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Genomic Scan of Recent Positive Selection Differentiating Aggression in Chimpanzees and Bonobos

By

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An abstract of a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in the Population Biology, Ecology, and Evolution program in the Graduate Division of Biological and Biomedical Sciences Department.

2020

1 Abstract

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By Carmen Shaw

Human's closest extant relatives are chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*), which share roughly 99% of their genome with each other. Despite their proximate phylogenetic relationship, these two great ape species differ substantially from one another in terms of social behavior and aggression. Bonobos live in female-dominant communities, more tolerant of conspecifics in competitive social contexts, and frequently substitute sexual behavior and eroticism for aggression. Chimpanzees coexist in male-dominant social groups, actively patrolling territory boundaries between communities, where aggression and inter-group killings are commonly employed during moments of conflict. Chimpanzees are known to commit lethal aggression, whereas bonobos have no such inclinations. Identifying the genetic underpinning that predisposes an individual to aggressive behavior is largely complex due to difficulties in understanding genetic heterogeneity, diversified environmental conditions, and the unknown role evolutionary forces play on behavior. Recent studies on genome-wide transcripts and epistasis, as well as artificial selection studies and GWAS studies have revealed that a substantial portion of the genome contributes to the expression of aggressive behavior.

To further understand the neurogenetic and evolutionary underpinnings of this universal fitness trait, we have detected selection signatures across the genome in order to help elucidate mechanisms of selection and pinpoint candidate genes of interest impacting aggression. In this study, the detection of selection signatures was conducted in chimpanzees (n = 70) and bonobos (n = 13). We employed two complementary haplotype-based statistics of integrated haplotype scores (iHS) and cross-population extended haplotype homozygosity (XP-EHH) tests. From these selection scans, we were able to identify regions subjected to recent, positive selection in chimpanzees and bonobos. These genomic regions contained 15 significant genes relating to aggression including serotonin receptor 1A (HTR1A), cadherin 13 (CDH13), aldehyde dehydrogenase (ALDH2), and tryptophan hydroxylase 2 (TPH2). These genes were enriched in gene ontology terms involved in the stress response, interspecific interactions, and defense response to other organisms. These findings ultimately contribute to the identification of candidate genes of interest that impact the aggression pathway in nonhuman primates and aid in further understanding the evolutionary and biological mechanisms for differences in aggression observed between chimpanzees and bonobos.

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3 Introduction

3.1 Selective Pressures on Aggression Following *Hominin-Panim* Speciation

Two African great apes are the closest living relatives to modern-day humans: chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). Fossil records indicate that the last common ancestor for *Hominin-Panin* existed at least 5 million years ago (Mya) ago and is believed to be around 6-7 Mya (Jensen-Seaman, Deinard, & Kidd, 2001; Langergraber et al., 2012; Tocheri, Orr, Jacofsky, & Marzke, 2008; Young, Capellini, Roach, & Alemseged, 2015). Recent genomic analyses of chimpanzees and bonobos suggest that speciation occurred roughly 1.45–2.55 Mya (Takemoto, Kawamoto, & Furuichi, 2015). Since their divergence, chimpanzees and bonobos have maintained their close genetic relatedness, sharing roughly 99.6% of their genome with one another and 98.7% with the human genome (Prüfer et al., 2012). However, despite their extensive genetic and phenotypic similarities, they differ in terms of sociality and aggression.

Chimpanzees display intense forms of lethal and non-lethal aggression both intra- and inter-specifically. Within their communities, chimpanzees regularly use aggression to acquire food resources, intimidate and/or attract members of the opposite sex, and contend with a male-dominant linear hierarchical structure. Bonobos, on the other hand, live in female-centered social groups in which eroticism is substituted for aggression and inter-group killings have never been observed (R. Wrangham, 2019). Therefore, whereas chimpanzees are known to commit lethal aggression; bonobos have no such inclinations (Wilson et al., 2014). Moreover, it was a longstanding belief that the last common ancestor between the *Homo-Pan* clades most closely resembled that of present-day chimpanzees, both morphologically and behaviorally (Duda & Zrzav, 2013; Groves, 1988); with bonobos exhibiting more derived characteristics (Shea, 1983; R. Wrangham & Pilbeam, 2002).

Across this diverse range of ecological and evolutionary histories, these two congenic primate species represent an important pair to elucidate the evolutionary selective pressures on aggressive behavior. Recent studies have strengthened the hypotheses that lethal aggression could be the result of natural selection as a kind of adaptive strategy (Ben-ari, 2014; Power, 2005; Sussman & Cloninger, 2011). This is based on the idea that aggressive behaviors incur survival and reproductive benefits to the individuals who are able to eliminate their rivals when the cost of killing is minimized, especially for males (Gruber & Clay, 2016; Williams, Oehlert, Carlis, & Pusey, 2004). Through adaptive selection and evolution, chimpanzees and bonobos have developed specialized ways of dealing with aggression, as well as stress and anxiety-coping mechanisms. These patterns of selection should be traceable to distinct signatures within specific regions of the genome. Therefore, illumination of these genomic regions displaying such patterns of selection signatures may help to connect the genetic and biological mechanisms of aggression, as well as identify candidate genes of interest.

3.2 Evolutionary Divergence between Chimpanzees and Bonobos

Knowledge about the initial cause of divergence between chimpanzees and bonobos is inconclusive, as it is unclear when and to what extent the Congo River has been a natural geographic barrier (Kawamoto et al., 2013; Kuhlwilm, Han, Sousa, Excoffier, & Marques-Bonet, 2019). The widely-accepted hypothesis is that at the beginning of the Pleistocene era, the formation of the Congo River separated the common ancestor of chimpanzees and bonobos into two distinct species (Langergraber et al., 2012). Therefore, for this hypothesis to be supported, the estimated time of speciation should reflect the time of formation for the Congo River system. However, current biogeographical evidence suggests that there is a discrepancy between these two timepoints - the Congo River was formed much earlier, roughly up to 34 Mya (Takemoto et al., 2015). This information has now supported a different hypothesis that when the river was first formed, the ancestor of bonobos did not inhabit the current range of the species on the left bank of the Congo River.

Instead, it is believed that during the Pleistocene era, the Congo River experienced a significant reduction in water levels, corresponding to the glacial-interglacial cycle. As a result, specific regions in the eastern and northern parts of Africa experienced intense aridity around 2.8, 1.7, and 1.0 Mya (Takemoto et al., 2015). During this period of intense drought, one or more founder individuals of ancestral *Pan* crossed the river to its left bank at a time when the water levels subsided, ultimately resulting in the speciation of bonobos. Since this divergence, episodes of migration and gene flow have been described during different glacial periods. There are many lines of evidence suggesting that two separate events of admixture occurred from bonobos into central and eastern chimpanzee subspecies between 200,000 and 550,000 years ago; with a more recent instance of contact from 100,000 to 200,000 years ago (De Manuel et al., 2016). From these periods of interbreeding, it has been discovered that bonobos contributed less than 1% to the chimpanzee genomes (Prüfer et al., 2012).

3.2.1 Chimpanzee Behaviors and Inter-community Relations: "Proactive Warfare"

Chimpanzees are divided into four different subspecies: Central, Western, Eastern, and Nigeria-Cameroon. They have a widespread distribution throughout equatorial Africa, from southern Senegal across the northern border of the Congo River to western Tanzania (Figure 1) (Tokuyama & Clay, 2019). Each subspecies generally coexists in male-centric and male-dominated social groups called "communities", which consist of several solitary females with their offspring and a more limited number of gregarious adult males (Goodall, 1986). These communities range in size from 20 to 100 individuals, with certain members gathering to form temporary foraging subgroups averaging 4 to 6 individuals (Manson et al., 1991).

Inter- and intracommunity relations are highly antagonistic and occasionally lethal, with warfare aggression being common in their communities (Stanford, 1998). Within communities, male chimpanzees engage in elaborate displays to threaten rivals and females, sometimes resorting to intense physical aggression to interfere with copulation (Watts, 1998). Male chimpanzees use aggression towards females partly as an act of sexual coercion (Muller & Wrangham, 2009). Adolescent male chimpanzees intentionally attack adult females as a means of proving their social dominance to all adult females (Muller & Wrangham, 2009). Compared with males, aggression levels amongst females are typically lower but can be equally as severe in leading to grave wounds or even fatality. Between communities, chimpanzees are largely territorial. Subgroups of mostly males patrol the borders of the community's home territory, becoming uncharacteristically quiet while listening and watching intently in search of unfamiliar individuals. If members of the neighboring community are detected, the presence and abundance of males largely impacts their subsequent moves as most attacks are almost exclusively directed towards males. While lone females may still be chased, bullied, and beaten, 90% of adult and infant victims of fatal aggression between communities are male (R. W. Wrangham, Wilson, & Muller, 2006). This male-targeted approach means that the individuals more inclined to die tend to be the current and future protectors of the territory. When a group is successful, they have ultimately undermined their rivals capacity to defense themselves, while simultaneously increasing their own relative strength and overall sustainability (Williams et al., 2004). The pugnacious nature of these attacks is evident in that they are sometimes unprovoked by immediate contact with the neighboring community.

