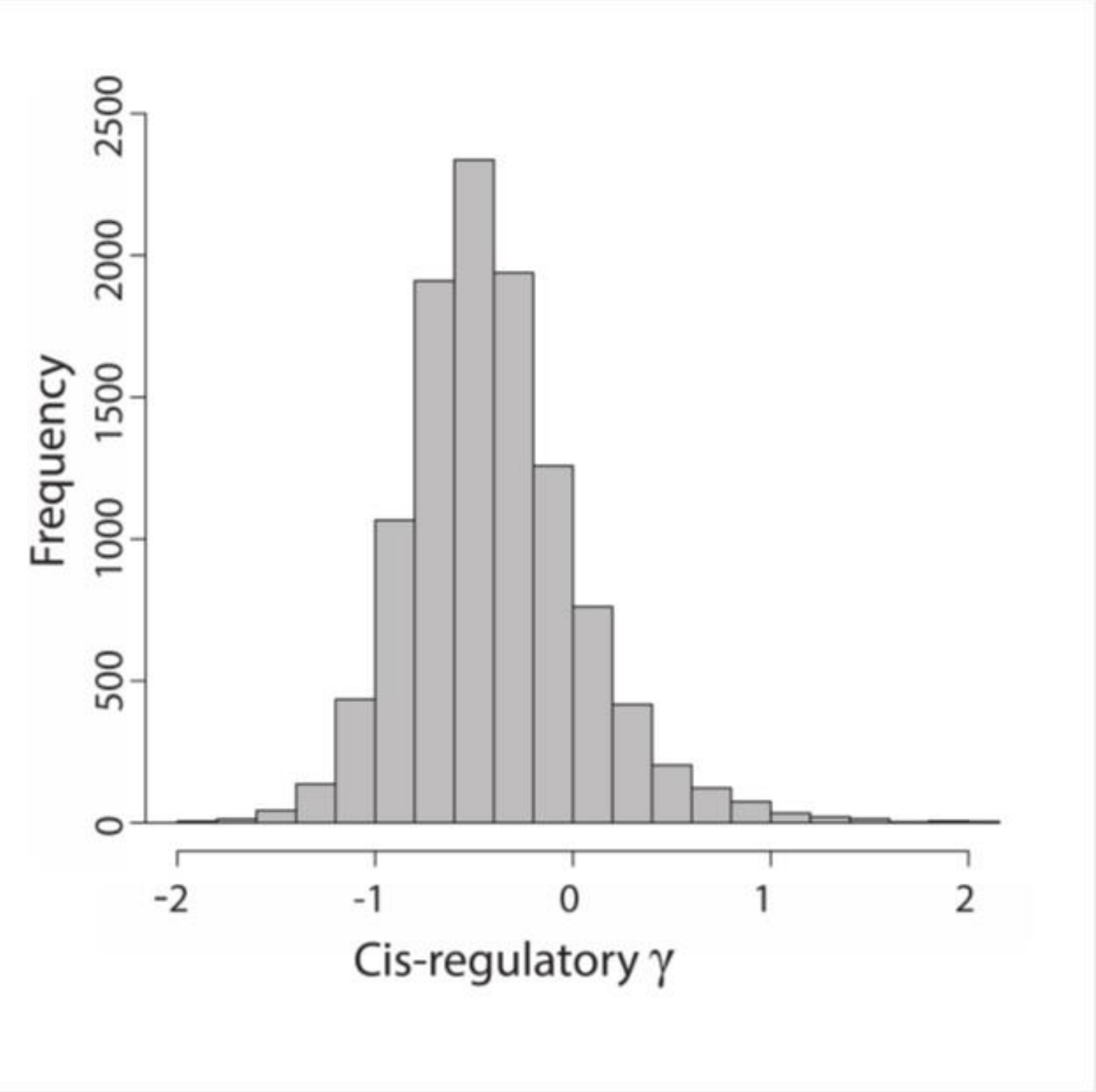

Figure 1: Distribution of average population size scaled selection coefficients (γ) on *cis*-regulatory mutations in 10,807 genes in the honey bee genome**.** Ten genes with *cis*-regulatory γ>2 were omitted from the histogram for readability.