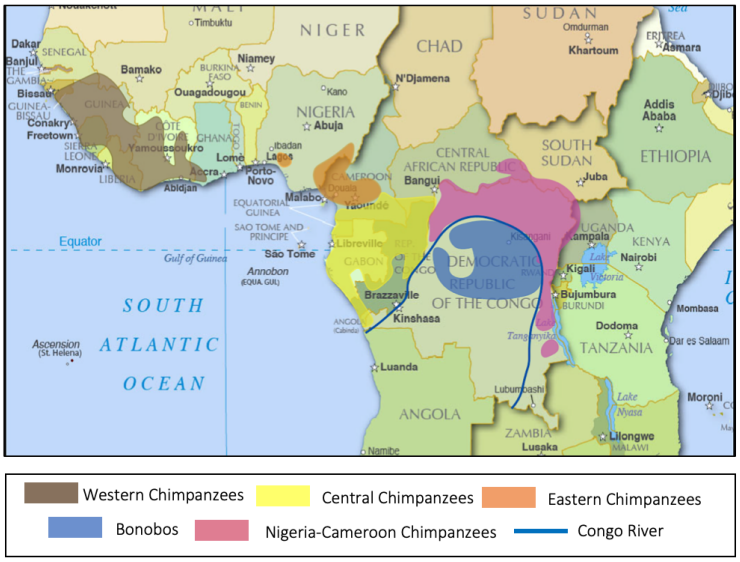

Figure 1: Geographical distribution of bonobos and chimpanzees (Western, Eastern, Central, and Nigeria-Cameroon)

One behavioral commonality between humans and chimpanzees is their similarly high rates of lethal aggression and conflict – both intra and inter-specifically (Knauft et al., 1991). In a comparative study, chimpanzees and humans living in subsistence societies were found to have similarly high rates of death from intraspecific violence, while chimpanzees had rates of non-lethal physical aggression between two and three orders of magnitude higher than humans (R. W. Wrangham et al., 2006). These results supported previously held beliefs that humans and chimpanzees had comparable rates of mortality due to intraspecific aggression,

while chimpanzees had higher rates of non-fatal physical assaults than humans (Boehm, 1999). Conclusively, the difference in frequency of fighting between chimpanzees and humans is large; while the difference in lethal aggression is virtually nonexistent. The occurrence of fatal attacks during intergroup encounters suggests that aspects of chimpanzee and human aggression are explicable in similar ways (Goodall, 1986; Manson et al., 1991). Despite extensive research efforts, little is known about the genetic underpinnings of lethal aggression and to what extent humans and chimpanzees share genomic regions that could help to elucidate this behavioral phenotype.

3.2.2 Bonobo Behaviors and Inter-community Relations: "Free-Loving Egalitarianism"

Bonobos inhabit the southern region to the Congo River, endemic to the Democratic Republic of the Congo where the world's second largest tropical rain forest, the Congo Basin, is located (Figure 1). Some anthropologists suggest that in the time span separating bonobos from chimpanzees – bonobos lost their appetite for violence (Waal & Lanting, 1998). Bonobos are markedly less aggressive – both toward their own group members and toward members of other groups (Hare & Kwetuenda, 2010). They live in cohesive female-centric and female-dominant social groups (Stanford, 1998), more inclined to feed together and actively share food amongst members of their group (Hare & Kwetuenda, 2010). Bonobos engage in overt hetero- and homosexual behaviors to resolve issues related to dominance and hierarchy (Kano, 1992), and have very low-intensity displays compared with those of chimpanzees (De Waal, 2012). Displays by male bonobos involve running and dragging branches at or near other members, but they rarely end in physical aggression.

Males do not interfere with each other's copulation and do not form alliances with one another to manipulate matings. Instead, male bonobos engage in the strongest bonds with their mothers, and cross-sex alliances between male and females are more frequent (Kano, 1992). Male aggression towards females is likewise suppressed, and any attempt to intimidate a female is quickly retaliated against by a coalition of females (Kano, 1992). Between communities, bonobos are significantly less aggressive. Although, like chimpanzees, they can be territorial and engage in hostile inter-community interactions, infrequently resulting in physical aggression but more often resulting in one community leaving a dispute without incident (Badrian & Malenky, 1984). Just as frequent, inter-community interactions can sometimes be social events with members of both communities sitting in close proximity to one another - playing, grooming, and even copulating. Bonobos do not engage in routine patrols on the boundaries of their territory with no evidence for lethal aggression being observed (Whiten et al., 1999). Therefore, whereas chimpanzees and humans are known to commit lethal aggression, bonobos have no such inclinations.

Although aggression in bonobos is less severe than in chimpanzees, bonobos are not nonaggressive. Female coalitions can attack and severely harm males. Additionally, while bonobos tend to not attack non-

community members, they are not always entirely tolerant of them (Hohmann, 2001). It was previously believed that bonobos did not hunt and kill monkeys, like their chimpanzee cousins. This hypothesis was often used to emphasize the divergent evolution of these two *Pan* species wherein aggression was selected against in bonobo evolution, while being selected for in chimpanzee evolution (R. W. Wrangham, 1999). However, there are observed cases of bonobos hunting, capturing, and then consuming monkeys in the Salonga National Park, though this occurrence is known to be rare (Surbeck & Hohmann, 2008). Similar observations were also made at other sites in the Salonga National Park, including Lilungu – where the bonobos were observed catching colobus monkeys but did not consume them and at Wamba, the bonobos and colobus monkeys were observed grooming one another mutualistically (Ihobe, 1990). Therefore, there was much inter-site variation in the hunting behaviors of bonobos, and more data are necessary before strong conclusions can be drawn about the correlation between sociality and hunting. Although aggression is observed within bonobo communities to varying degrees, these practices are considered a kind of rarity and inter-group lethal aggression amongst bonobos is not observed, which contrasts traditional warfare violence-based inclinations rampant in human and chimpanzee evolution. Although it is yet to be observed, it is possible that forms of severe aggression only observed in chimpanzees might be observed occasionally in bonobos, suggested by their similar sexual dimorphic features of canine teeth height and body mass (Payne, 2018).

In 2012, the bonobo genome was sequenced for the first time, confirming that bonobos shared roughly the same percentage of DNA with humans as chimpanzees do, 98.7% (Prüfer et al., 2012). The genomic analysis also revealed that bonobos and chimpanzees share 99.6% of their DNA with each other, showing that the two species are still highly similar genetically, though they diverged over 1 million years ago. Additionally, when comparing bonobo genomes directly with those of chimpanzees and humans – roughly 1.6% of human DNA is shared exclusively with bonobos and not chimpanzees; and the same amount (1.6%) of human DNA was shared only with chimpanzees, and not bonobos. These slight differences suggest that the ancestral population of apes that gave rise to humans, chimpanzees, and bonobos were quite expansive and diverse genetically. And yet, given their close genetic relatedness, these two species resemble one another in their genetics, development, and overall anatomy. By studying the genome of these species in depth, we could potentially identify candidate genes that contribute to the differences in aggression between chimpanzees and bonobos.

3.3 Genetic and Evolutionary Underpinnings of Aggressive Behavior

Identifying the genetic mechanism that predisposes individuals to aggressive behavior is challenging due to the complex relationship between genetic heterogeneity, diverse environmental conditions, and the undetermined impact evolutionary selective forces play on behavior (Craig & Halton, 2009). Aggression is defined as any type of behavior intended to cause harm or injury to others (Nelson & Trainor, 2007). It is a pattern of behavior that an individual exhibits in an attempt to damage oneself or the environment. Aggressive behavior can be considered both an advantageous trait for individual survival, as well as a hindrance to social cohesion, suggesting that its evolutionary origins may be complex. Aggression can be beneficial to the safety of an individual, especially for males in the community, as it provides a competitive edge in obtaining resources and incurs reproductive success (Eibl-Eibesfeldt, 1977). Expression of high aggression levels could also aid in counterbalancing any lack of physical ability when establishing social hierarchies (Hand, 1986). Aggressive behavior being displayed by females can provide protection for their offspring against environmental and social threats (Smith & Harper, 1988). Conversely, aggression can also result in negative physical effects like the risk of injury or even death. Even in the absence of physical injury, aggression can also lead to significant physiological (i.e. immune system suppression and elevated cortisol levels) and psychological (i.e. chronic anxiety and depression) costs (Georgiev, Klimczuk, Traficonte, & Maestripieri, 2013).

Reactive aggression, or an excess of emotional sensitivity, is characteristically associated with emotions including anger and/or anxiety (Tremblay, Hartup, & Archer, 2005). When considering brain regions associated with aggression, the amygdala is an important component of the neural circuit that processes negative emotional stimuli that can cause fear and anxiety. It is involved in a complex network involving the hypothalamus, hippocampus, periaqueductal gray (PAG), and regions of the prefrontal cortex (Siever, 2008). Additionally, some organisms that show violent behaviors tend to have dysfunctional serotonergic projections of their amygdala, which is consistent with the long-standing hypothesis that disruption of the serotonin system is a crucial feature in predisposing aggression. The disruption of other receptor subunits, such as mutations in the catechol-O-methyl transferase (COMT) gene, monoamine oxidase A (MAOA), dopamine, norepinephrine, and GABA neurotransmitters have all been implicated in studies pertaining to aggression as well (Gouveia et al., 2019; Stimpson et al., 2016). The neurobiological origin of behavioural differences in aggression between chimpanzees and bonobos is generally unknown. Nonetheless, there is some evidence that the adult brain of bonobos differs from that of the chimpanzee brain in specific areas related to emotional-reactivity and motor coordination (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 1998). Additionally, bonobos have been shown to possess more grey matter in areas implicated in perceiving distress in others, as well as a larger pathway linking the amygdala to anterior cingulated cortex (Rilling &

Sanfey, 2011).