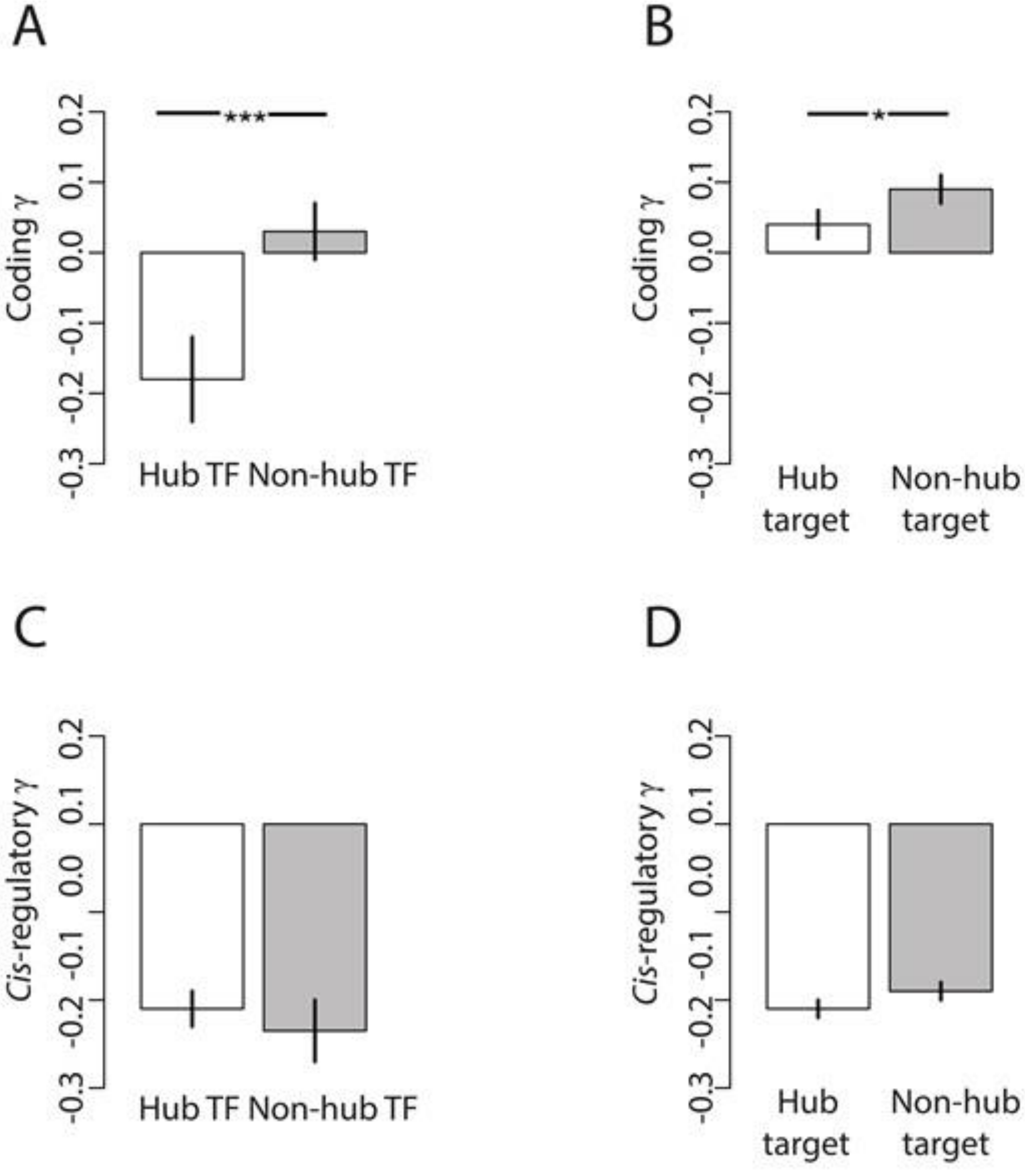

Figure 2: Connectedness reduces the seletion coefficient on coding but not regulatory mutations across the honey bee TRN. Both (A) hub TFs and (B) hub target genes have signficantly stronger negative selection on their coding sequences (i.e. lower coding γ) relative to non-hub TFs and non-hub targets, respectively. The selection coefficient on putative *cis*-regulatory sequences of (C) hub TFs and (D) hub target genes do significantly differ relative to non-hub TFs and non-hub targets, respectively. Bars indicate Mean ± SEM, * = $p<0.05$, ** =$p<0.01$, *** =$p<0.001$