3.4 Genome Scan of Recent Positive Selection in Chimpanzees and Bonobos

Chimpanzees and bonobos have evolved a unique repertoire of behaviors and inclinations since the ancestral lineage diverged eons ago. Moreover, the question remains: Why have chimpanzees and bonobos taken such divergent evolutionary paths where aggression is concerned? Genes affect aggression through various biological mechanisms, including the response to stress, the circuit of anxiety, serotonin-neurotransmitter pathway, differences in activation of the hypothalamic-pituitary-adrenal (HPA) axis, and the differentiation of sex (Curran & Chalasani, 2012; R. Wrangham, 2019). In this study, we looked for signatures of recent positive selection on a genome-wide scale in chimpanzees and bonobos in order to pinpoint candidate genes of interest impacting the many iterations of behavioral aggression. Our methods were based on properties of extended haplotypes within the genome. We employed two complementary haplotype-based statistics of integrated haplotype scores (iHS) and cross-population extended haplotype homozygosity (XP-EHH) tests to infer evidence of past selection (Sabeti et al., 2002; Voight, Kudaravalli, Wen, & Pritchard, 2006). We predict that chimpanzees would exhibit selection on alleles increasing lethal and physical aggression, while bonobos would exhibit no selection favoring this behavioral phenotype.

4 Methods

The first selection scan we used was the cross-population extended haplotype homozygosity (XP-EHH) test (Sabeti et al., 2002), which identifies regions with unusually long-range haplotypes and a high population frequency, as a means to observe evidence of recent selective sweeps across the genome. The second approach was the integrated haplotype score (iHS) created by (Voight et al., 2006), which is based on comparisons between the extended haplotype homozygosity (EHH) of derived and ancestral alleles within a given population. Selection statistics are based on the concept of directional selection favoring new mutations, resulting in a rapid increase in frequency of the selected variant along with its adjoining background haplotype and existing variation. Thus, there is an increase in linkage disequilibrium (LD) on the chromosomes that harbor the derived (or selected) allele, but not the unselected allele, which therefore acts as a control. Consequently, these statistics are most keen to a rapid increase in the frequency of the derived allele at a selected loci, but the derived allele must have existed only on a distinct haplotype prior to selection and must not have reached fixation yet (Sabeti et al., 2007; Voight et al., 2006). After fixation, the iHS statistic may continue to identify regions of high LD *surrounding* the selected site, but may not detect selection *at* the selected site itself because recombination will have eliminated variation at/near the selected site.

4.1 Data and Alignment

Data from 70 high-coverage chimpanzee and bonobo genomes was obtained from a previous study (De Manuel et al., 2016). This dataset includes 18 central chimpanzees, 13 western chimpanzees, 19 eastern chimpanzees, 10 Nigerian-Cameroon chimpanzees, and 10 wild bonobos. The blood samples were collected in sanctuaries in Africa (Ivory Coast, Guinea, Liberia, Equatorial Guinea, Gabon-East, Tanzania, Uganda) and from wild-born chimpanzees in European zoos. All chimpanzees were wild-born, except for two in the Western chimpanzees. Blood samples were taken during routine health checks and sequencing was carried out on Illumina sequencing machines using standard library preparation protocols (De Manuel et al., 2016). High coverage sequence data from 3 captive bonobos were added from Prado-Martinez et al (Prado-Martinez et al., 2013). To match the genotype calls of the 10 wild bonobos, the FASTQ files from the three captive bonoboos were aligned to the hg19 human reference genome with BWA-MEM v0.7.17 (Li & Durbin, 2009). After removing PCR duplicates using PICARD v1.91, SNPs were called using FREEBAYES v1.3.1 using the following parameters (Garrison & Marth, 2012): –standard-filters –no-population-priors -p 2 –report-genotype-likelihood-max –standard-gls –prob-contamination 0.05, utilizing the callable sites reported in de Manuel et al (De Waal, 2012). The combined VCF file of the 74 individuals (60 chimpanzees, 13 bonobos, and the hg19 human reference genome) was filtered for sites out of Hardy-Weinberg Equilibrium with a p-value below 1 x 10^{-5}. We excluded polymorphic sites that were not biallelic, regions with quality scores < 30, and missing genotypes - resulting in 6,576,834 high-quality sites. Kinship relatedness was also assessed between the sampled individuals using the KING software, which determines proportion of SNPs with identical state between individuals (Manichaikul et al., 2010). It was confirmed that there was no relationship between individuals greater than a second degree.

4.2 Phasing

In order to contrast haplotype-based selection in chimpanzees with that in bonobos, we phased the population sets (60 chimpanzees and 13 bonobos) separately and aligned them to the human genome reference (hg19) using Beagle v5.17 (Browning, Zhou, & Browning, 2018). In order to avoid a potential bias from the human genetic map, we set the genetic distance to be estimated via positions from the VCF file. The bonobo effective population size was set to 29,100, which was inferred in a previous study (Kuhlwilm et al., 2019). Although a lower effective population size has been inferred for western chimpanzees (9,200), we set the effective population size for the chimpanzees to that inferred for the central chimpanzees (65,900) (Kuhlwilm et al., 2019), as a larger effective population size has been shown to decrease phasing error rates utilizing Beagle (Pook et al., 2020). We also used a set of parameters that are optimized for organisms lacking large

reference panels, which untimely affects the structure of the haplotype cluster (Pook et al., 2020). To that end, the number of burnin iterations was set to 50, the iterations used to estimate genotype phase was set to 40, and the number of model states used to estimate the genotype phase was set to 280.

4.3 Haplotype-based Selection Scans

Footprints of selection per population were analyzed based on extended haplotype homozygosities (EHH) which is a measure of the breakdown of linkage disequilibrium with increasing distance from a SNP (Sabeti et al., 2002). Based on *EHH*, we calculated iHS and XP-EHH scores using the REHH v3.0.1 R package (FDR corrected P-value <0.05) (Gautier, Klassmann, & Vitalis, 2017; Sabeti et al., 2007; Voight et al., 2006). For both scans, the minor allele frequency threshold was set to 0.01, and monomorphic sites were removed. To calculate XP-EHH, which does not require ancestral information, the site-specific integrated EHH (iES) for a given focal marker was calculated on each chromosome as follows:

$$XP-EHH = \frac{LRiES - med_{LRies}}{\sigma_{LRiES}}$$

The log ratio of iES was calculated for bonobos over chimpanzees as:

$$LRies = log(\frac{iEH_{Bonobos}}{iEH_{Chimpanzees}})$$

The med_{LRies} is the median of LRies, while σ_{LRiES} is the standard deviation. In this case, the chimpanzees serve as the reference population and the Bonobos as the observed population. The p-value was assigned to both sides of the distribution (approximately Gaussian under neutrality) of the standardized XP-EHH values. The p-values are presented on a negative log10 scale as follows:

$$p_{XP-EHH} = -log_{10}(1 - 2|\phi_{XP-EHH} - 0.5|)$$

where $\phi_(x)$ represents the Gaussian cumulative distribution function.

To calculate the iHS for the Bonobos and Chimpanzees, the ancestral allele was set to the hg19 reference. If the site did not match either the reference or segregating allele, then the site was set to missing. The iHS statistic compares the integrated EHH profiles between two alleles at a focal SNP in the same population and was calculated according to (Voight et al., 2006) as follows:

$$iHS = \frac{UniHS - \mu^{Ps}_{UniHS}}{\sigma^{Ps}_{UniHS}}$$

where μ_{UniHS}^{Ps} = average of the UniHS computed overall all SNPs and σ_{UniHS}^{Ps} = standard deviation. UniHS = $log(iHH_{ancestral}/iHH_{derived})$, where iHH is defined as the area under the EHH curve with respect to the map position. The iHS score was computed for each variant and the frequency bins were set to 0.05. The resulting iHS values were transformed as follows:

$$p_{iHS} = -log_{10}(1 - 2|\phi_{iHS} - 0.5|)$$

4.4 Analysis of Putative Selection Signatures

Candidate regions with positive selection footprints were defined as containing at least two SNPs with a significant iHS or XPEHH score. P-values for the iHS and XP-EHH statistics were subjected to multiple test correction using a FDR cut-off of < 0.01. The use of a lower FDR was necessary to reduce the number of results for a more focused analysis. To carry out gene ontology term enrichment, SNPs were annotated to genes of interest using the ANNOVAR software (Yang & Wang, 2015) which, when supplied with a list of markers from one genotyping platform, will provide a list of genes within, upstream, or downstream of a gene in that region.

4.5 Gene Expression Profiles via Haploreg v4.1

Upon compiling a list of candidate genes putatively under positive selection, we then performed a comparative study of gene expression patterns in our primate species. Comparing gene expression across species provides statistical evidence on gene function. For this process, we used HaploREG (version 4.1) to obtain regulatory genomic data information, including maps of enhancers, or transcription factor binding sites to infer candidate gene function. In particular, we applied annotations of the variant genes selected on haplotypes from the selection scans. HaploReg uses linkage disequilibrium (LD) information on each variant from the 1000 Genomes Project, as well as SNP effects on gene expression from eQTL studies and protein binding and chromatin state annotation from the ENCODE (Roadmap Epigenomics and the Encyclopedia of DNA Elements) Project (Ward & Kellis, 2016).

4.6 Gene Ontology Enrichment Analysis

Lastly, we submitted the entire list of variants in the top 0.1% of hits, irrespective of association with aggression-related phenotypes, to Gene Ontology (GO). GO is an online resource providing enrichment for different pathways, processes, and functions for a gene list. By accessing the GO Term Enrichment tools, we obtained annotations describing the biological network between individual genes based on ontology clas-

sification (Ashburner et al., 2000; Consortium, 2015). Afterwards, we obtained graph structures consisting of classes of biological processes to which the top 0.1% of variants contribute.

5 Results

5.1 Overview of iHS and XP-EHH Scans

We detected recent positive selection in chimpanzees and bonobos by analyzing long-range haplotypes at several candidate genes using *extended haplotype homozygosity* (EHH). EHH scores were designed to detect recent selective sweep regions that have occurred in a given population (iHS), or comparatively - in one population compared to another (XP-EHH). For the iHS selection scans, we ran chimpanzee and bonobo populations individually. For XP-EHH, we compared the bonobo genome against the chimpanzee genomes. All chromosomes displayed regions with significant scores of $P_{\text{iHS}} = -log_{10}(1-2|\phi_{\text{iHS}}-0.5|)$ and $P_{\text{XP-EHH}} = -log_{10}(1-2|\phi_{\text{XP-EHH}}-0.5|)$, indicating a specific sweep region. We further applied the Benjamini-Hochberg false discovery rate (FDR P-value < 0.01) to correct for multiple testing. Candidate regions were considered to be those positions containing at least two SNPs with $P_{\text{iHS}} \geq 2$ or $P_{\text{XP-EHH}} \geq 2$ and "aggression-related" - i.e. the associated genes have been known to influence one or more of the following pathways: stress response, the anxiety circuit, activity of hypothalamic-pituitary-adrenal (HPA) axis, the serotonin neurotransmitter pathway, or other brain neurotransmitters regulating emotionality and behavior.

5.2 (iHS) Detection of selection signatures *Intra*-specifically in Bonobos and Chimpanzees

In this particular study, we utilized 6,576,834 high-quality SNPs for analysis of a genome selection signature in bonobos and chimpanzees. The average coverage of the genomes in the analysis was 30x. We investigated potential evidence of recent positive selections based on the iHS score. The value of the score was calculated for each variant and then averaged across the genome. All SNP sites were normalized and then used for identification of candidate regions. In following the threshold of the top 0.1%, we finally identified 509 regions as candidate regions in the bonobo population and 353 regions in the chimpanzee population. As shown in Figures 2 and 3, the genome-wide distribution of iHS values was generated to visualize the chromosomal distribution of selection signatures. The top 20 significant iHS genomic regions for bonobos and chimpanzees are shown in Tables 1 and 2 respectively. Additionally, the candidate genes relating to the aggression pathway in the top 0.1% of hits is shown in Table 4 and 5.

Upon applying the above requirements to the dataset, 11 candidate regions containing 39 SNPs remained

significant from the iHS selection scans: 7 genes from the iHS bonobo scan (Table 4) and 4 genes from the iHS chimpanzee scan (Table 5) with one gene (*ROCK1*) showing up in both selections scans. Figure 2 illustrates the outputs of the iHS scan from the bonobo dataset consisting of 13 wild individuals at 509 SNPs spanning the 22 autosomes. Among all 7 genes from the selection scan, all candidate regions were known to affect the anxiety and stress response. The methylation of one candidate gene, odd-skipped related transcription 1 (*OSR1*), a type of mammalian protein kinase involved in the modulation of GABAergic neurotransmission, has been implicated in EWAS association studies of aggressive behavior (Geng, Byun, & Delpire, 2010; Yang & Wang, 2015). Another candidate gene, serotonin 1A receptor (*HTR1A*), relates to brain serotonin metabolism and has been linked to agonistic social behavior in primates (INOUE-MURAYAMA, 2009; Staes et al., 2019). Knockout mice lacking the HTR1A gene show increased anxiety and decreased exploratory tendencies when compared to the wildtype mice (Shattuck et al., 2014). The inhibition of one candidate gene with a significant iHS score in both selection scans, Rho associated containing protein kinase (*ROCK1*), induces anxiety-like behavior in mice (Greathouse, Henderson, Gentry, & Herskowitz, 2019).

Figure 3 illustrates the results obtained from the chimpanzee dataset consisting of 70 wild individuals at 353 SNPs spanning the 22 autosomes. Unlike the results obtained from the bonobo population, the candidate gene list for chimpanzees was considerably varied. One of the four genes, zinc finger 266 (*ZNF266*) has been linked to physical aggression in males and females (Guillemin et al., 2014). Other genes affected the anxiety and depression pathway, including (*ROCK1*) and aldehyde dehydrogenase 2 (*ALDH2*). The ALDH2 gene has been further researched in alcohol dependence studies, wherein a neurobiological network containing functional alleles of this gene paired alongside the dopamine receptor D4 (*DRD4*), serotonin transporters (*5-HTT*), and monoamine oxidase A (*MAOA*) alters the stress response, anxiety/negative effect, and impulsivity/aggression (S.-Y. Lee et al., 2009; Lesch, 2005). Lastly, the CNTNAP3 gene was associated with regulation of the synaptic development and social behavior as CNTNAP3$^{-/-}$ mice exhibit defects in social behavior, repetitive behavior, and cognitive tasks (Tong et al., 2019).

5.3 (XP-EHH) Detection of selection signatures *Inter*-specifically of Bonobos and Chimpanzees

We used XP-EHH to identify genomic regions potentially under recent positive selection between chimpanzees and bonobos. For each SNP, we calculated XP-EHH values between bonobos and chimpanzees and considered SNPs with extreme values as candidates for recent positive selection; specifically, SNPs with values above the cutoff threshold ($\geq$ 2). In the top 0.1% of hits, we identified 3,086 regions as selection signatures in the bonobo-chimpanzee comparison dataset. As shown in Figure 4, the genome-wide distribution of standardized

XP-EHH scores were plotted against the chromosomal position for the pairwise species comparison. The top 20 significant XP-EHH genomic regions are shown in Table 3.

Of the 6 candidate regions from the selection scan, one gene (*OSR1*) was also found in the iHS Bonobo dataset. The other top 5 XP-EHH signals within genic regions of the two species harbor some important genes associated with aggression (*SLC38A11* and *TPH2*) and anxiety (*HCN1* and *EPB41L4A*). Neurexin 3 (*NRXN3*) is a type of surface receptor that forms complexes at synapses in the central nervous system that is required for efficient neurotransmission. In an exon-specific knockout study of the NRXN3 gene, excitatory synaptic transmission was severely reduced when this gene was inhibited - displaying its importance in addictive disorders (Kasem, Kurihara, & Tabuchi, 2018). Interestingly, tryptophan hydroxylase 2 (*TPH2*), which is the rate-limiting enzyme of brain serotonin synthesis and closely related to the hypothalamic-pituitary-adrenal (HPA) axis, appeared as a top signal on our selection scan (Chen et al., 2010). There have been several studies linking this gene to intermale aggression and depressive-like immobility in forced swim tests for mice (Kulikov, Osipova, Naumenko, & Popova, 2005).

5.4 Linkage Disequilibrium analysis via HaploReg (version 4.1)

We applied our candidate regulatory SNPs at aggression-associated loci to HaploReg v4.1 to explore annotations such as protein binding, effects on regulatory motifs, or effects on expression from eQTL studies (Ward & Kellis, 2016). We obtained 9 genetic variants located around four different genes: XPNPEP1 (2 SNPs), ROCK1 (2 SNPs), ZNF266 (2 SNPs), and HCN1 (4 SNPs). We were only able to obtain information on four genes, and this was probably in large part because HaploReg uses hg19, a human reference genome. Information on the LD analysis about these variants has been included in Table 7. When delving into the two variants (rs115015904 and rs181123712) for the XPNPEP1 gene, the results display roadmap epigenomes with various cell types. Under the chromatin 25-state model, it was observed that both of the SNPs for XPNPEP1 are relatively specific brain enhancers. We found a cluster of enhancer activity (classified as transcribed enhancers by the 25-state model) in different brain regions including the hippocampus and dorsolateral prefrontal cortex, which are two areas highly implicated in aggression. Similarly, we found two variants (rs433301 and rs115517283) associated with the ROCK1 gene. These SNPs lie in a histone modification region (H3K4me3) in one brain region, the brain angular gyrus. This region of the brain is located in the parietal lobe and is involved in processes relating to language, attention, and theory of mind.