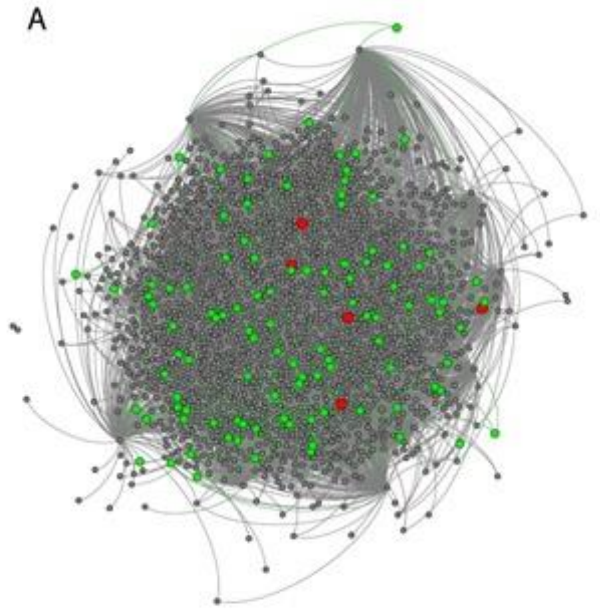

Figure 3: The honey bee brain TRN highlighting genes with adaptively evolving (A) *cis*-regulatory and (B) coding sequences. Adaptively evolving transcription factors are highlighted in red, while adaptively evolving targets are highlighted in green

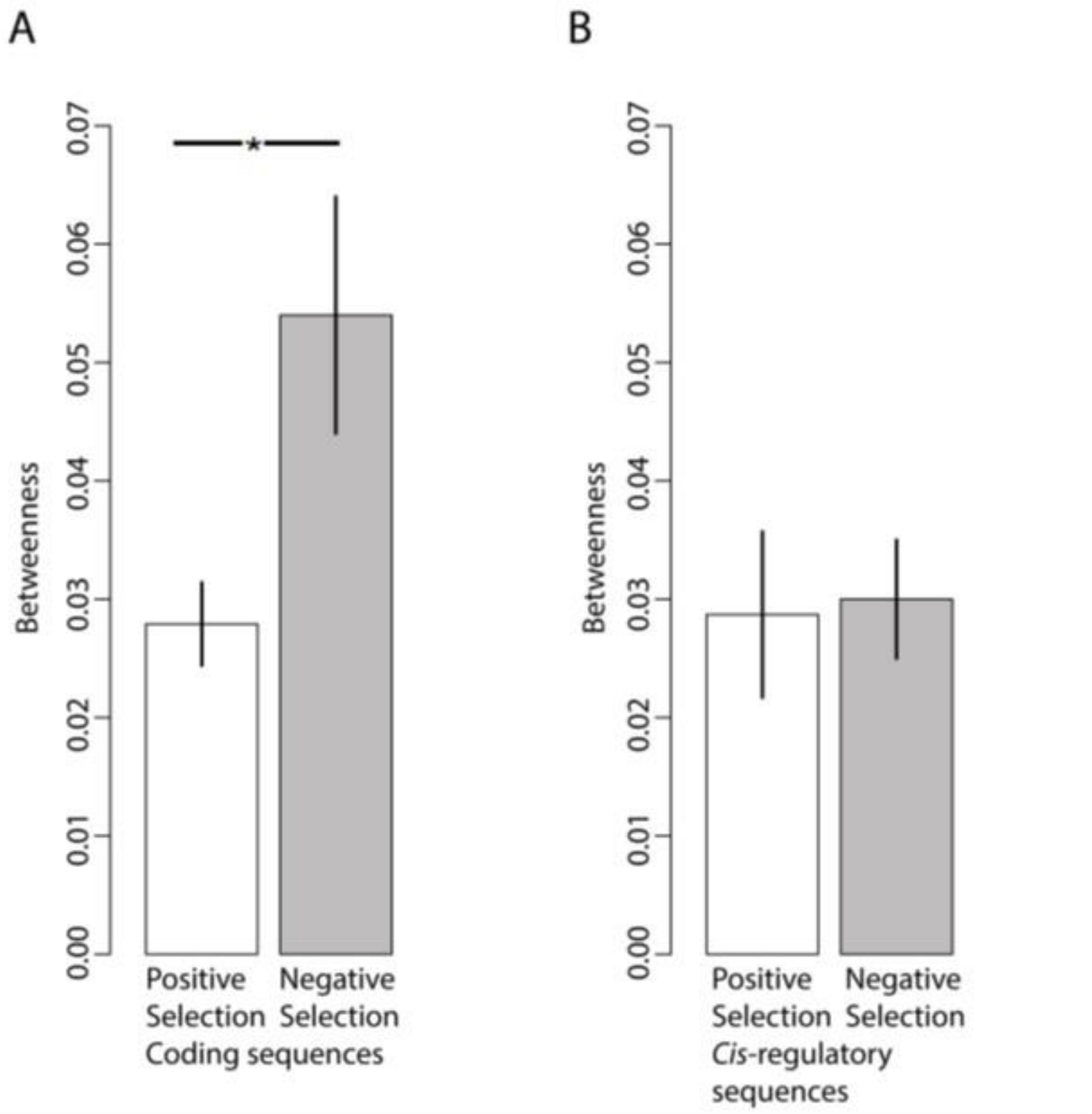

Figure 4: Network position is associated with differences in coding sequence evolution but not regulatory sequence evolution. **A.** Genes experiencing positive selection (γ>1)on their coding sequences (N=105) have significantly lower *Betweenness* centrality estimates (i.e. are further away from the network core) relative to genes experiencing negative selection (γ <-1) on their coding sequences (N=7). **B.** The average *Betweenness* centrality of genes experiencing positive selection (γ>1) on their regulatory sequences (N=16) does not significantly differ relative to that of genes experiencing negative selection (γ <-1) on their regulatory sequences (N=92). Bars indicate Mean ± SEM. * = p<0.05]