5.5 Gene Ontology Enrichment Analysis of Genes in Selection Scans

Across all selection scans, only the genes identified in the iHS Bonobo analysis were found to be statistically significant. Of this analysis, 199 uniquely mapped IDs show association enrichment at FDR P $<$ 0.01. Examination of these GO terms show an enrichment (FDR-P-value $<$ 1.66E-02) highlighting certain processes such as the interferon-gamma-mediated signaling pathway and the antigen processing and presentation of exogenous peptide antigen via MHC class II (FDR-P-value $<$ 6.96E-02) (Figure 5 and 6). Upon exploring the interferon-gamma-mediated signaling pathway, several associations were highlighted as being significant including response to external biotic stimulus (GO:0043207), response to stress (GO:00006950), interspecies interaction between organism (GO:0044419), defense response to other organisms (GO:0098542), as well as response to cytokines (GO:0034097) and response to interferon-gamma (Consortium, 2015). The significance of these results is that cytokines and the interferon-gamma pathway act as neuromodulators. Circulating cytokines can cross into the central nervous system via diffusion through the blood-brain-barrier, active transport through saturated cellular transporters, or binding to receptors that can relay cytokine signals to brain regions such as the hypothalamus or amygdala (Coccaro, Lee, & Coussons-Read, 2015). Additionally, several studies have implicated interleukins in norepinephrine, serotonergic, and dopamine metabolism in the brain (Quan & Banks, 2007). The interferon-gamma-mediated signaling pathway supports the hypothesis that activation of the inflammatory immune system, of which are many of the top 0.1% of variants in the bonobo population, might affect behavioral and/or mood disorders like stress, anxiety, and ultimately aggression.

6 Discussion

In this comparative study, two haplotype-based test statistics, iHS and XP-EHH, were calculated to detect genome-wide selection signatures within and between chimpanzees and bonobos. Both statistics are based on Sabeti et al. EHH statistics (Sabeti et al., 2002). Previous studies have reported that iHS detects variants that have increased rapidly enough in frequency that their long-range associated haplotypes have not yet been disintegrated by recombination. Thus, iHS is a power test to detect very recent, partial selective sweeps. XP-EHH, on the other hand, detects selected variants that have risen to or near fixation by comparing haplotypes from two populations. Both of these selection scans have been applied to a variety of other populations including parasites (Mu et al., 2010), humans (Sabeti et al., 2002), and sheep (ZHAO et al., 2016) populations. These combined methods identified 15 genomic regions as strong candidates for selection in chimpanzees and bonobos. This study will be one of the first to apply these statistical approaches to nonhuman primate populations.

Chimpanzees and bonobos diverged roughly one million years ago during the Pleistocene era. Since then, both species have migrated and settled in different regions of Africa - with bonobos habituated in the Democratic Republic of Congo and chimpanzees being more widespread throughout equatorial Africa. As these two individual species have migrated, they have encountered numerous environments - each with unique ecological conditions. Despite their genetic and phenotypic similarities, these species have evolved to inhabit considerably different behaviors in terms of sociality and aggression. As these species have been the targets of natural selection, it would be expected that their genomes would show evidence or markers of many signals of positive selection, potentially accounting for these differences in aggressive behavior observed. Given that previous experiments have shown that artificial selection against aggression can generate phenomenons like the domestication syndrome in dogs (Akey et al., 2010), the question remains as to whether an analogous phenomenon can from result from natural selection acting against aggression in nonhuman primates.

The group of candidate genes identified from the statistical tests have all been implicated as impacting aggression in the following ways: the stress response; the serotonin (5-HT) neurotransmitter pathway (including receptors); synaptic formation in the mammalian central nervous system impacting glutamatergioc transmission and therefore, excitatory synapses in the hippocampus; deficiencies in social interactions; anxiety-depression alcohol dependence, physical aggression; glutamine/glutamate and GABA cycles of metabolism in excitatory/inhibitory nerve terminals, amongst others. These genes include: *TAC1, CYP3A4, XPNPEP1, CDH13, CNTNAP3, OSR1, SLC38A11, HCN1, EPB41L4A, TPH2,* and *NRXN3*. We observed multiple signals for each of these genes with significant haplotype scores.

It was observed in this study the presence of poorly annotated genomic regions that showed high evidence

of recent selection. For example, genomic regions with extremely low P-values were on chromosome 16 at position 35,163,952 in chimpanzees, but no genes have yet been documented in that particular region. This highly suggests the idea that noncoding regions of the genome may have a significant role to play in adaptive evolution. However, this could also be due to poor annotation of the chimpanzee genome.

Upon looking at specific variant annotation for our candidate genes within our species of interest, we found clusters of brain enhancers for some of our candidate genes using HaploReg v4.1, in regions relating to the hippocampus, dorsolateral prefrontal cortex, and parietal lobe. The results from this analysis are limited, as we were only able to look at variant information for four of our fifteen candidate genes. This represents an insufficiency of genomic and variant data in the more understudied mammalian species, like bonobos and chimpanzees. After performing the Gene Ontology Enrichment Analysis on the top 0.1% of genes in the iHS bonobo, iHS chimpanzee, and XP-EHH - we only obtained statistically significant (FDR < 0.05) results from the iHS Bonobo gene list. Examining these GO terms showed an enrichment of one particular pathway of interest, the interferon-gamma-mediated signaling pathway, with several associations being made including defense response to other organisms, response to stress, and interspecies interaction between organisms.

The relevance of this pathway is due to significant positive correlations between aggressive behavior with proinflammatory cytokines (Coccaro et al., 2015). We propose that there may well be a link between the general pattern of aggression in terms of perception of external threats and altered cytokine-related changes in specific brain areas like the prefrontal cortex. Thus, the interferon-gamma-mediated signaling pathway supports the hypothesis that the activation of the interferon-gamma pathway, of which are many of the top 0.1% of variants being positively selected for in the bonobo population, might affect behavioral and/or mood disorders like aggression.

These analyses revealed multiple genes relating to aggression under positive selection in both chimpanzees and bonobos. Our findings can contribute to the further identification of candidate genes underlying other important behavioral traits in nonhuman primates.

7 Conclusion

To further understand the neurobiological and genetic underpinnings of aggressive behavior and its differentiating expression between chimpanzees and bonobos, we have successfully detected selection signatures across the genome using two complementary haplotype-based statistics. From this methodology, we were able to compile a list of candidate genes impacting aggression that were under recent, positive selection in both chimpanzees and bonobos. Our results displayed higher gene expression in the prefrontal cortex and

cerebellum of chimpanzees, contributing to previous results showing evidence of differences in brain regions between these species in areas related to emotional-reactivity. Upon performing the gene ontology enrichment analysis, we found a significant pathway pertaining to the top 0.1% of genes in the bonobo population relating to the interferon-gamma-media pathway with several associations being made including the stress response and defense response against other organisms. The findings from our present study will contribute to further elucidating the genetic pathway contributing to aggression in chimpanzees and bonobos.

8 Appendix

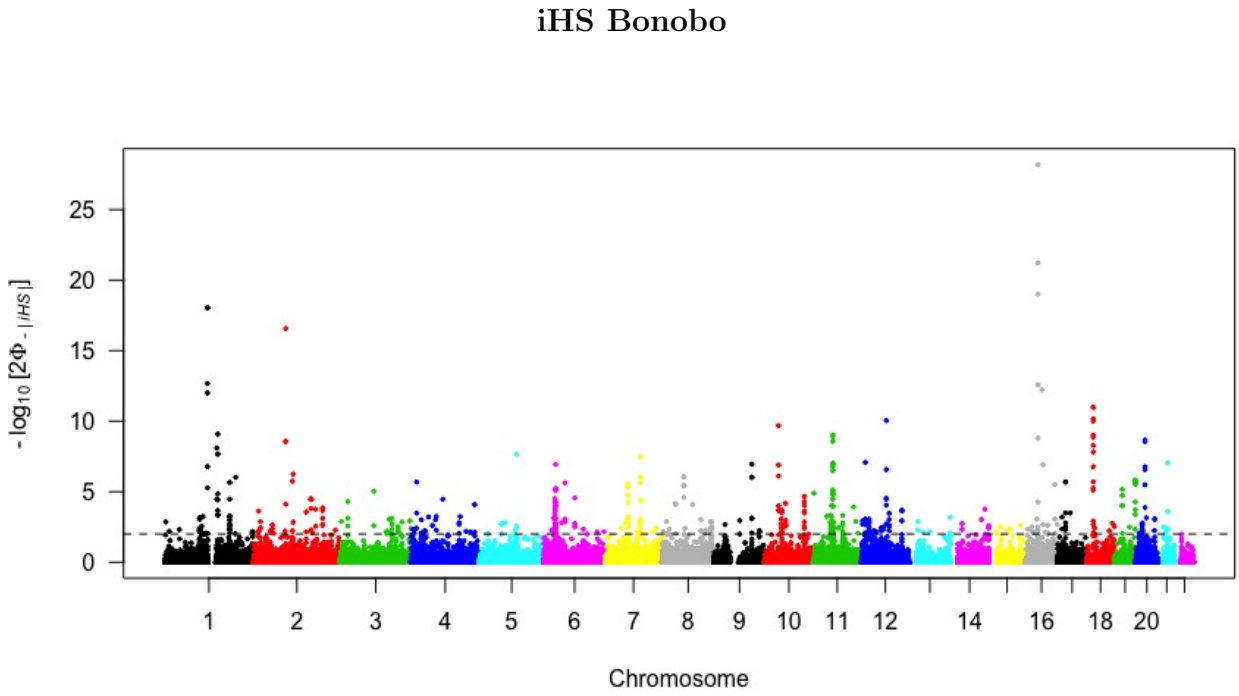

Figure 2: Genomic distribution with selection signals in Bonobos using the iHS statistic.