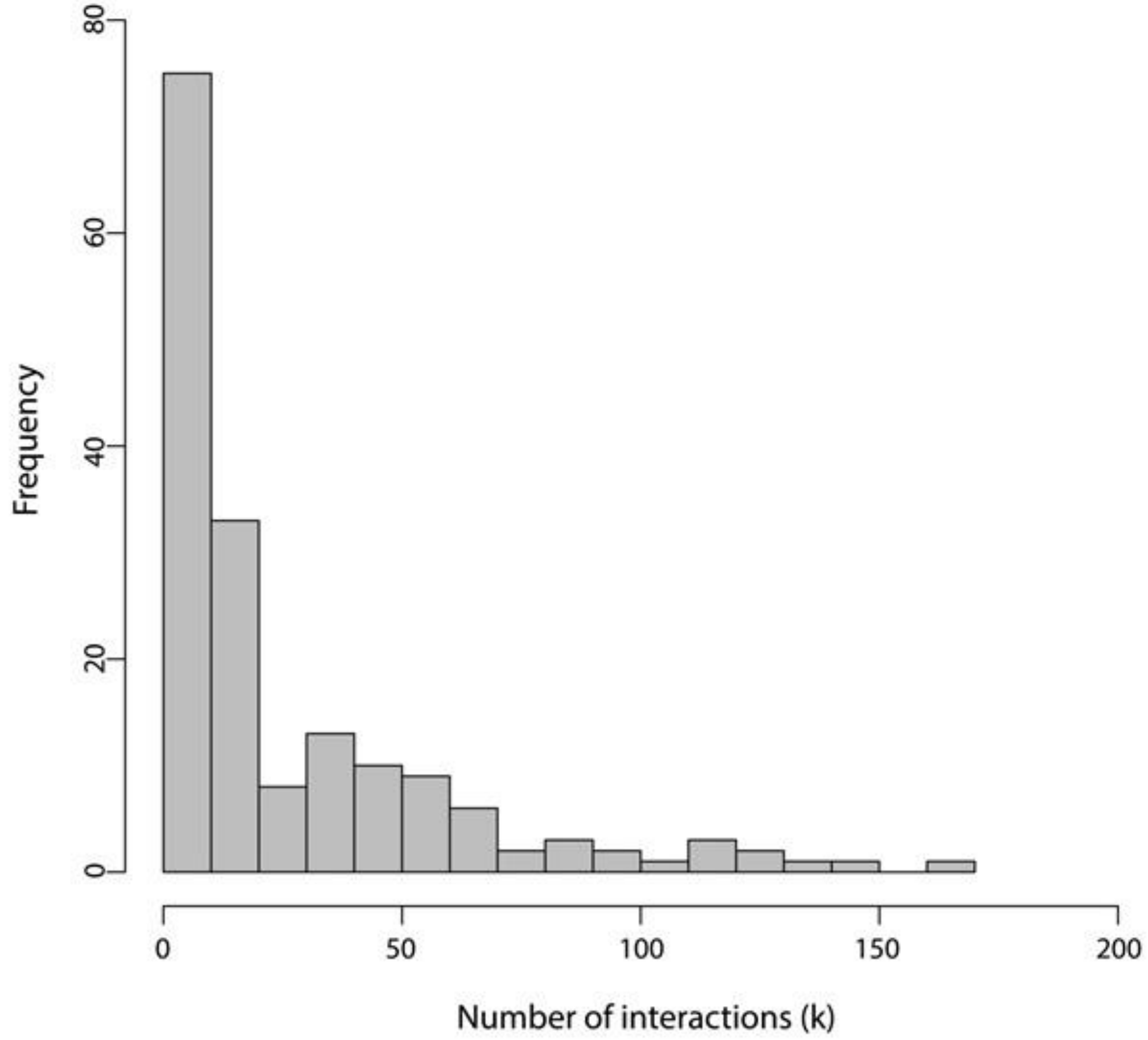

Figure S1. Degree distribution of connectedness of TFs and their targets in the TRN.

Appendix “A”

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Appendix “B”

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