iHS Chimpanzee

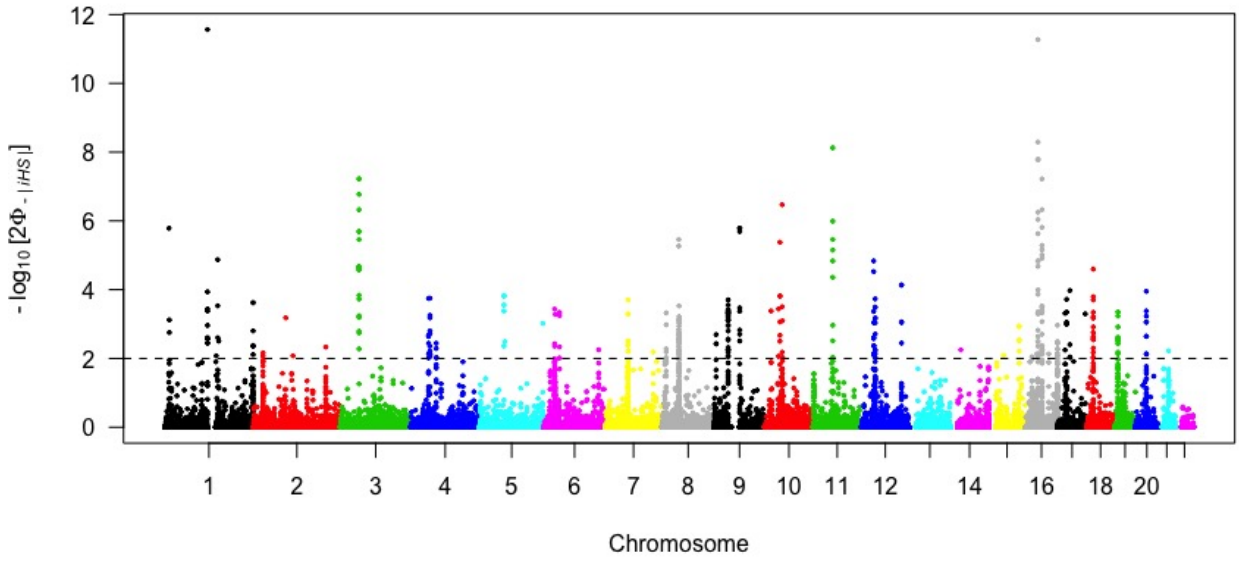

Figure 3: Genomic distribution with selection signals in Chimpanzees using the iHS statistic.

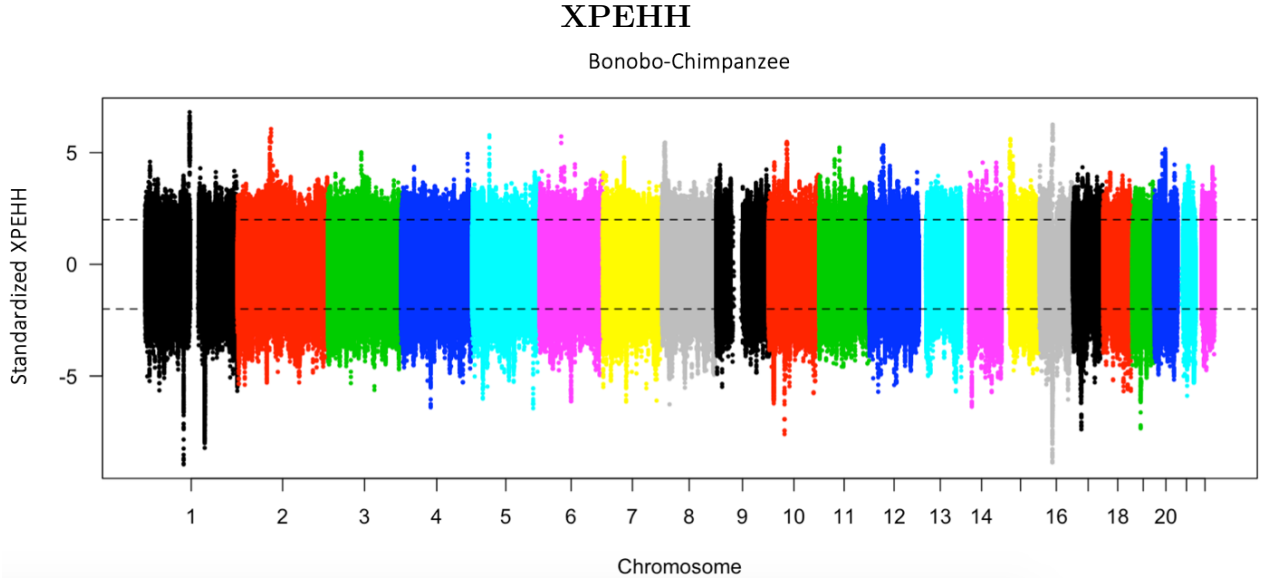

Figure 4: Genomic distribution of standardized cross-species extended haplotype homozygosity (XP-EHH) scores in pairwise chimpanzee and bonobo populations.

Table 1: Genomic regions and associated genes for top 20 significant |iHS| Bonobo.

Chr	Position (Mbp)	Position Range	Total of SNPs examined (n)	Mean LogPvalue	Gene Reference	Gene Name
16	35.14	34.76 - 35.14	9	3.774	LINC02167	Long Intergenic Non-Protein Coding RNA 2167
1	120.45	120.45 - 120.50	6	3.647	NOTCH2	Notch Receptor 2
2	90.25	90.24 - 90.25	4	6.375	MIR4436A	MicroRNA 4436a
1	120.43	120.43	2	12.373	NBPF7;ADAM30	NBPF Member 7;ADAM Metallopeptidase Domain 30
16	46.54	46.54	1	12.224	ANKRD26P1	Ankyrin Repeat Domain 26 Pseudogene 1
18	18.57	18.6 - 18.7	15	3.586	ROCK1	Rho Associated Coiled-Coil Containing Protein Kinase 1
12	69.69	69.69	7	4.411	CPSF6;LYZ	Cleavage And Polyadenylation Specific Factor 6;Lysozyme
10	38.61	38.57 - 38.61	5	5.538	HSD17B7P2	Hydroxysteroid 17-Beta Dehydrogenase 7 Pseudogene 2
1	149.21	149.21 - 149.22	7	5.236	RNVU1-17;RNVU1-18	RNA, Variant U1 Small Nuclear 17; RNA, Variant U1 Small Nuclear 18
11	54.83	54.83 - 54.86	9	3.661	TRIM48	Tripartite Motif Containing 48
0	26.20	26.20	6	5.48	MIR663AHG	MIR663A Host Gene
1	146.52	146.52	2	5.84	NBPF19	NBPF Member 19
5	103.93	103.93	2	3.887	NUDT12;RAB9BP1	Nudix Hydrolase 12; RAB9B, Member RAS Oncogene Family Pseudogene 1
7	99.38	99.37 - 99.38	6	3.455	CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
12	11.18	11.18 - 11.20	6	3.253	PRH1-PRR4	PRH1-PRR4 Readthrough
21	27.05	27.05	3	3.565	JAM2	Junctional Adhesion Molecule 2
11	55.24	55.14 - 55.24	17	3.24	OR4A15;OR4C15	Olfactory Receptor Family 4 Subfamily A and C Member 15
9	105.04	105.04	6	3.246	GRIN3A;LINC00587	Glutamate Ionotropic Receptor NMDA Type Subunit 3A; Long Intergenic Non-Protein Coding RNA 587
6	32.73	32.73	2	5.142	HLA-DQB2	Major Histocompatibility Complex, Class II, DQ Beta 2

Table 2: Genomic regions and associated genes for top 20 significant in |iHS| Chimpanzee.

Chr	Position (Mbp)	Position Range	Total of SNPs Examined (n)	Mean LogPvalue	Gene Reference	Gene Name
1	120.5	120.48-120.53	11	3.711	NOTCH2	Notch Receptor 2
16	35.2	35.14 - 35.18	24	3.25	LINC02167	Long Intergenic Non-PRotein Coding RNA 2167
11	54.8	54.83 - 54.86	9	3.244	TRIM48	Tripartite MOtif Containing 48
16	46.5	46.52 - 46.58	18	3.321	ANKRD26P1	Ankyrin Repeat Domain 26 Pseudogene 1
3	52.4	52.41	25	3.467	DNAH1	Dynein Axonemal Heavy Chain 1
10	48.7	48.65	3	3.308	GDF10;PTPN20	Growth Differentiation Factor 10; Protein Tyrosine Phosphatase Non-Receptor Type 20
9	71.1	71.04 - 71.13	8	3.576	PGM5	Phosphoglucomutase 5
1	12.8	12.84	1	5.786	PRAMEF12	PRAME Family Member 12
8	47.0	46.93 - 46.96	8	3.252	ASNSP1	Asparagine Synthetase Pseudogene 1
10	42.5	42.47 - 42.51	6	3.479	LOC441666	Zinc Finger Protein 91 Pseudogene
1	149.0	149.04	2	4.229	NBPF25P	NBPF Member 25, Pseudogene
12	34.3	34.26 - 34.82	14	3.119	ALG10	ALG10 Alpha-1,2-Glucosyltransferase
17	34.5	34.48	4	2.973	CCL4;CCL3L1	C-C Motif Chemokine Ligand 4;C-C Motif Chemokine Ligand 3 Like 1
20	29.8	29.84	5	3.035	FRG1BP;DEFB115	FSHD Region Gene 1 Family Member B, Pseudogene; Defensin Beta 115
5	68.8	68.80 - 68.81	5	3.172	OCLN	Occludin
18	18.6	18.55 - 18.65	15	2.977	ROCK1	Rho Associated Coiled-Coil Containing Protein Kinase 1
4	52.8	52.80 - 52.84	9	2.978	DCUN1D4;LRRC66	Defective In Cullin Neddylation 1 Domain Containing 4;Leucine Rich Repeat Containing 66
4	49.0	48.99 - 49.04	5	2.999	CWH43	Cell Wall Biogenesis 43 C-Terminal Homolog
7	64.43	64.43	5	3.261	ZNF273;ZNF117	Zinc Finger Protein 273;Zinc Finger Protein 117
9	38.72	38.66 - 38.72	27	2.933	FAM201A;CNTNAP3	Family With Sequence Similarity 201 Member A;Contactin Associated Protein Family Member 3

Table 3: Genomic regions and associated genes for top 20 significant in |XP-EHH| Bonobos and Chimpanzees.

Chr	Position (Mbp)	Position Range	Total of SNPs Examined (n)	Mean LogPvalue	Gene Reference	Gene Name
16	34.36	34.36 - 34.38	185	3.439	CCNYL3;UBE2MP1	Cyclin Y Like 3;Ubiquitin Conjugating Enzyme E2 M Pseudogene 1
1	104.16	104.15 - 104.16	23	4.819	AMY2B;AMY2A	Amylase Alpha 2B and 2A
1	160.88	160.86 - 160.90	322	3.436	ITLN1	Intelectin 1
17	22.20	22.2	29	3.893	MTRNR2L1	MT-RNR2 Like 1
19	22.59	22.59 - 22.60	68	3.443	ZNF98	Zinc Finger Protein 98
1	104.31	104.30 - 104.31	51	3.592	AMY1C	Amylase Alpha 1C
16	34.41	34.41 - 34.42	112	3.469	UBE2MP1	Ubiquitin Conjugating Enzyme E2 M
1	120.51	120.45 - 120.52	103	3.457	NOTCH2	Notch Receptor 2
4	79.18	79.17 - 79.19	36	3.327	FRAS1	Fraser Extracellular Matrix Complex Subunit 1
8	20.30	20.30 - 20.37	46	3.264	LZTS1;SNORD3F	Leucine Zipper Tumor Suppressor 1; Small Nucleolar RNA, C/D Box 3F
10	13.48	13.44 - 13.48	134	3.249	SEPHS1;BEND7	Selenophosphate Synthetase 1;BEN Domain Containing 7
16	34.44	34.43 - 34.45	180	3.357	LOC112268173;LINC01566	Uncharacterized LOC112268173
6	85.36	85.33 - 85.36	28	3.289	LINC01611;TBX18-AS1	Long Intergenic Non-Protein Coding RNA 1611;TBX18 Antisense RNA 1
7	144.59	144.59	5	3.837	TPK1;CNTNAP2	Thiamin Pyrophosphokinase 1; Contactin Associated Protein 2
17	21.89	21.89 - 21.90	32	3.228	FAM27E5	Family With Sequence Similarity E5
1	160.84	160.84 - 160.85	14	3.501	CD244;ITLN1	CD244 Molecule; Intelectin 1
10	120.71	120.71	4	3.276	CACUL1;NANOS1	CDK2 Associated Cullin Domain 1;Nanos C2HC-Type Zinc Finger 1
16	34.41	34.41 - 34.42	112	3.644	UBE2MP1;LOC112268173	Ubiquitin Conjugating Enzyme E2 M Pseudogene 1; Uncharacterized LOC112268173
6	58.76	58.75 - 58.76	2	4.361	LINC00680-GUSBP4	LINC00680-GUSBP4 Readthrough
14	80.61	80.61	7	3.723	NRXN;DIO2	Neurexin 1;Iodothyronine Deiodinase 2

Table 4: Genomic regions with significant evidence (FDR corrected) for recent positive selection in Bonobos on the iHS statistic.

Candidate regions (Chr, Mb)		Significant Log Pvalue	Total of SNPs Examined	Genes in region	Full gene name	Trait associations	Reference
chr 2	19.6	2.426 – 2.878	2	OSR1	Odd-skipped related transcription factor 1	Aggression; Anxiety-like Behaviors	(Geng, Byun, & Delpire, 2010; van Dongen et al., 2015)
chr 5	62	2.672 – 2.737	2	HTR1A	Serotonin 1A Receptor	Cortisol Stress Response; Anxiety; Agonistic behavior	(Armbruster et al., 2011; Staes et al., 2019)
chr 7	97.4	2.536 – 3.033	4	TAC1	Tachykinin Precursor 1	Anxiety and Depression	(Bilkei-Gorzo, Racz, Michel, & Zimmer, 2002; Hay et al., 2014)
chr 7	99.3	2,213 - 7.457	6	CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4	Stress	(Duerfeldt & Blagg, 2010)
chr 10	110.7-110.8	2.403 – 4.672	8	XPNPEP1	X-Prolyl Aminopeptidase 1	Stress; bipolar disorder	(Xu et al., 2014)
chr 16	82.2	3.065 – 5.517	2	CDH13	Cadherin 13	Violent Criminality; ADHD	(Arias-Vásquez et al., 2011; Tiihonen et al., 2015)
chr 18	18.5-18.6	2.104 – 10.992	15	ROCK1	Rho Associated Coiled-Coil Containing Protein Kinase 1	Anxiety	(Greathouse, Henderson, Gentry, & Herskowitz, 2019)

Table 5: Genomic regions with significant evidence (FDR corrected) for recent positive selection in Chimpanzees on the iHS statistic.

Candidate regions (Chr, Mb)		Significant Log Pvalue	Total of SNPs Examined	Genes in region	Full gene name	Trait associations	Reference
chr 9	38.6-38.7	2.051 – 3.703	27	CNTNAP3	Contactin Associated Protein Family Member 3	Social Behavior; Autism	(Tong et al., 2019)
chr 12	112.2	2.447 – 4.135	5	ALDH2	Aldehyde Dehydrogenase 2 Family Member	Anxiety; Depression; Alcohol Dependence	(Huang et al., 2004; S.-Y. Lee et al., 2010; Lu et al., 2018)
chr 18	18.5-18.6	2.014 – 4.598	15	ROCK1	Rho Associated Coiled-Coil Containing Protein Kinase 1	Anxiety	(Greathouse, Henderson, Gentry, & Herskowitz, 2019)
chr 19	9.5	2.137 – 3.348	11	ZNF266	Zinc Finger Protein 266	Physical Aggression	(Binder & Klengel, n.d.; Guillemin et al., 2014)

Table 6: Genomic regions with significant evidence (FDR corrected) for recent positive selection in Cross Population on the XP-EHH Statistic

Candidate regions (Chr, Mb)		Significant SNPs (P-value)	Total of SNPs Examined	Genes in region	Gene Full name:	Trait associations	References
chr 2	19.6	2.010 – 3.408	6	OSR1	Odd-skipped related transcription factor 1	Aggression and Stress Tolerance	(van Dongen et al., 2015)
chr 2	165.9	2.002 – 3.208	15	SLC38A11	Solute Carrier Family	Aggression	(Chowdhury, Chan, & Kravitz, 2017)
chr 5	46.3	2.18 – 4.12	5	HCN1	Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 1	Anxiolytic and Antidepression	(Knoll, Halladay, Holmes, & Levitt, 2016)
chr 5	111.5	2.076 – 3.152	13	EPB41L4A	Erythrocyte Membrane Protein	Anxiety disorders	(Smoller, Block, & Young, 2009)
chr 12	72.6	2.764 – 3.238	9	TPH2	Tryptophan Hydroxylase 2	Aggression and Depression	(Osipova, Kulikov, & Popova, 2009)
chr 14	80.6	2.675 – 4.00	7	NRXN3	Neurexin 3	Aggression and Fear Behavior	(Grayton, Missler, Collier, & Fernandes, 2013)

Table 7: LD Analysis via HaploReg v4.1.

Regulatory Chromatin States										
SNP	**chr**	**pos (hg19)**	**LD (r2)**	**LD (D')**	**Ref**	**Alt**	**Gene**	**Functional annotation**	**Group Description**	**Chromatin States**
rs115015904	10	110825750	0	0	C	T	XPNPEP1		Brain Hippocampus	19_Dnase
rs181123712	10	110825765	0	0	C	T	XPNPEP1		Anterior Caudate	19_Dnase
									Cingulate Gyrus	19_Dnase
									Inferior Temporal Lobe	19_Dnase
									Brain Angular Gyrus	19_Dnase
									Dorsolateral Prefrontal Cortex	19_Dnase
									Germinal Matri	19_Dnase
									Fetal Brain Female	19_Dnase
									Fetal Brain Male	7_Enh
										19_Dnase
										H3K4me1_Enh
rs433301	18	18588929	0	0	A	G	ROCK1	Intronic	Brain Angular Gyrus	H3K4me1_Enh
rs115517283	18	18588948	0	0	G	A	ROCK1	Intronic		
rs28838691	19	9572609	0	0	C	G	ZNF560		Brain Hippocampus	H3K4me3_Pro
rs8107808	19	9566116	0	0	C	T	ZNF560		Substantia Nigra	H3K4me3_Pro
									Inferior Temporal Lobe	H3K4me3_Pro
									Dorsolateral Prefrontal Cortex	H3K4me3_Pro
rs140659129	5	46310625	0	0	A	G	HCN1		Brain Anterior Caudate	H3K4me3_Pro
rs188763608	5	46310635	0	0	G	A	HCN1		Inferior Temporal Lobe	H3K4me3_Pro
rs140659129	5	46310625	0	0	A	G	HCN1			

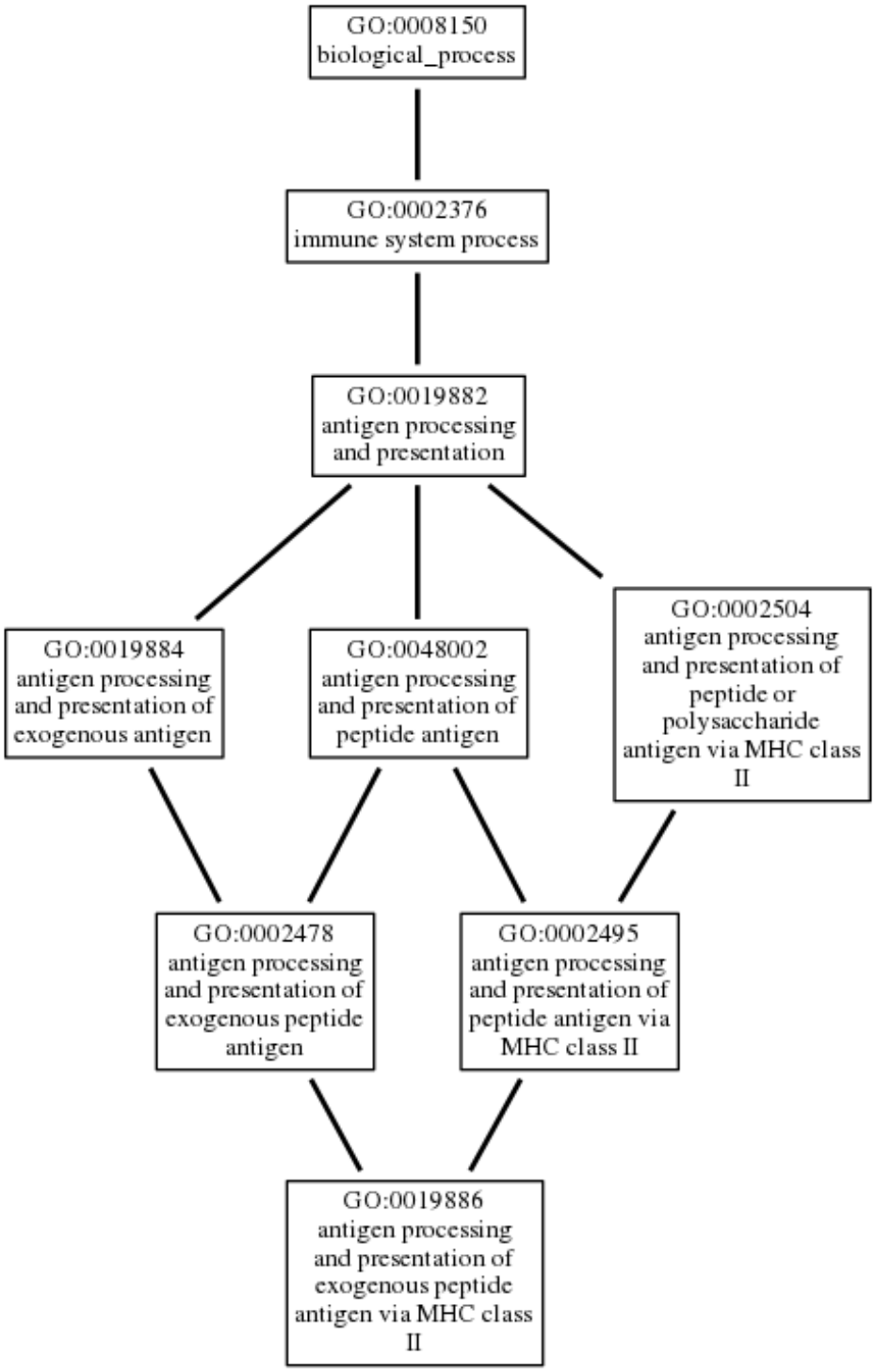

Figure 5: Antigen processing and presentation of exogenous peptide antigen via MHC class II

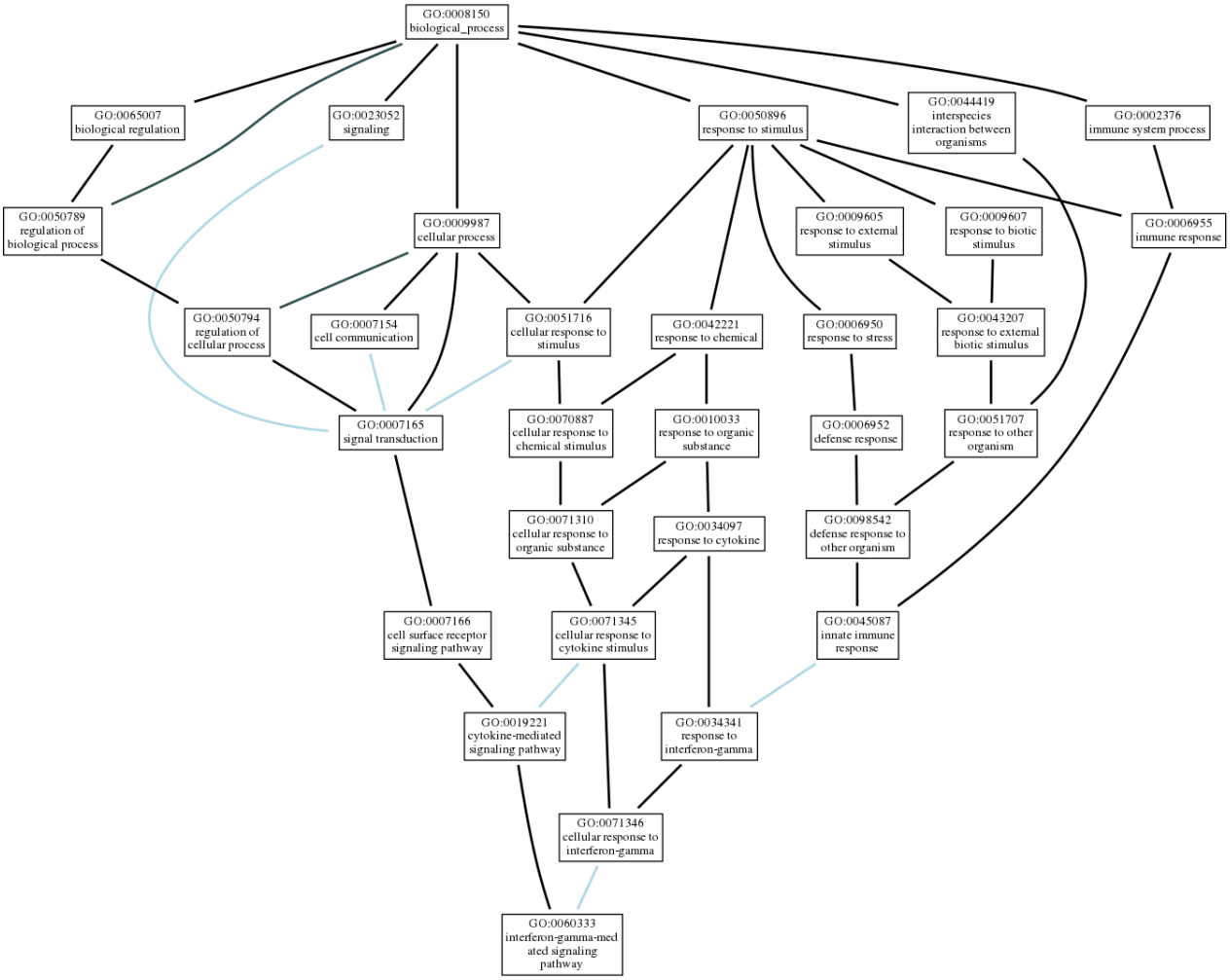

Figure 6: Interferon-gamma-mediated signaling pathway.

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